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Le rôle des connaissances préalables dans l'apprentissage en mémoire déclarative : une étude dans l'amnésie, le vieillissement et la maladie d'Alzheimer

Pierre-Yves Jonin

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Université
de Toulouse

Thèse

En vue de l'obtention du

DOCTORAT DE L'UNIVERSITÉ DE TOULOUSE

Délivré par

L'Université Toulouse 3 Paul Sabatier

Présentée et soutenue publiquement par

Pierre-Yves Jonin

le mardi 21 mai 2019

« Prior knowledge contribution to declarative learning.
A study in amnesia, aging and Alzheimer's disease »

Ecole doctorale et discipline ou spécialité:

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List of Acronyms

AD:	Alzheimer's Disease
BIC:	Binding In Context model
CLS:	Complementary Learning System model
CRAFT:	Convergence, Recollection And Familiarity Theory
DD:	Domain Dichotomy model
EK:	Experimental Knowledge, i.e. knowledge acquired on a particular stimulus, initially unknown to the subject, through pre-study exposures
ERC:	EntoRhinal Cortex; lERC: lateral part; mERC: medial part
LOP:	Levels-Of-Processing framework
MCI:	Mild Cognitive Impairment
MIM:	Multiple Input Model
MTL:	Medial Temporal Lobe
PEK:	Pre-Experimental Knowledge, i.e. knowledge associated with long-term memory representations related to the stimuli, that were present before the study phase
PHC:	ParaHippocampal Cortex
PMAT:	Postero-Medial / Anterior Temporal framework
PRC:	PeriRhinal Cortex
PRS:	Perceptual Representation System
REMERGE:	REcurrence and episodic MEMory Results in GEneralization
SAB:	Speed and Accuracy Boosting procedure
SDT:	Signal Detection Theory
SLIMM:	Schema-Linked Interactions between Medial prefrontal and Medial temporal lobe
vmPFC:	Ventro-Medial PreFrontal Cortex

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Recherche clinique hospitalière & académique

En cours

- ✓ **Exposition Préalable et Mémoire de Reconnaissance** dans la Maladie d'Alzheimer, Centre Mémoire de Ressources et de Recherches de Rennes ; CHU Rennes (CORECT 2014) ; Fondation de l'Avenir (2015) ; Institut des Neurosciences Cliniques de Rennes (2015) ; Université de Rennes 2 (Département de Psychologie) ; Plateforme Neurinfo ; Unité Projet Visages U1228, Inria, CNRS, Inserm, Université de Rennes 1, Rennes ; Centre de Recherches Cerveau et Cognition, CNRS UMR 5549, Toulouse.
- ✓ **Bases neurales de l'apprentissage** de nouvelles connaissances dans l'amnésie développementale. Collaboration avec la plateforme de neuroimagerie Neurinfo (CHU Pontchaillou)
- ✓ **Projet SAB-Fame**: Impact des connaissances préalables sur la reconnaissance ultra-rapide (CerCo Toulouse, Centre de Recherche en Psychologie, Cognition et Communication, Université de Rennes 2)
- ✓ **Projet DRM-MST**: l'implication des processus de séparation de pattern dans la genèse des faux souvenirs (Centre de Recherche en Psychologie, Cognition et Communication, Université de Rennes 2)
- ✓ **Projet SAB2Rf** : apprentissage en mémoire de reconnaissance (CerCo Toulouse, Centre de Recherche en Psychologie, Cognition et Communication, Université de Rennes 2)
- ✓ « La **variabilité cognitive intraindividuelle** peut-elle marquer le déclin cognitif et prédire la démence ? ». Collaboration avec A. Noël, MCU au Centre de Recherche en Psychologie, Cognition et Communication, Université de Rennes 2.
- ✓ Elaboration et validation d'une tâche d'**apprentissage verbal, spatial et associatif**. Collaboration avec A. Noël, MCU au Centre de Recherche en Cognition et Communication, Université de Rennes 2.

2007-20014

- ✓ **Substrats cognitifs et cérébraux des troubles de mémoire** dans la maladie d'Alzheimer pré-démentielle. Collaboration avec l'unité Inserm U1077 du Prof. F. Eustache, CHU Côte de Nacre, Caen.
- ✓ Suivi exploratoire d'une cohorte de patients atteints de **démence sémantique** (Dr S. BELLARD, CHU PONTCHAILLOU, Rennes) : organisation psychologique et neurologique des connaissances sémantiques chez l'humain.
- ✓ PHRC « **Imagerie Multimodale de la maladie d'Alzheimer Précoce** » (depuis 2008, Dr G. CHETELAT, Inserm U1077 Caen). Inclusion et suivi des participants
- ✓ Participation (inclusions et administration des tests) aux **essais cliniques** pharmaceutiques en cours dans le CMRR

2005-2006

- ✓ PHRC « Origine du manque du mot dans la maladie d'Alzheimer débutante » (2005-2006, Dr S. BELLARD, HIA Clermont Tonnerre, Brest) Co-investigateur en charge des aspects neuropsychologiques
- ✓ PHRC « Elaboration d'une épreuve de mémoire épisodique visuo-spatiale » (2005-2006, Dr S. BELLARD, HIA Clermont Tonnerre, Brest) Co-investigateur en charge des aspects neuropsychologiques

2002-2003

- ✓ PHRC « Stimulation corticale directe per-opératoire : résection tumorale et fonctions supérieures » (2002-2004 Prof. S. Bakchine, CHU Maison-Blanche, Reims & Prof. H. DUFFAU, APHP Salpêtrière, Paris : élaboration et rédaction de la partie neuropsychologique)
- ✓ PHRC « Traitement visuo-spatial dans la maladie de Huntington » (Prof. S. BAKCHINE, CHU Maison-Blanche, Reims : élaboration et rédaction d'une sous-partie du protocole, inclusion et évaluation des patients)
- ✓ PHRC « Recherche de marqueurs biologiques et neuropsychologiques des syndromes démentiels » (Prof. S. BAKCHINE, CHU Maison-Blanche, Reims : inclusion et évaluation des patients)

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“The art of remembering is the art of thinking.

When we wish to fix a new thing in (...) our own mind (...), our conscious effort should not be so much to impress and retain it as to connect it with something else already there. The connecting is the thinking; and, if we attend clearly to the connection, the connected thing will certainly be likely to remain within recall.”

William James, 1983, p. 87, cited in Lockhart & Craik, (1990)



Willem de Kooning.

Unused preparatory drawing for *In Memory of My Feelings* (Franck O'Hara), 1967

General Introduction

General Introduction

Why and how can we remember some past experiences while others just fade away? What are the cognitive (psychological) and neural determinants of successful learning in humans? Why and how past memories interact with the on going learning process?

These fascinating questions have challenged cognitive sciences for decades, and remain under investigation within various disciplines. Cognitive neuropsychology has been particularly fruitful in providing models that aimed to account for the dissociations observed in brain-injured patients, putting forward multiple memory systems with various specific properties. Experimental psychology has provided comprehensive frameworks that predict the optimized conditions where learning may, or not, occur. Contemporary cognitive and computational neurosciences more recently provided some mechanistic accounts for various aspects of successful learning. Still, the dynamics of the cognitive systems involved in learning and their relationships remain only partly known, as are their neural implementation.

The clinical phenotypes of degenerative diseases like Alzheimer's disease or Semantic dementia dramatically illustrate the typical episodic-semantic distinction. Episodic memory is a system dedicated to the storage of so-called "events", while semantic memory is dedicated to the storage of general knowledge (about the world, including oneself biography), or "facts" (e.g. Tulving, 1972). To define a memory as semantic or episodic in nature will entirely depend on its content. If the by-product of retrieval processes is the association between one autobiographical event (e.g. the birth of my eldest daughter) and the unique context where that event has occurred (e.g. at 3:44 pm, a rather cloudy Friday of December, 2008), then both the event and its unique context have been remembered bound together, and that is an instance of episodic memory. However, whenever retrieval processes result in a simple fact (e.g. December is the month when the fall ends and the winter begins), or even in an event that is not bound to any specific, unique, context (e.g. We used to listen to Malian music dancing with my eldest daughter when she started learning to walk), then this is an instance of semantic

memory. Available evidence show that the hippocampal formation – acknowledged as the heart of episodic learning – is impaired to the same extent in both diseases (i.e. Alzheimer’s disease and Semantic Dementia), thus ruling out the temptation to simply associate one memory system (e.g. episodic memory) to one single brain structure (e.g. the hippocampus). Similarly, while theories of explicit learning generally agree to consider the medial temporal lobe (MTL) as the main functional region underlying new learning, functional dissociations within the MTL are still debated. Strikingly, clinical evidence is mixed, pointing either towards the absence of new declarative learning after damage to any MTL structures, or to some preserved learning as long as subhippocampal structures are preserved. There is, therefore, room for improvement of our understanding of a very common but critical phenomenon for our adaptation to the world, namely new learning.

In the field of memory research, the emphasis has been traditionally put on highlighting the differences between semantic and episodic memories. For the episodic component, the experiments generally require subjects to learn and recall series of stimuli, or to recall remote memories. For the semantic component, experiments usually involve retrieving knowledge from memory, categorizing stimuli or generating exemplars related to a given concept. Accordingly, the search for neuropsychological dissociations between these memories has largely contributed to shape our understanding of learning in terms of multiple memory systems (e.g. model SPI, Tulving, 1995). Still, while brain pathology can lead to some kinds of dissociations isolating one form of memory – either semantic or episodic –, inferences that can be made on the normal functioning of learning and memory in humans are limited because under physiological conditions, these memory systems work together. Thus, when neuropsychological data do inform us about the possible architectures of memory systems, the method leads to compare the normal expression of the coordinate works of distinct memory systems with the pathological performance of brain-damaged patients who rely upon one single kind of memory system. In such a comparison, what is missing in neuropsychological studies is the amount of performance that is determined not only by one or another system, but by the relationships between systems. In other words, within the multiple memory systems framework, thorough studies of brain-damaged patients with impaired episodic or

semantic memory are not sufficient to inform us on how the different systems interact, and whether these interactions alter performance.

Yet, these interactions must be taken into account for the building of any comprehensive theory about learning and memory.

Consider the following situation: weeks ago, you had to buy a new car. Let's suppose you are not really interested in cars, so your goal here is just to find a new one as quickly as possible. Let's suppose again that you finally have chosen a Volkswagen Golf. Great, the job is done; you bought this car, and started driving for a few weeks. Now, didn't you ever experience that strange feeling making you think: "It's as if since I bought my own Golf, I feel like I see it everywhere"....?

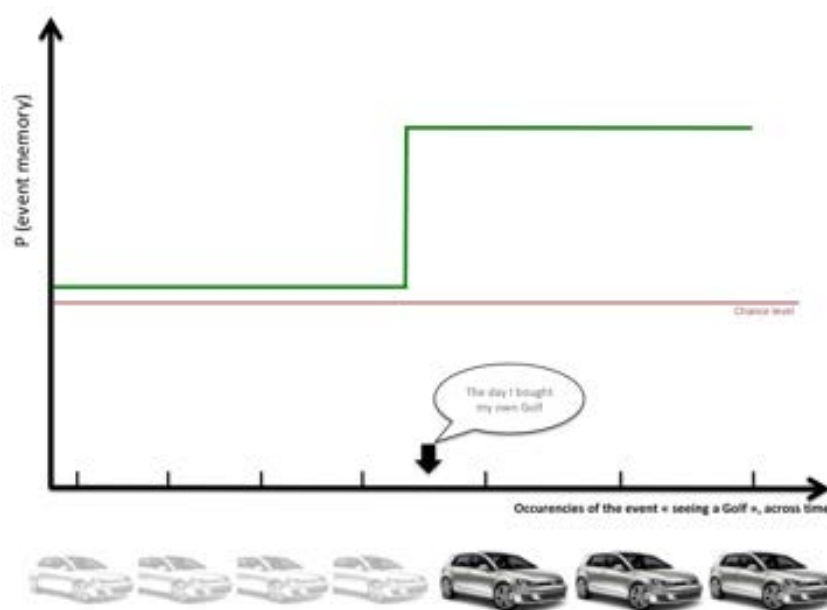


Figure 1. Why, since I bought a Golf, do I feel like I see it everywhere?

I suppose everyone would agree that this feeling is unlikely to be due to an extraordinary coincidence, namely that by chance, at the time you have bought your car, there was a sudden massive increase in Golfs sales in your area. More seriously, that feeling can hardly be experienced without declarative learning. Being able to consider that your frequency of encounters with that particular car has incredibly increased since you bought your own, requires that you have kept some record of these events during some period of time. Given that there is no logical reason why you would not have had the same frequency of "Golf encounters" before your purchase, something else must explain why you got that feeling. In other words, *why do the very same event* (i.e.

bumping into a VW Golf), likely involving the same stimuli across very similar contexts, *seems to lead to memory formation in one case, but just fades away in the other case?*

Similar examples can be mentioned, sometimes even more striking. One colleague explained me that since the day she knew she was pregnant, she felt like she saw pregnant women everyday and everywhere around her. As for myself, since I was first explained how to discriminate between a herring gull and a great black-black gull, not only did I become good at doing so, but also for months if not years I had the feeling that the headcount of black gulls kept increasing, when this gull remained even quite constantly rare at that time. A last example again illustrating how very similar events can turn into long-term memories or just rapidly fade away. The classmate my youngest daughter plays the more with is named Lola. Some time after we met her – I can remember how this first name sounded rather funny and original to me in the first place -, I realized that actually a lot of little girls in my daughter's school were named Lola, and it was definitely not as unusual as I first thought.

More empirical evidence highlighting the critical role of prior knowledge on subsequent learning comes from the psychology of expertise. One of the most famous experiments, back in the early 1970's, has shown that adult with chess expertise (either a "class A" player or a Master) were far more accurate at recalling from short-term memory chess positions than an adult chess novice (Chase & Simon, 1973a) (see [Figure 2](#)). The most important result though was that, when chess positions were randomly organized rather than inspired from real games, experts were not better anymore.

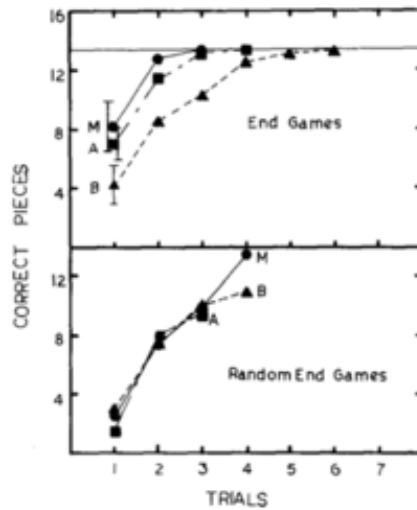


FIG. 2. Learning curves for the end-game and random end-game positions. The brackets are standard errors based on five positions.

Figure 2. Learning curves of a Chess Master and a Class A Player vs. a Novice, immediate recall of pieces positions on a chessboard. Chess experts outperform novice only for actual games, but not for random, unlikely, games. Taken from Chase & Simon (1973a), p. 61.

This result is even more striking when considering that there is no significant difference between novices and experts in terms of gross perceptual processing of the chessboard (De Groot, 1978). The critical role of expertise – that can be viewed as a domain-specific knowledge – has also been put forward for cognitive development. Consider for example that when asked to recall from short-term memory chessboard displays, children “experts” in chess are better than novice adults (Chi, 1978). In the meantime, the adults still showed the expected superiority in the more classical, digit-span, short-term memory task. Similarly, fourth-graders children experts in football were more accurate than novices in recalling short passages about soccer games, but more importantly they outperformed adult novices for this verbal long-term memory task (Weinert, 1984, 1986). In a quite unusual report, Chi & Koeske, (1983) have studied a 4.5 years old boy who, as is quite often the case, became an expert in dinosaurs. Strikingly, one year after his intense interest for dinosaurs was over, this boy was far better at recalling the names of the dinosaurs that fell within his initial “expertise”, and thus had been familiar to him, than the names of unfamiliar dinosaurs. Finally, there is evidence that these “intense interests” in childhood may be of great matter for early memory development, in that they have proven beneficial for knowledge acquisition, persistence, attention heightening, and deeper information processing (Hidi, 2000; Renninger, 1992; Renninger & Wozniak, 1985; Schiefele & Krapp, 1996).

These examples suggest that the cognitive processing of a given event seems to be biased towards memory formation when prior knowledge is available. If we come back to the car example, before your purchase, each event involving a VW Golf might just be processed minimally, e.g. includes some “there’s a car”. The probability of subsequent memory for that event may be at chance level; indeed it does not seem to serve any relevant adaptive purpose. By contrast, imagine yourself as the recent proud owner of a brand new Golf. Each time you bump into a Golf, that event could be processed quite differently, because your perceptual processing now matches to a large amount of personally relevant knowledge that you have just acquired about that vehicle. Importantly, this altered processing can serve the simple purpose of being able to discriminate from now on your own car from the other Golfs, which of course is critical in parking areas... We can argue that in that situation (being the recent owner of a Golf), the fact that perceptual processing at encoding relates to recently acquired prior knowledge not only allows you better identifying the object, but might also enhance the probability of subsequent memory for the event. After a few similar events, you may well form the feeling that you bump into the same car as yours everywhere, when you cannot remember you ever even noticed Golfs around you before! Here it is important to emphasize that while these phenomena clearly depends on learning and memory functioning, still they differ in one critical aspect, namely repetition effects. The most acknowledged factor leading to memory formation is repetition: repetition of the same stimulus leads to memory effects observable from the cellular level (i.e. Long-Term Potentiation) to the behavioural level (faster responses in perceptual priming, increased recall accuracy in words-list tasks). However, the phenomenon we are interested in here apparently does not relate to repetition. If we come back to the first name example, the amount of repetitions of a target event (i.e. seeing or hearing the first name “Lola”) does not differ before and after the moment when you really met one “Lola”. Similarly, there is no reason why you would have been exposed to more VW Golfs after you bought your own one than before (actually it is even more likely that you experienced more crossings of such a car before your purchase). So, if there is some alteration of learning and memory for a particular event after the acquisition of relevant knowledge about it, this phenomenon is by no way resulting from a “learning curve” effect. Rather, it seems that some qualitative difference may drive this effect, rather than a quantitative difference in terms of the number of prior exposures, for example.

Thus, the role of the relationships between what we know and what we learn, in the service of learning, is of great matter. How do we learn what we know?

Noteworthy, the idea that prior memories may alter new learning can be tracked back to Hermann Ebbinghaus, in very concrete terms. When Ebbinghaus attempted to rigorously investigate human learning, his use of meaningless syllables was purposeful: Robert Bjork reminds us that the German scientist “wanted new learning not to be corrupted by, sort of...*learning you already knew*” (quote from an interview of Robert Bjork, retrieved at <https://www.youtube.com/watch?v=TT035X2rqls> on May, 25th). Far from the Plato’s metaphor of the wax tablet (see Roediger, 1980), new learning never occurs in a vacuum: instead and typically, new episodes are processed in relation to existing knowledge, namely, prior memories may have a major influence on learning. While the typical learning experiments in psychology or neuropsychology require subjects to learn lists of rather unfamiliar stimuli (e.g. words) in an unfamiliar environment (i.e. the lab), everyday learning occurs with highly familiar stimuli within highly familiar contexts (routines are a big part of our lives, aren’t they?). Thus, within the continuous flow of information that we process everyday, our need for later remembering some episodes, or to simply recognize some situation as familiar, can be viewed as closely relying on the relationships between perceptual processing and the relevant prior knowledge available – or its absence – at encoding. Little effort however has been made to improve our understanding of how knowing influences learning, by comparison to the large amount of experiments dedicated to learning (e.g. “verbal learning” period within a short history of the science of memory, see Tulving, (2000), to episodic memory or to semantic memory specifically. The work I have done during that thesis was aimed at contributing filling this gap.

The present thesis aimed at improving our understanding of how learning occurs, both at a cognitive and at a neural level. Among the various factors known to strongly predict whether learning will occur or not, we aimed at investigating whether prior knowledge plays a role; if so, how can we better characterize that influence, namely, which memory processes are altered at retrieval when prior knowledge is available at encoding, and does the kind of prior knowledge matter, or does any sort of prior knowledge exerts the same influence. Moreover, we aimed at shedding some light upon the neural substrates underlying the role of prior knowledge in learning. To this end, we will first report a

thorough case study of patient KA, a patient with severe developmental amnesia. **Meeting patient KA was indeed the neuropsychological starting point of that thesis.** That is, the first series of experiments with this patient brought strong evidence that despite no residual episodic learning, and massive damage to the whole hippocampal system, KA presented with supranormal levels of explicit learning and semantic knowledge. These findings in patient KA were in sharp contrast with **his inability to recognize simple meaningless items**, which has led us **to focus on the interactions between what we know and what we learn**, as stated above. The second series of experiments aimed at testing the very basic idea that when available, prior knowledge at encoding can be a powerful learning enhancer. These included an investigation of whether aging alters prior knowledge-dependent learning the same way it does for typical instances of learning. The third experiment used functional neuroimaging to test data-driven hypothesis resulting from our behavioural results regarding the brain networks involved in memory encoding, depending on the kind of existing prior knowledge. That experiment also aimed at testing whether mildly memory impaired patients could benefit any kind of prior knowledge. Finally, we will report on a last experiment with patient KA, that aimed at testing whether more severe amnesia could nonetheless be reduced for stimuli with prior knowledge derived from experimental procedures.

The problem of learning and memory

The problem of learning and memory

« Memory is a biological abstraction. There is no place in the brain that one could point at and say, Here is memory. There is no single activity, or class of activities, of the organism that could be identified with the concept that the term denotes. There is no known molecular change that corresponds to memory, no known cellular activity that represents memory, no behavioural response of a living organism that is memory. Yet the term memory encompasses all these changes and activities. »

Endel Tulving, 1995, p. 751.

Like for many concepts that are widely used, the concepts of learning and memory prove hard to define. This section is aimed at clarifying why classical definitions of learning are problematic, and how a recently proposed definition may better fit with the purposes of the present thesis.

“Learning” as an ill-defined concept

In a classical textbook, Alan Baddeley himself starts a chapter entitled “What is memory?” stating that “Memory is something we complain about” (Baddeley, Eysenck, & Anderson, 2015), but does not provide a clear definition. Strikingly, despite the thousands of scientific studies addressing the question of how learning and memory work, that topic being one of the main topics of experimental psychology over the 20th century, researchers hardly define precisely what “learning” means. Still, any scientific approach first needs a clear definition of its matter.

One very straightforward way to define learning is the adoption of a simple functional definition like “Learning is the modification of behaviour resulting from experience”. In fact, most of the classical textbooks adopt such a functional definition: “Learning refers to a relatively permanent change in behaviour as a result of practice or experience”

(Lachman, 1997). The expected by-product of learning is memory, which can simply be defined as the faculty by which the mind stores and remember information. Defined this way, any behaviour that would be experience-dependent (e.g. quote from Larry Squire, retrieved at <https://www.youtube.com/watch?v=NyDNxlaTgPM&t=100s>) could be an instance of memory, resulting from some learning. Such a simple definition of learning takes his roots in the behaviourist approach to learning, where “all one needs to predict someone’s behaviour is a catalogue of specific facts and generalizations about his or her past responses to situations resembling the present one” (Bower, p. 59, in Allan et al., 2000).

The first problem with that definition is that it makes unlikely any experimental attempts to study learning. Since one can infer that some learning has occurred only if one has identified a memory, learning becomes unobservable. That is, if we were interested in learning, following that definition, any investigation of learning would be indirect: learning cannot be explored independently from its consequence, i.e. memory, so that at the time we would infer anything on how learning takes place, such learning would already have occurred. Typically, learning experiments involve a study and a test phase. Whether learning has occurred or not is inferred based on the test’s variable, that is, far from when learning has supposedly occurred.

The second problem with such a simple, functional definition is that it is over-inclusive. Not all experience-dependent changes in behaviour reflect learning; conversely, not all experiences yield memory formation. As an example, imagine you walk into a new room, an odd-colored light fills the room, and then a loud and threatening rattling noise goes off and persists. You exit with haste (Eichenbaum, 2002, p.3). Here, the change of behaviour is a direct consequence of experience, although it may hardly be considered an instance of learning. Other changes in behaviour like the slowing of information processing speed or the decrease in response accuracy can be experience-dependent, like in the case of fatigue or lack of motivation. Still, these experiences cannot be considered as causes of learning.

The third problem with the classical functional definition is that it also excludes well-acknowledged instances of learning, like classical conditioning. In the example of Pavlovian conditioning, the learned association between a tone and the food does not yield any change in behaviour: the salivation behaviour pre-existed to learning, however, a change in stimulus effectiveness has occurred due to learning. Here, what has changed

as a result of experience is the Stimulus-Response relationship, rather than the behavioural response *per se*.

Unsatisfactory alternatives

Alternative definitions have therefore been proposed, however, they also present with difficulties casting some doubt on how useful they can be for the experimental study of learning (de Houwer, 2011; De Houwer, Barnes-Holmes, & Moors, 2013). These definitions generally assume a mechanistic, rather than functional, approach to the problem of learning. Thus, (Lachman, 1997) proposes, “Learning is the process by which a relatively stable modification in stimulus-response relations is developed as a consequence of functional environmental interaction via the senses“ (p.479), while (Domjan, 2010) states: “Learning is an enduring change in the mechanisms of behaviour involving specific stimuli and/or responses that results from prior experience with those or similar stimuli and responses“ (p. 17). These alternative definitions assume that learning is better characterized by a series of mechanisms mediating the relationships between the experience and the behavioural change. A strong advantage is that learning is considered as one series of processes among others that determine behaviour, making a change in behaviour unnecessary to infer that learning occurred. However, they imply that some change in the organism has occurred, reflecting the above-mentioned mechanisms, and that these changes have a direct (or contiguous) causal relationship with learning. Typical learning effects are observed after a delay, that is, the experience at time 1 that supposedly includes these learning mechanisms are no longer present at time 2, when the behaviour is tested. Tenants of these mechanistic accounts therefore suggest that a change in the organism – the core basis of learning – occurs with experience, and that it lasts over time so that it is still present at test, therefore being responsible for the observed change in behaviour (de Houwer, 2011). Thus, defining that change in the organism and having accurate proxies for it is inherent to the mechanistic definition of learning. Unfortunately, we currently miss a clear description of what changes in the organism as a result of experience, as well as how to assert that such a change has occurred or not. It follows that we also miss a taxonomy of these changes in the organism that may reflect the different kinds of learning acknowledged at the psychological level (associative learning, item learning, declarative vs. non declarative learning), making it unlikely to move forward on the scientific investigation of the learning phenomenon. It therefore seems that the use of behavioural proxies for learning

remains mandatory. A recent definition of learning has been proposed that may solve the pitfalls arising from the simple functional definition, or the mechanistic approach.

Towards a new definition of learning

De Houwer et al., (2013) have brought a new definition of learning as follows: *“Learning can be defined as changes in the behaviour of an organism that are the result of regularities in the environment of that organism“* (p. 633). Below we will argue that this definition is very relevant to the question of “how do we learn what we know?” and how it avoids the above-mentioned limitations of prior definitions.

Putting forward that regularities in the environment of an organism are a necessary condition for learning to occur sounds to us like a critical progress in the definition of learning. Prior functional definitions evoked “experience” or “prior experience with stimuli” or “functional environmental interactions via the senses”, and thus included virtually all experiences as potential learning triggers. Mechanistic definitions in particular assume that any information processing can trigger learning, thus the locus of learning is restricted to the mechanisms underlying behavioural changes. The causal experience would not have any relevant property for understanding learning; only the processes supporting behavioural changes would be the matter of interest. Yet, it is acknowledged that the repetition of the same experiences, or the extraction of shared properties across similar yet distinct experiences (“experiences” here not only include stimuli processing, but also response processing and stimulus-responses associations) is a major condition for learning. Putting forward the “regularities” in the environment therefore includes the likely possibility that some features of the environment itself are a core determinant of learning.

For present purposes, this is quite relevant since the investigation of the role of prior knowledge in learning implies that learned stimuli have already been experienced before, under various circumstances and with various regularities. Consider for example the classical distinction between explicit and implicit learning: while implicit learning as assessed within priming paradigms typically relies on a few recent prior exposures, explicit learning often involves stimuli that has been exposed many times, across the entire life of the subject. The definition from De Houwer et al., (2013) allows one to explore whether distinct regularities prior to learning could trigger distinct learning mechanisms, as observed through distinct changes in behaviour. Moreover, it makes it

possible to establish a direct relationship between some cause (i.e. some specified type of regularity) and some kind of learning (i.e. a specific behavioural change), thus attempting to model functional learning rules. Prior definitions, by contrast, allow the investigation of only one side of the coin, namely, behavioural changes on the one hand or change in the organism on the other hand.

Finally, that new definition of learning also presents the benefits of avoiding the pitfalls mentioned before. First, the concept of regularity avoids the over-inclusion of experience-dependent behaviours that cannot be considered instances of learning. If an experience produces some behavioural change but is not associated with regularity in the environment (e.g. to bend down when hearing a loud bang), then it won't count as an instance of learning. Second, that definition avoids the need to assume that some change in the organism, and therefore in behaviour, must occur at the time of "study" and lasts enough until the time of "test", like in the mechanistic definitions. Instead, De Houwer et al., (2013) definition states that only the functional relationship between some environmental regularity (e.g. recognizing a face under different orientations) and some behavioural change (e.g. being accurate at identifying that face across different contexts) constitutes an instance of learning. Thus, there is no need to assume any behavioural change at both points in time to identify that learning has occurred. Moreover, this allows avoiding the dependency on accurate proxies for an organism's changes that would be learning-specific, proxies that we still currently miss. However, by adopting a broad definition of "behavioural changes", encompassing "every observable response that a living organism can make, regardless of whether the response is produced by the somatic nervous system (e.g., pressing a lever), the autonomic nervous system (e.g., salivation), or neural processes (e.g., electrical activity in the brain)" (De Houwer et al., 2013, p. 633), this functional definition includes every research using physiological measurements within the scope of learning research, as long as environmental regularities are manipulated as independent variables.

In the present thesis, we will thus refer to learning within that conceptual framework, asking whether distinct regularities in the environment, resulting from distinct kinds of prior knowledge, can result in distinct kinds of learning.

Introduction: state-of-the-art

Introduction: state-of-the-art

Overview

“Few problems in science are as difficult as those of working out the precise relation between two complex concepts that are deceptively similar. The relation between episodic and semantic memory belongs in this category.”

Endel Tulving, 1993, “What Is Episodic Memory”, p. 67

In the present thesis, we will focus on how what we *know* (general knowledge of the world) influences what we *remember*. Following the widely acknowledged distinction between episodic and semantic memory, we will thus address the question of how semantic memories (i.e. prior existing context-free representations) influence the acquisition of new episodic memories (i.e. new context-rich representations). The importance of this topic can be highlighted if one considers the expected benefits in the field of education (e.g. van Kesteren, Krabbendam, & Meeter, 2018), neurological conditions responsible for memory disabilities (e.g. amnesia, Irish & van Kesteren, 2018; Kan, Alexander, & Verfaellie, 2009). More generally, factors allowing the most efficient memorization are increasingly scrutinized (e.g. Tabibian et al., 2019), and our hope is to offer some contribution here.

In the **first Introduction section**, we will present the *concepts of declarative memory together with the idea of the Medial Temporal Lobe as a functional entity*, focusing on *recognition memory tasks*. We will here explain why we chose recognition memory as the main behavioural method for the assessment of learning and memory. Most importantly, we will present the current theoretical frameworks for recognition memory performance, putting the emphasis on how the fractionation of declarative has progressed since the earthquake for memory research driven by the study of the patient HM.

The second and third Introduction sections will be devoted to provide a historical sketch on how *experimental psychology and cognitive neuropsychology* have led to the divorce between remembering general facts and remembering facts related to the self, opening the still in use era of the semantic - episodic memory distinction. This oriented overview will highlight the close interactions between these memories that may have been overlooked. At that point, we will underscore one critical issue remaining with respect to the relationships between semantic and episodic memories. We will argue that neuropsychological evidence for distinct brain systems underlying semantic and episodic learning is actually incomplete, thus weakening the hypothesis of *separate* memory systems (i.e. distinct biological entities).

A fourth Introduction section will address the *long story of the relationships between semantic and episodic memories*, highlighting the key contributions of the psychology of expertise. We will honour the inspiring and sometimes underrated works of psychologists from the late 19th/early 20th centuries. This short historical sketch will make the point that early experimental studies considered *knowing* and *remembering* as naturally married in healthy subjects, i.e. exerting a mutual influence on each other.

A fifth Introduction section will deal with the limitations of the traditional expert-novice paradigm for the study of how knowing affects remembering, *therefore making the case for the need of equalizing the perceptual processing differences across subjects*. The special case of faces will be addressed, by presenting the current understanding of how prior knowledge about faces changes further remembering. At that point, we will further develop the reasons why human faces were chosen as the main materials under investigation in this work.

A last Introduction section will review the *contemporary neurocognitive accounts for the role of prior knowledge* in declarative learning, including the models supporting the key role of Novelty (thus to some extent, the absence of prior knowledge) in learning, and the respective core predictions.

We will finally highlight some unresolved issues related to the interactions between what we know, and what we remember. More specifically, we will put the emphasis on

- the **lack of neuropsychological evidence making clearly the case for two separate learning pathways**, one supporting semantic, the other episodic, learning;
- the **lack of unified theory regarding the influence of prior knowledge** on episodic learning as assessed through recognition memory;
- the divergences regarding as to **whether recognition memory is changed broadly when prior knowledge is available at encoding, or if its impact targets specific retrieval processes**
- the **contradiction** between some theoretical frameworks, predicting **either that novelty detection or integration to prior knowledge are core determinants** of learning
- the **lack of knowledge** regarding whether prior knowledge influences on episodic learning **change with age**, in striking contrast with the acknowledged fact that the elderly have built a large amount of knowledge and keep largely intact access to it
- the absence of data regarding whether prior knowledge influences on episodic learning **change with Alzheimer's disease**

As stated above, the project of this thesis was born with the meeting of patient KA, with an atypical syndrome of developmental amnesia. Because it soon became obvious that 1) this patient had an unexpected superior level of general knowledge; and 2) surprisingly he could learn new context-free memories for meaningful, but not meaningless stimuli, the present thesis explores two distinct paths.

First, we aimed at establishing whether KA could retrieve and acquire new explicit memories like controls, and to seek evidence for related abnormalities in his brain. Second, we wished to explore whether and how prior knowledge affects new declarative learning.

We further present an overview of the experimental section accordingly.

The first series of experiments of this thesis will be presented, along the single case study of patient KA, which hopefully will directly address the issue of whether distinct functional systems can underlie semantic vs. episodic learning.

We will present a *second experiment* with patient KA showing that preserved explicit learning in amnesia may not generalize to meaningless memoranda. This finding has launched the central issue addressed in this thesis, namely, to what extent and how prior knowledge can provide for new learning? In a nutshell, how do we learn what we know?

A *third series of 2 experiments* will then be presented, where we attempted to contrast the impact of novelty and of two kinds of prior knowledge on subsequent item and associative memory, within a lifespan perspective.

The fourth experiment will address the question of the neural basis for the influence of two kinds of prior knowledge on associative learning, both in healthy elderly and in a group of memory-impaired patients with prodromal Alzheimer's disease.

The fifth experiment will come back to the study of patient KA, investigating whether prior knowledge availability can benefit new learning despite amnesia.

Finally, in the discussion section, some perspectives regarding the mechanisms underlying the impact of prior knowledge on new learning will be suggested, amongst which we have ran 2 *new experiments* that will be presented in the Appendix.

Chapter I

Declarative memory, Medial Temporal Lobes, and Recognition Memory

I.1. Overview

One could summarize briefly the story of the link between declarative memory, recognition memory, and the medial temporal lobe as follows. The large removal of the bilateral MTL in the patient HM has dramatically demonstrated that learning depended on these structures. Further investigations in the patient revealed that some learning abilities were eventually preserved, leading to the distinction between Declarative and Procedural (Non-declarative) memories. In the quest of preserved learning functions in HM and other amnesic patients, controversies emerged as to whether recall and recognition tests similarly tapped on declarative memories. Reports of proportional impairments in recall and recognition in other amnesic patients seemed to confirm that recognition memory tasks did tap on declarative memory (Haist, Shimamura, & Squire, 1992). Yet, disproportionate impairments in recall were also observed (e.g. Huppert & Piercy, 1976; Hirst, Phelps, Johnson, & Volpe, 1988; see for review Aggleton & Shaw 1996). Such inconsistent reports occurred in the context of new research in mathematical psychology supported by the information-processing theory, which soon provided a solid framework for accurate modelling of recognition performance. Supported by animal research on the neural basis of recognition memory (Meunier, Bachevalier, Mishkin, & Murray, 1993; Mortimer Mishkin, 1978; Murray & Mishkin, 1998; Zola-Morgan, Squire, & Amaral, 1989b, 1989a; Zola-Morgan, Squire, Amaral, & Suzuki, 1989), the idea that the preservation or impairment of recognition memory could depend on whether extra-hippocampal structures within the MTL are damaged has emerged. Aggleton & Shaw, (1996) ran a meta-analysis of recognition memory performance for faces and words (Recognition Memory Test, Warrington, 1984) reported in N=112 amnesic patients. They connected findings of impaired recognition after selective damage to the rhinal cortices (perirhinal and entorhinal cortices) in monkeys (Meunier et al., 1993) with their findings of preserved recognition memory in amnesic patients when damage was supposedly restricted to the hippocampus. A dissection of the processes underlying recognition memory therefore started, pointing towards distinct retrieval processes. Shortly, the

revolution of in vivo imaging techniques has led to better characterizing the extent of the MTL damage in amnesic patients. In the early 2000's, this yielded convergent findings across experimental psychology (especially with the processing approach, e.g. (Atkinson & Juola, 1974) and neuropsychology (amnesic cases of apparent dissociation between recall and recognition, e.g. (Aggleton et al., 2005; Barbeau et al., 2005; Bastin et al., 2004; Holdstock et al., 2002; Holdstock, Mayes, Gong, Roberts, & Kapur, 2005; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Turriziani, Fadda, Caltagirone, & Carlesimo, 2004; Vargha-Khadem et al., 1997), highlighting the very likely duality of recognition memory. This resulted in strong neuroanatomical accounts for recognition memory performance within the MTL that we will tackle below, generally acknowledging that correct recognition can rely on two independent pathways within the MTL, each supporting one kind of recognition memory process, namely familiarity and recollection. In the meantime, in the middle of the nineties, it has become evident that declarative memory had to be fractionated (Vargha-Khadem et al., 1997), distinguishing episodic from semantic memory systems. A very clear idea of the importance of these progresses for the cognitive neurosciences of human memory can be made from *Figure 3*.

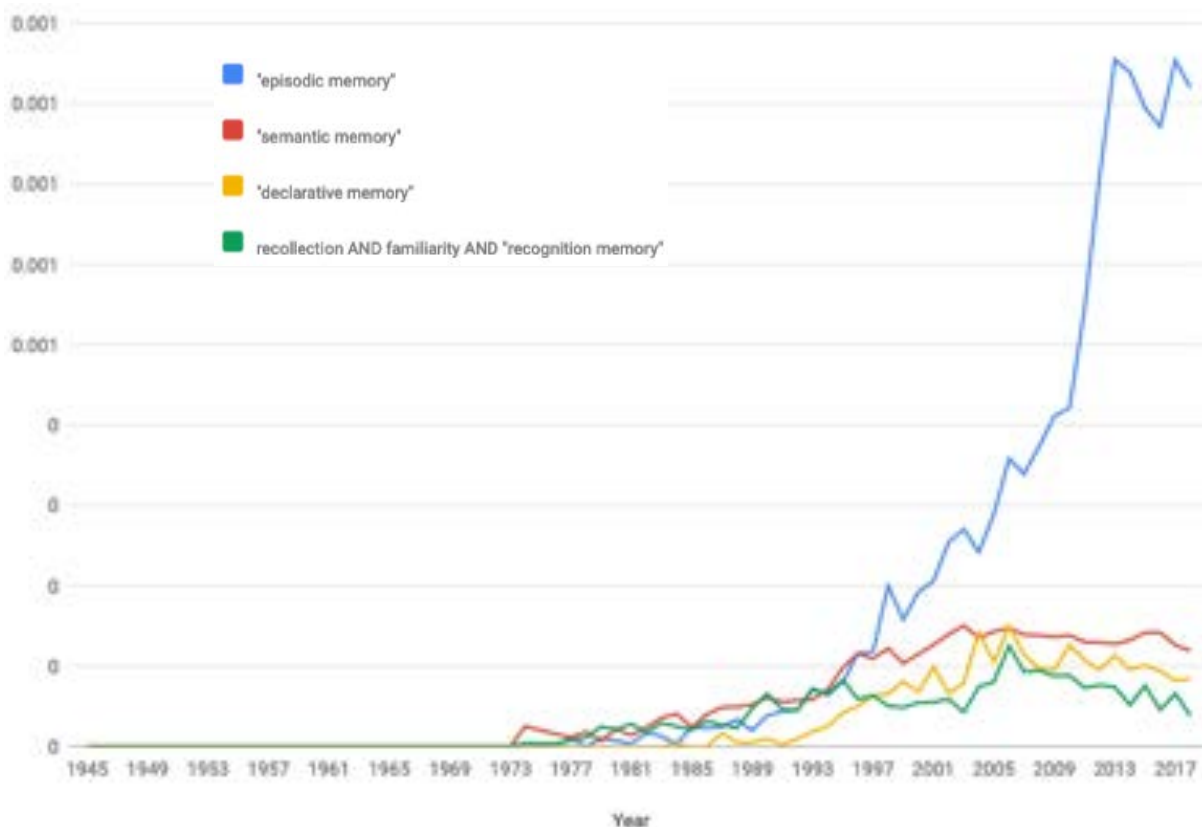


Figure 3. Episodic memory » citations have literally skyrocketed from the mid-1990's. Y-axis shows the absolute proportions of citations per year (source: <https://esperr.github.io/pubmed-by-year/>)

Figure 4 and Figure 5 depict an overview of both the situation of the MTL structures and the complexity of their anatomy. We further detail shortly this historical background to finally expose the main theoretical frameworks for recognition memory, as well as its neural substrates since, as will be shown later, almost all the experiments run in the present thesis have in common the interest for the computations performed by the MTL structures, and / or the behavioural consequences of damage to some of these structures.

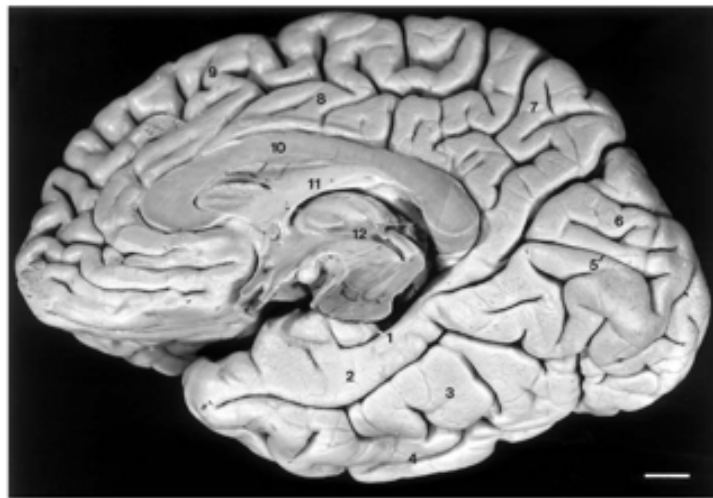


Figure 4. Macroscopic anatomy (dissection) of the temporal lobe, medial view of a human right hemisphere. Taken from Duvernoy, (2005). (1) portion of the hippocampus; (2) parahippocampal gyrus; (3) fusiform gyrus; (4) inferior temporal gyrus; (5) calcarine sulcus; (6) occipital lobe (cuneus); (7) parietal lobe (precuneus); (8) cingulate gyrus; (9) superior frontal gyrus; (10) corpus callosum; (11) fornix; (12) third ventricle.

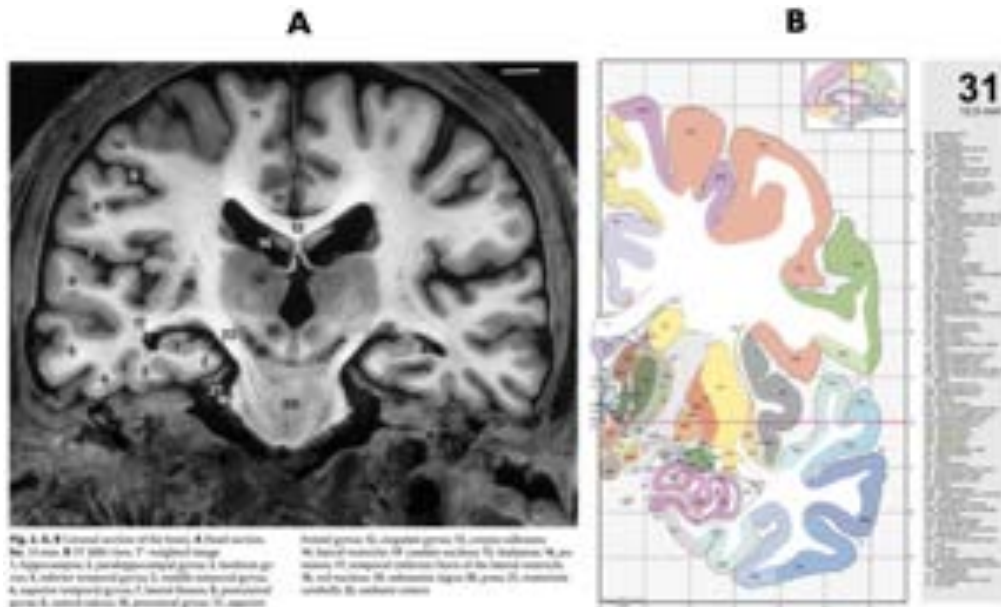


Figure 5. Detailed anatomy of the MTL, taken from Duvernoy (2005) (Figure 5A) and Mai, Paxinos, & Voss, (2008) (Figure 5B).

1.2. Definition and relevance for the present thesis

Recognition memory can be simply defined as our ability to decide whether or not a given object or event has been experienced before (Atkinson & Juola, 1974). More specifically, we are interested in the recognition of the prior occurrence of an event (Mandler, 1980). This can be considered as an elementary manifestation of memory in our everyday lives: as our everyday routines unfold, we consistently rely upon recognition memory processes to further guide our behaviour. Many situations actually involve this simple form of declarative memory (Squire & Schacter, 2002), like during social interactions. As you meet one relative in the street, your ability to quickly identify not only that you know this person, but also to access details related to your last encounter, will be decisive in adopting an appropriate behavior. As a neuropsychologist working in a Memory clinic setting for 15 years, I have countless anecdotes revealing how impaired recognition memory can be debilitating. A typical illustration is when Mrs. X, spouse of Mr. Y suffering early Alzheimer’s disease, recall how confused she felt when her husband asked some news about Mrs Z, their neighbour’s sister, the day after the neighbour sadly said that his sister had died. For Mr. Y, encountering his neighbour did not yield accurate recognition of their prior encounter when he announced this sad news. Even more common are the instances when patients’ family circle states that day after day, they have to say “But I

told you that already”, illustrating what happens when one information given in a conversation is not associated with a sense of prior occurrence, thus yielding repetitive questioning.

In the present work, we thus used recognition memory tasks, rather than recall tasks for three main reasons.

First, judgment of prior occurrence intuitively seemed to be the most ubiquitous manifestation of declarative memory retrieval in everyday lives. Accordingly, recognition memory abilities can be identified as early as in the first days of life, and are strongly predictive of cognitive outcome up to 6 years of age in pre-terms new-borns (Pascalis & de Schonen, 1994; Rose, Feldman, & Jankowski, 2004; Rose & Wallace, 1985). Considering a typical working day, instances of recognition memory decisions seem much more regular than instances of free recall. This is because virtually each and every perceptual processing can result in positive or negative judgment for prior occurrence, while situations where we engage ourselves in the recall of prior events are generally independent from the continuous flow of information processing.

Second, recognition memory tasks allow to controlling experimental variables involved in memory retrieval much more than recall tasks, where the mental operations carried out by the subjects remain more elusive. Consider the following extreme example of learning a list of words. A recall task can lead to the accurate retrieval of one word resulting from e.g. free association operations, with no chance for the experimenter to separate this from an instance of recall resulting from correct retrieval of the study episode. By contrast, a simple “Old”/”New” recognition memory task provides multiple metrics (e.g. see below the signal detection theory account of recognition memory) that allow to accurately model performance, as controlling for chance level.

Third, we aimed at investigating how knowledge and memory interacts, implying to dig into the underappreciated but strong interactions between encoding and retrieval processes. Any alteration of new memory formation (learning) resulting from knowledge (past experiences) necessarily raises the question of the role of retrieval processes at encoding. The Transfer Appropriate Processing theory (Morris, Bransford, & Franks, 1977) illustrates this very well, by stating that successful learning critically depends on the degree of overlap between cognitive operations at encoding and at retrieval. Because we are interested in determinants of new declarative – i.e., explicit – memories, recognition

tasks looked appropriate: these tasks require the subject to consciously retrieve past events, and if at encoding they attended to conceptual more than perceptual features of the stimuli, they are likely to perform better. This is in sharp contrast with implicit retrieval tasks like perceptual identification priming where attending to conceptual features at encoding won't matter, while attending to perceptual ones will make the difference (e.g. Dallas & Jacoby, 1981; Klavehn, Gardiner, & Java, 1994). In other words, encoding processes are not “good or bad” (Wimber, Heinze, & Richardson-Klavehn, 2010): what really matters is whether the aspects of the tasks subjects attended to at study will be relevant or not at retrieval. In our case, as stated above, we were concerned with how past experiences shape new learning in a day-to-day routine, that is, when 1/ much knowledge is available at “encoding” and 2/ later retrieval processes must flexibly guide behaviour. To our knowledge, the judgment of prior occurrence is the most efficient instance of memory retrieval making available to awareness the by-product of learning processes.

As long as the quest of psychology is ideally to find universal laws and functional explanations for naturalistic aspects of behaviour (Bronfenbrenner, 1979), recognition memory tasks seemed to us as an ideal compromise.

I.3. Patient HM: an earthquake in memory research

The seminal case of the patient HM, who has undergone an experimental surgical procedure in 1953 in an attempt to treat a severe epilepsy resisting to high doses of anticonvulsant medication, revealed the critical role of the medial temporal lobe in new learning (Scoville & Milner, 1957). The surgical procedure resulted in the removal of the bilateral medial structures of the temporal lobe. The tragic outcome of this surgery was a very severe anterograde amnesia, which patient HM himself described as “like waking from a dream.... everyday is alone in itself..” (Milner et al., 1968, p. 217; cited in Squire, 2009). Most important, perhaps, was the observation that patient HM did not present with any other sensory, motor or cognitive impairment. The idea that a selective damage to the medial temporal lobe (MTL) could result in a selective disruption of learning abilities was already in the mind of Brenda Milner and William Penfield at the time. One year before HM's surgery, Dr Milner was a PhD student at McGill University when she

encountered two patients (PB and FC) who became amnesic following unilateral removal of the left MTL, also in the context of treatment of epileptic seizures. It is after the presentation of patients PB and FC at the 1955 meeting of the American Neurological Association that W. Scoville called W. Penfield to further talk about the similarities between patient HM and his patients (Squire, 2009). This was the starting point of the fruitful collaboration between Scoville and Milner, resulting in the 1957 paper, one of the most cited neuroscience papers ever. The reason is that such observations were a real earthquake in the field of memory research.

It has put an end to the previous view that any part of the brain could actually perform the computations required for high level functions, as first suggested by Jean-Pierre Flourens following extensive lesion studies in birds. Strikingly, in 1950, Karl Spencer Lashley had generalized this view, also after an extensive research program purposely designed to “locate the [memory] engram”. Lashley concluded that, due to effective neural plasticity, virtually all the regions of the cerebral cortex could mediate learning, a principle he termed “equipotentiality”. A finding of a selective disruption of new learning following the removal of a very circumscribed region in a human brain was thus unexpected.

I.4. Declarative and Non declarative memories

In the following years, it became obvious that patient HM had some preserved learning abilities. For example, the patient could learn and remember tracking or mirror-tracing tasks as well as controls, despite lacking any recollection of the repeated learning episodes (Brooks & Baddeley, 1976; Cohen and Squire, 1978 - cited in Cohen & Squire, 1980). But the demonstration that not only basic perceptual-motor skills learning, but also more sophisticated skills like mirror-reading, that clearly involved highly integrated perceptual abilities with little motor involvement could be learned despite severe amnesic patients (Cohen & Squire, 1980), led to the proposal that “knowing that” and “knowing how” could rely on distinct memory systems. This opened the era of the multiple memory systems view in neurosciences, considering declarative (conscious memory for facts and events) and non declarative or procedural (habits and skills memory, inaccessible to conscious processing) memories, extensively developed from

neuropsychological evidence along Neil J. Cohen PhD dissertation (Neuropsychological evidence for a distinction between procedural and declarative knowledge in human memory and amnesia. PhD thesis. Univ. Calif., San Diego, 1981). Declarative memory was therefore considered to rely on the so-called “medial temporal lobe memory system” (Squire & Zola-Morgan, 1991), including the hippocampal region (cornu Ammonis with its subfields, the dentate gyrus, and the subicular complex) and adjacent entorhinal, perirhinal and parahippocampal cortices making up much of the parahippocampal gyrus (Squire, Stark, & Clark, 2004).

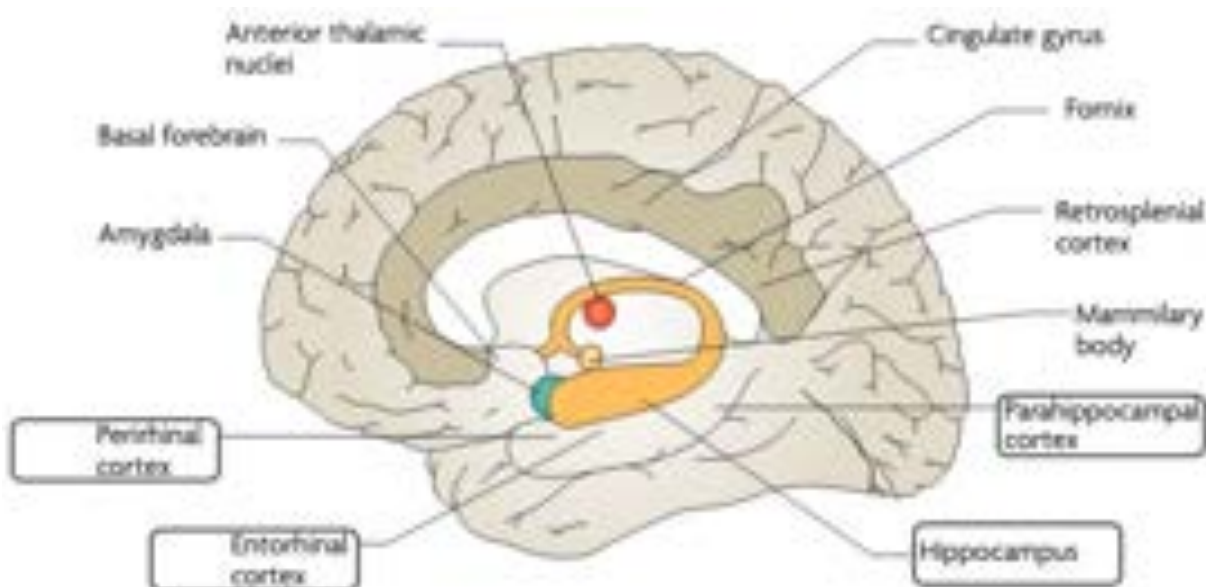


Figure 6. The Medial Tempal Lobe structures. Adapted from Bird & Burgess, 2008

It should be stressed from here that subsequent lesion studies both in humans and animals further revisited this view mainly focused on the Medial Tempal Lobe structures, and thus revisited the neuroanatomy of amnesia. A major breakthrough is summarized in Aggleton & Brown, (1999) who integrated the available evidence and highlighted that not only the MTL, but rather the “Extended Hippocampal System”, was critical for new declarative learning. Indeed, damage to any part of this system (including the hippocampus, fornix, mammillary bodies, mammillothalamic tract, anterior thalamic nuclei, and retrosplenial cortex; Aggleton et al., (2010) has been shown to result in amnesia (Aggleton & Saunders, 1997; Vann & Nelson, 2015). Moreover, other structures outside the MTL are also involved, although less critically, in declarative learning, like the prefrontal cortex and some nuclei of the basal forebrain (see Figure 6).

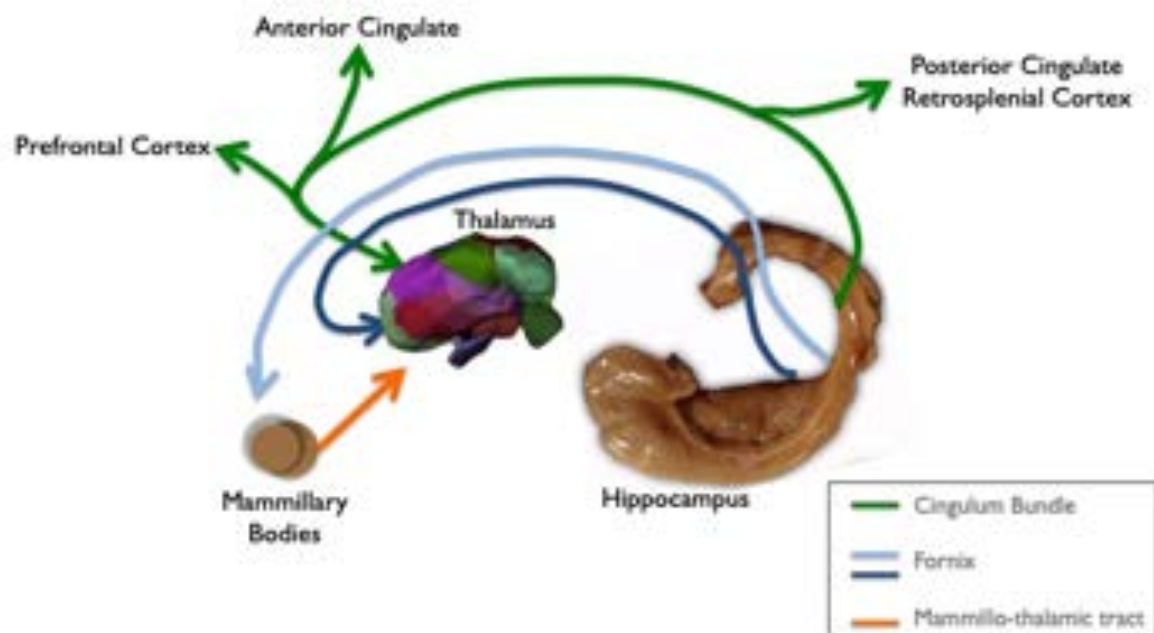


Figure 7. Illustration of the Extended Hippocampal System: main structures and connections. (Thalamus image adapted from Krauth et al., (2010))

1.5. Anatomy of the Medial Temporal Lobes

Neuropsychological evidence from amnesic patients has led to the identification of the Medial Temporal Lobe (MTL) structures as a functional system in the brain devoted to declarative memory. We further briefly summarize its anatomy after Duvernoy, (2005); Mai, Paxinos and Voss, (2008); Squire, (2004); Suzuki & Naya, (2014); Witter, Doan, Jacobsen, Nilssen, & Ohara, (2017).

- The first structure of the MTL is the **hippocampus**. The hippocampus bulges into the temporal horn of the lateral ventricle, and is arched around the mesencephalon. The arch can be divided into three segments, the head (rostral segment) and the tail (caudal segment) that are transversally oriented, and the body (middle segment) that is sagittally oriented. The hippocampus consists of a bilaminar structure: the cornu Ammonis, also

called hippocampus proper, and the dentate gyrus, one lamina being rolled up inside the other. The cornu Ammonis has a heterogenous structure resulting from distinct aspects of its pyramidal neurons, which has led to the most acknowledged description of four subfields: CA 1-4, with the CA 1 subfield being by large the most extended subfield.

The dentate gyrus has a simpler structure by comparison with the cornu Ammonis, with its three plainly visible layers (stratum granulosum, stratum moleculare and polymorphic layer) enclosing the CA 4 subfield.

Anatomically, the CA 1 subfield continues from **the subiculum**, also referred to as the “bed” of the hippocampus. While the subiculum is anatomically a part of the parahippocampal gyrus, it is often studied as a component of the hippocampal formation.

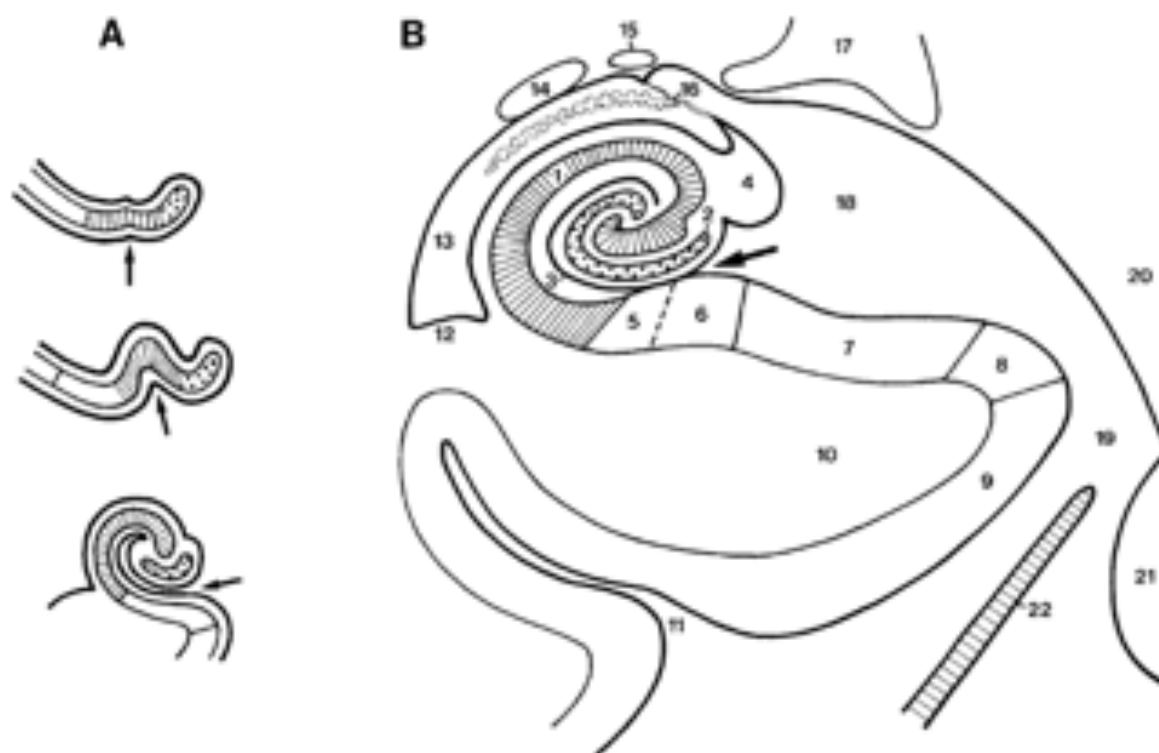


Figure 8. (A). Illustration of how the developmental trajectories of the dentate gyrus (dotted area) and the cornu Ammonis (hatched area) result in their mutual coiling. (B). Schematic drawing of a coronal view of a right medial temporal lobe. (1) cornu Ammonis; (2) dentate gyrus; (3) hippocampal sulcus; (4) fimbria; (5) prosubiculum; (6) subiculum proper; (7) presubiculum; (8) parasubiculum; (9) entorhinal area; (10) parahippocampal gyrus; (11) collateral sulcus; (12) collateral eminence; (13) temporal horn of the lateral ventricle; (14) tail of the caudate nucleus; (15) stria terminalis; (16) choroid fissure and choroid plexuses; (17) lateral geniculate body; (18) lateral part of the transverse fissure; (19) ambient cistern; (20) mesencephalon; (21) pons; (22) cerebellum tent ; Taken from Duvernoy, 2005.

Apart from the hippocampus, the MTL system is composed of other structures located below (i.e. ventrally) the hippocampal formation, further referred to as the “subhippocampal anterior structures”.

- One of the most poorly demarcated structures within the MTL is **the entorhinal area** (Brodmann’s areas 28 and 34), especially regarding its posterior extension along the parahippocampal gyrus. The entorhinal area typically continues ventrally from the most medial section of the subiculum (the parasubiculum), medially to the parahippocampal gyrus. The entorhinal cortex is subdivided between a lateral and a medial part (lERC and mERC), along a functional view (Witter et al., 2017), and it forms the main cortical input towards the hippocampus.

- **The perirhinal cortex** (Brodmann’s areas 35 and 36) lies on both sides of the collateral sulcus, its caudal boundary is the parahippocampal cortex, while the entorhinal cortex ventrally and medially borders it.

- Finally, the **parahippocampal cortex** (which, along with the perirhinal and the entorhinal cortices, composes the parahippocampal gyrus) is caudally adjacent to the perirhinal cortex. As a useful reminder, the anterior part of the parahippocampal gyrus includes the perirhinal and the entorhinal cortices, while the parahippocampal cortex alone forms the parahippocampal gyrus in its more caudal part.

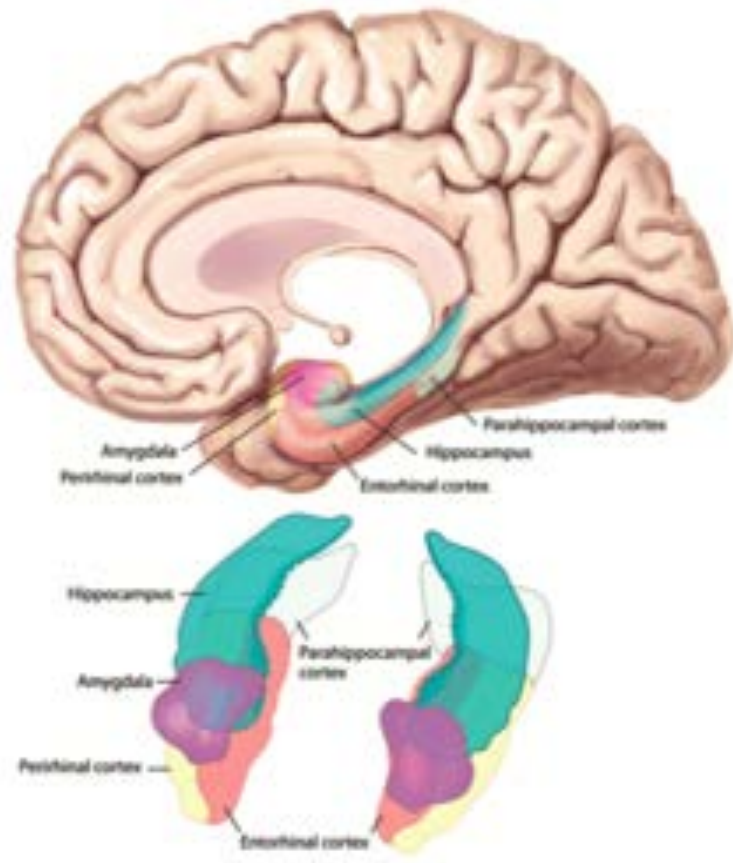


Figure 9. Overview of the Medial Temporal Lobe. Taken from Raslau et al., 2015, Am J Neuroradiol; retrieved from https://www.researchgate.net/publication/268791398_Memory_Part_2_The_Role_of_the_Medial_Temporal_Lobe on February, 6th, 2019.

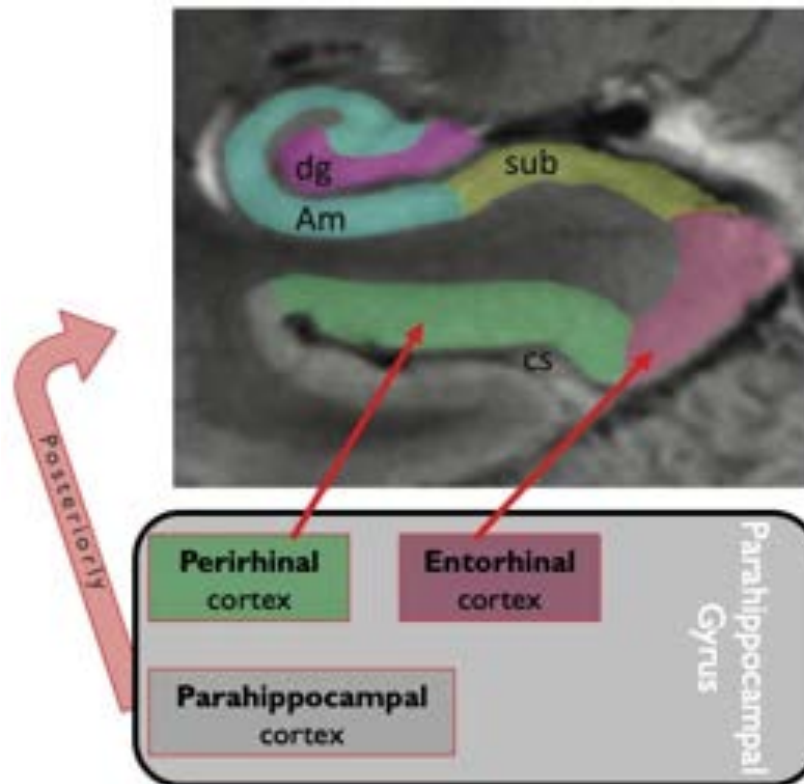


Figure 10. Coronal section of the medial temporal lobe. Adapted from Raslau et al., 2015, *Am J Neuroradiol*; retrieved from https://www.researchgate.net/publication/268791398_Memory_Part_2_The_Role_of_the_Medial_Temporal_Lobe

The main feature of the MTL anatomy that should be highlighted for the present purposes is that it is *hierarchically organized*, and that such an organization accordingly supports hierarchical information processing along its structures (e.g. see Mishkin, Suzuki, Gadian, & Vargha-Khadem, 1997; but for some evidence and discussion against this view, see Barbeau et al., 2011; Lacot et al., 2017). Animal studies have been critical in establishing the connectivity of the MTL structures. First, the parahippocampal cortex (further named PHC) and the perirhinal cortex (further named PRC) received most of their afferences from the dorsal and the ventral pathways, respectively. In the monkey, the majority of the neocortical input to the entorhinal area comes from the PRC and PHC; the entorhinal cortex in turn is, by large, the main source of cortical input for the hippocampus (CA 3 subfield and dentate gyrus), making of this area the principal gateway between the entire neocortex and the hippocampus, which is at the top of the MTL hierarchy. The entorhinal cortex and the hippocampus are mutually interconnected with bidirectional pathways. The hippocampus projects onto the ERC, which in turns projects towards the PRC and PHC so that the information flows back to the neocortex.

Moreover, structures within this hierarchy are also interconnected (e.g. PHC & PRC), and the hippocampus also receives afferences, albeit reduced, directly from the PHC and PRC. Finally, within the so called “extended hippocampal system”, information is processed in a hierarchical way, starting from stimuli low-level features processing in the dorsal and ventral streams up to item-context bindings represented in the hippocampus, that transmits this information through the fornix to the mammillary bodies, then to the anterior thalamus through the mammillothalamic tract. From the thalamus, much of the information is relayed through the cingulum bundle towards medial prefrontal and parietal lobes areas (anterior and posterior cingulate gyri, retrosplenial cortex) as well as back to the hippocampus.

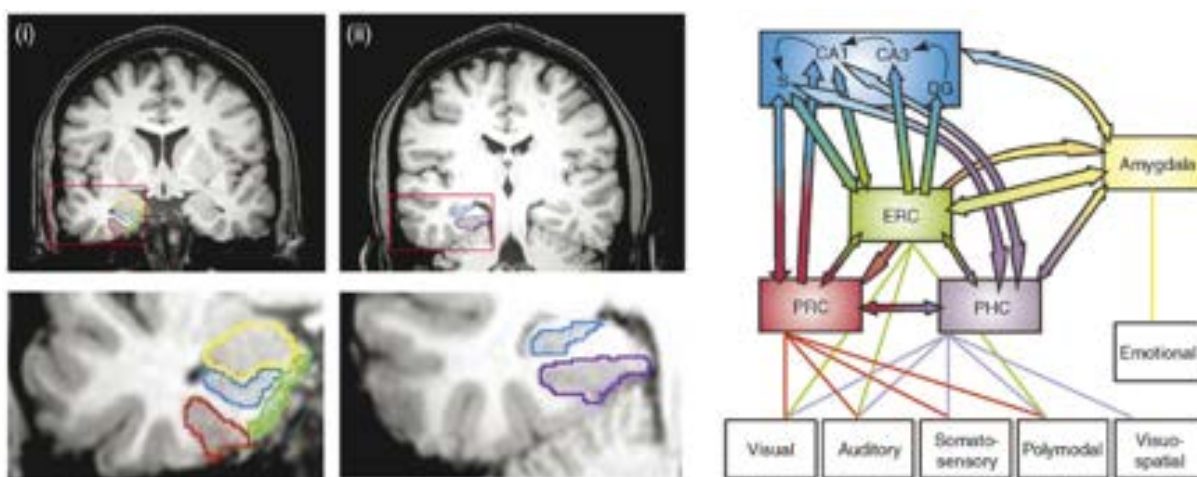


Figure 11. Hierarchical organization of Medial Tempal Lobe structures and their connections.
 Taken from (A. Mayes, Montaldi, & Migo, (2007). Left images show (i) an anterior and (ii) a posterior coronal section of the brain, below which the MTL structures are outlined. Yellow line corresponds to the amygdala, blue to the hippocampus, green to the entorhinal cortex, red to the perirhinal cortex and purple to the parahippocampal cortex. On the right, the same colour code is used to illustrate these MTL structures together with their connections.

1.6. Inconsistencies in recall vs. recognition dissociations in amnesia

To some extent, one can consider that inconsistent findings in recall vs. recognition performance in amnesic patients have favoured the shift from the structural (memory systems) to the process approach in our understanding of learning and memory. Neuropsychological single and multiple case studies have ended in three divergent patterns of results with that respect.

First, amnesic patients were found to present a disproportionate impairment in recall tests, in accordance with the old tradition that the main clinical feature of these patients is that they lack the recollective processes supporting recall from memory. For example, patients with Korsakoff syndrome were able to recognize words and pictures as well as alcoholic controls, even after a delay of several weeks, and with a normal forgetting rate (Huppert & Piercy, 1976). However, when asked to discriminate between distinct targets presented ten minutes or 24hrs ago, the patients were severely impaired (see also Huppert & Piercy, 1978). Similarly, after controlling for the exposure time at study, patient HM was found to have preserved visual recognition memory and normal forgetting by comparison with controls: HM accurately recognized 78.8% of 120 pictures after studying the stimuli for 20 seconds each, vs. 78.2% in controls who were allowed spending only 1 second per target picture (Freed et al., 1987; 1988). Using a supplementary exposure time for amnesic, or an extended interval before testing in Controls yielded similar conclusions of a disproportionate impairment in recall (Hirst, Phelps, Johnson, & Volpe, 1988). Altogether, these early findings suggest that recall and recognition tasks could rely on distinct cognitive substrates: a mere sense of familiarity or “trace strength” would be favoured by the patients in recognition judgments, because they lack the recollective processes which are more involved in recall tasks.

Second, a meta-analysis of case reports and small group studies led by Aggleton & Shaw (1996) (see also Aggleton & Brown, 1999) suggested that damage to any component of the “extended hippocampal system” (restricted to the hippocampus, the fornix, the mammillary bodies, the mammillothalamic tract or the anterior thalamus) always resulted in impaired recall but preserved recognition. Nonetheless, floor effects in recall scores of patients with large MTL lesions made any definitive conclusion hazardous. Another effort to characterize the recall / recognition dissociation involved 56 hypoxic patients who were reported as being less impaired in simple “Old/New” recognition memory tasks than in recall tasks (Yonelinas, 2002). This finding was challenged however because of one highly aberrant outlier who on its own was shown to drive the claimed dissociation (Wixted & Squire, 2004). Subsequent case studies yet confirmed that selective damage to the hippocampus, sparing the sub hippocampal structures, indeed led to severe disruption of recall but normal recognition. For example, patient YR who became amnesic following an ischemic infarct underwent 43 recognition memory tests, among which only 10% yielded impaired performance, while she failed 95% of the recall tests (Mayes et al.,

2002). Patient MR suffered from barbiturate and carbon monoxide poisoning resulting in damage to the bilateral pallidum, parietal lobe and hippocampus (Bastin et al., 2004), and was found impaired in 100% of the recall tests while his performance was normal for 5 distinct recognition testing procedures. Another single case study brought similar results (patient KN, meningoencephalitis, Aggleton et al., 2005). More robust evidence for the dissociation came from patient Jon with developmental amnesia (Vargha-Khadem et al., 1997; Baddeley, Vargha-Khadem, & Mishkin, 2001), a condition involving neonatal damage to the hippocampus, generally due to early hypoxia. Strikingly, modality-specific effects have been reported, like in the right-handed patient FRG who suffered herpes simplex encephalitis, leaving her with extended damage to the bilateral MTL, sparing the right parahippocampal gyrus (Barbeau et al., 2005). This patient was severely impaired in 8 distinct recall tasks, whatever visual or verbal memoranda were used. She also failed in 6 different verbal recognition memory tasks, but she succeeded at 14/18 visual recognition memory tests. A group study of patients with selective damage to the fornix (Tsvivilis et al., 2008) found a large deficit in recall contrasting with relative preservation of recognition. Finally, in a small series of 12 patients with left thalamic infarction, (Danet et al., 2015) highlighted the role of the mammillothalamic tract in verbal recall tasks. This highly consistent pattern of results suggests that the extended hippocampal system may be critical for recall, but not recognition, memory tasks.

Third, another series of amnesic patients were found to present equally severe disruption of recall and recognition memory (e.g. Haist et al., 1992; Manns, Hopkins, Reed, Kitchener, & Squire, 2003; Manns & Squire, 1999; Reed, Stefanacci, Hamann, & Squire, 1997). These four studies involved 20 unique patients overall, of which 5 participated in each study (Cases RC, PN, JW, AB, LJ). Importantly, the three first patients were amnesics following a Korsakoff syndrome, with no evidence of damage. AB had suffered anoxia in 1976 and was unable to undergo an MRI scanner, but a CT Scan in 2001 suggested limited damage to the hippocampal region (Schmolck, Kensinger, Corkin, & Squire, 2002). Finally, aetiology for the amnesic condition lacked in LJ. Considering the 15 remaining patients, 5 actually had either suspected or proven diencephalic damage without MTL involvement (NC, VF, DM, MG, NA); 2 lacked any clear aetiology or even cause (JL, PH); 4 had suffered hypoxia (LM, JRW) or respiratory failure following overdose (GW, RS); one had suffered CO poisoning (JS); one severe cerebrovascular disease (MJ); one suffered amnesia following surgery complications with hypotension (GD); and finally the most severely

amnesic patient (EP) had suffered herpes simplex encephalitis. If one only keeps the cases for which detailed MRI findings and clear aetiology was available, these findings thus suggest that damage to either the hippocampus or diencephalic structures led to proportionate recall and recognition impairments.

Beyond the differences in aetiology, and the lack of detailed knowledge of the extent of the lesions within the MTL of the extended hippocampal system, it has been demonstrated that recall and recognition performance could greatly vary even after well documented selective hippocampal damage (Holdstock et al., 2008). We certainly miss a critical part of the problem behind these inconsistencies.

At the time of the earliest investigation of recall / recognition dissociations in brain injured patients, decades of research in psychology had ended in theoretical frameworks stating that recognition memory was not unitary (first proposed by William James, 1890, but see Atkinson & Juola, 1974, Mandler, 1980).

1.7. Beyond signal detection theory: one single recognition process is not enough

Early works on recognition memory performance in humans have considered the interest of confidence ratings, namely the levels of confidence subjects had on their recognition judgments (Egan, 1958). To account for the observed uncertainties expressed by subjects in their judgment, it was proposed that the judgment of prior occurrence was made on the basis of a “familiarity signal”, in accordance with the Signal Detection Theory that was just developed in psychology (Tanner & Swets, 1954). Signal Detection Theory (SDT) basically aims at accounting for the patterns of performance achieved by any system that is supposed to discriminate a signal (e.g. a given stimulus) from noise (i.e. irrelevant inputs).

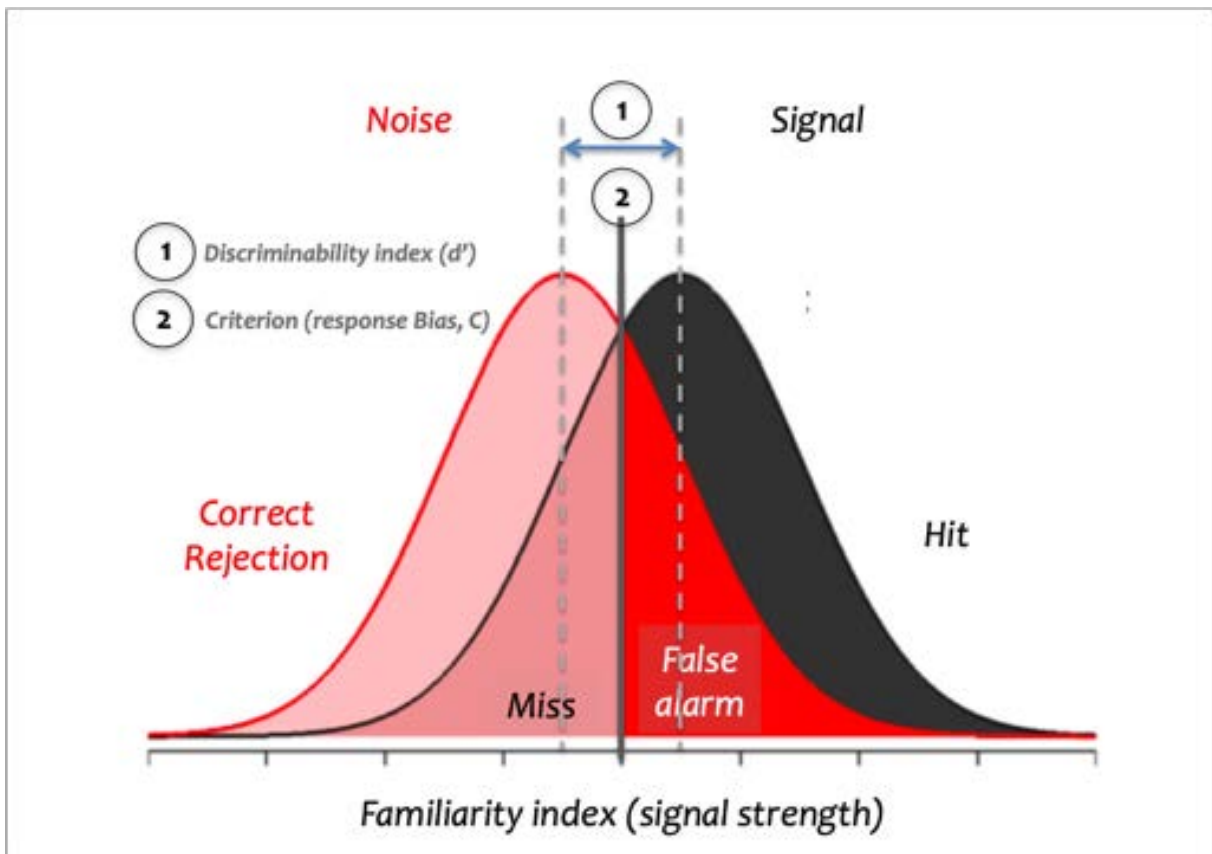


Figure 12. Signal Detection Theory as applied to Recognition Memory performance. The red Gaussian curve depicts the signal (familiarity index) distribution for noise, the black is for signal. Under the assumption of equal variance, an index of discriminability is computed as the difference between Signal and Noise central tendencies (i.e. Z-scores); while Response Bias is computed as half the distance between the distributions (here, Bias is equal to zero). Adapted from <http://gru.stanford.edu/doku.php/tutorials/sdt>

Applying the principles of the SDT to recognition memory resulted in the proposal that performance could be fully described by a function of the familiarity index. Subjects implicitly set a response criterion (Response Bias) along the familiarity index continuum, and will detect the signal whenever the familiarity strength reaches or exceeds the criterion. Whenever the familiarity strength is below such threshold, subjects will detect noise, i.e. novelty in the case of recognition memory (namely, a distractor item). This proposal further mapped the confidence ratings onto the familiarity index: confidence increases as the familiarity index moves from the criterion. Moreover, one can compute two indices of performance, the discriminability index and the response bias (see **Figure 12**) that fully describe the pattern of responses. The main advantage of this analysis is that *discriminability* and *bias* are independent measures, thus providing a complete account for participants' performance. *Discriminability* accounts for the overall ability to

discriminate signal from noise (i.e. targets from distractors), while *Bias* accounts for the relative trend to provide “Old” or “New” judgments (see **Figure 12**).

Subsequent work however revealed that in some instances, the familiarity index alone could not suffice to provide a recognition judgment (Kintsch, 1967; Atkinson, Hermann & Wescourt, 1974). In these cases, the authors proposed that a later explicit retrieval process (i.e. “after” recognition failure based on the familiarity signal strength) must be involved, allowing providing a memory judgment. These proposals have launched a list of attempts to better model recognition memory performance, resulting in at least one consensus: recognition memory relies on two distinct retrieval processes, namely *familiarity* and *recollection* (Mandler, 1980; Yonelinas, 2002).

I enter a friend's room and see on the wall a painting. At first I have the strange, wondering consciousness, 'surely I have seen that before,' but when or how does not become clear. There only clings to the picture a sort of penumbra of familiarity, - when suddenly I exclaim: "I have it, it is a copy of part of one of the Fra Angelicos in the Florentine Academy - I recollect it there!"

From The Principles of Psychology (p. 658) by William James, cited in Yonelinas, Aly, Wang, & Koen, (2010)

→**Recollection** can be defined as a memory retrieval process whereby subjects retrieve “qualitative information about a specific study episode, such as when and where an event took place”, typically inducing a moderate-to-strong confidence in memory judgment (Yonelinas et al., 2010).

→**Familiarity** rather refers to as a mere feeling of prior occurrence, without any information retrieval about the study episode, typically leading to a large range of confidence in memory judgment (Endel Tulving, 1985; Yonelinas et al., 2010).

One critical distinction between these recognition memory processes is therefore that only recollection involves recall of perceptually absent information. However, put this way, confidence is not a strictly defining feature of recollection vs. familiarity. That is, high-confidence judgments may reflect recollection but also familiarity, as long as no qualitative information from the study episode can be recalled. The most influential authors in the field (Tulving, 1985; Mayes & Roberts, 2001; Parks, 2007; Parks & Yonelinas, 2007; Squire, Wixted, & Clark, 2007; Wixted & Squire, 2010; Yonelinas & Parks, 2007) accept that the subjective experience of re-living the study episode can be an instance of qualitative information retrieval that is uniquely related to recollection. Such “re-living” is typically associated with

the highest confidence ratings. This is a strong assumption of e.g. the Dual-Process Signal Detection theory of recognition memory (Yonelinas & Jacoby, 1994) on which Receiver Operating Characteristic estimations of the two processes is grounded. Accordingly, we will consider as an acceptable approximation that correct recognition judgments associated with the highest confidence judgments are instances of recollection.

However, what remains under debate is whether these processes operate in a fully independent manner, in parallel, serially, or if they can better be accounted for by a unique (strength) signal (Diana, Yonelinas, & Ranganath, 2010; Squire et al., 2007). Very recent neural evidence from electrophysiology, for example, illustrates how challenging are these issues for the field (Weidemann & Kahana, 2019). While these debates are of great matter, they are beyond the scope of the present work. Here, we will retain the wide consensus on the existence of two distinct processes underlying recognition memory. This consensus has led to an impressive amount of neuropsychological, psychological and neuroimaging studies sharing the use of recognition memory tasks, resulting in the development of several models of episodic learning, mostly focusing on the contribution of the structures of the MTL described above. We will further summarize the most influential models proposed so far.

I.8. Models of episodic learning and recognition memory

The most influential frameworks can be distinguished on the basis of whether they focus on the *contents* of memory representations, or on the *processes* (or computations) performed by the MTL. However, growing evidence questions the relevance of considering the MTL as a functional entity specialized in declarative memory, yielding a shift towards a new paradigm in the cognitive neurosciences of memory that we will shortly mention in the last of the following sections. Importantly, none of these frameworks has so far refuted the idea of multiple memory systems, or the hierarchical organizational principles underlying the functional neuroanatomy of the MTL. We will therefore start with providing a short reminder of the SPI model and of the hierarchical organizational view of the MTL.

1.8.1. Serial Parallel Independent model and the hierarchical organization of the MTL

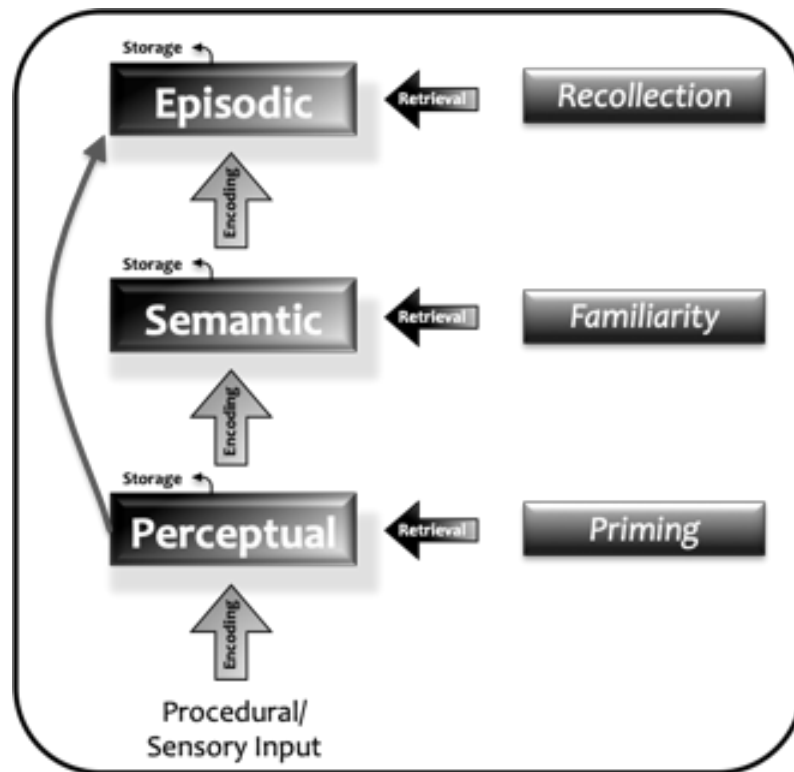


Figure 13. The SPI model (Tulving, 1995) including the direct perceptual-episodic route (Kim S. Graham, Simons, Pratt, Patterson, & Hodges, 2000). On the left are displayed three memory systems, on the right the kind of « retrieval » processes that typically give access to each system/store. Arrows depict the relationships between the systems: at encoding, the hierarchical-serial view posits a fixed sequential relation, which yield parallel storage in each system. At retrieval, representations can be rebuilt from each system independently.

The Serial Parallel Independent model (Tulving, 1995) emphasizes both a structural and a process approach. From a structural point of view, the core feature of the model lies in its modularity: memory is organized in five distinct systems (procedural, perceptual representation, semantic, primary (working memory), and episodic – note that only 3 systems are depicted in Figure 13). From a processing point of view, the relationships between these systems are described as dependent upon the operations carried out by *encoding*, *storage* and *retrieval* processes. Encoding is thought to occur serially, so that input must be encoded in the procedural system before being encoded in the perceptual representation system, and so forth up to the episodic system. This sequential encoding process results in parallel storage: encoding is supposed to create or modify the memory

trace in each system. Lastly, retrieval processes operate independently in each system, so that a semantic trace can be retrieved independently of an episodic trace, for example. Moreover, each system is assumed to have a distinct retrieval mode, or to be associated with a distinct retrieval process. Retrieval from the perceptual representation system is supposed to rely on priming, namely, through processing facilitation. Retrieval from the semantic system is thought to occur via familiarity-based processes (a feeling of knowing), and recollection is assumed to be the typical retrieval mode involved for the episodic system. Tulving further associates various kinds of consciousness to each memory system retrieval: anoetic consciousness is the correlate of the procedural and the perceptual representation systems, noetic consciousness characterizes retrieval from semantic memory, and auto-noetic consciousness features episodic retrieval. For the present purposes, a key aspect of this model is that episodic learning is predicted to depend on semantic knowledge. In other words, it should not be possible to acquire new episodic memories in the case of severe semantic memory disruption. This is perfectly in line with the idea developed early by Endel Tulving that Hermann Ebbinghaus's results when using meaningless materials do not contribute to our understanding of episodic learning (Tulving, 1985; Tulving, 1983). This also fits with the findings of improved episodic memory after semantic encoding (i.e. Craik & Lockhart, 1972; Craik & Tulving, 1975), and also with the reports of subnormal levels of semantic knowledge despite impaired episodic memory (e.g. Vargha-Khadem et al., 1997).

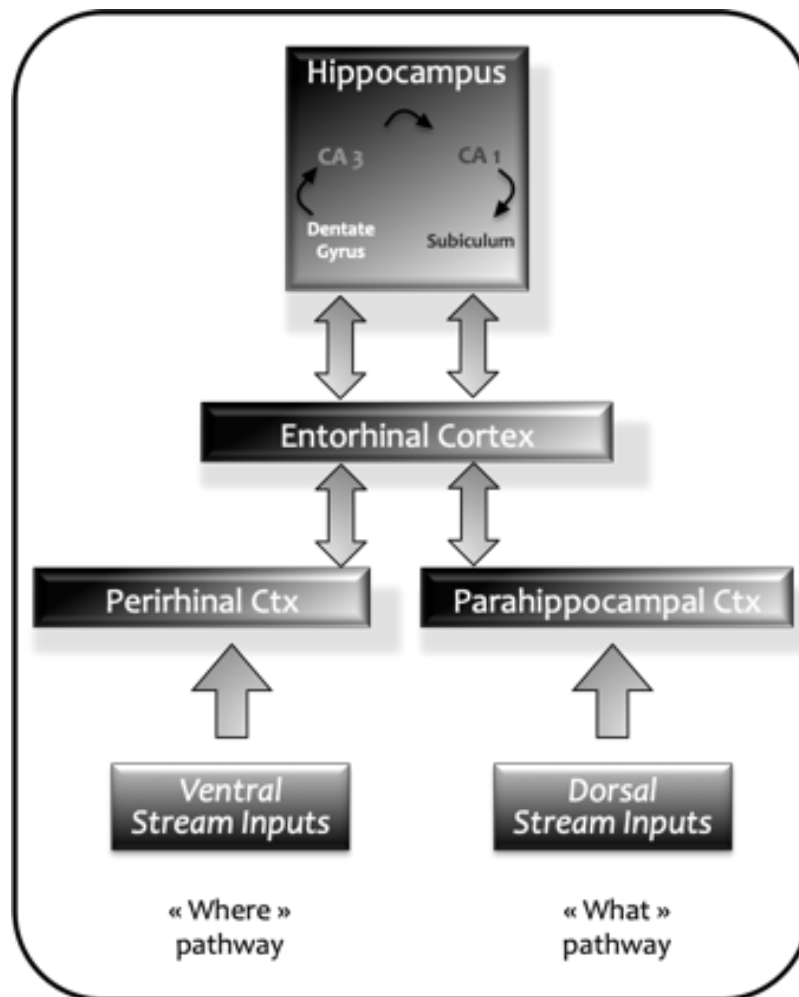


Figure 14. The hierarchical organization of the Medial Temporal Lobe as supporting « cognitive memory » after Mishkin et al., 1997.

Neuropsychological findings supporting this model, along with animal research with the delayed non-matching-to-sample procedure (see Chapter III), has led to an anatomofunctional model of memory largely consistent with the SPI model (Mishkin et al., 1997) (see *Figure 14*). Altogether, this framework highlights a correspondence between the hierarchical anatomical organization of the MTL and Tulving’s idea of serial memory encoding along a set of hierarchically organized memory systems. Here, episodic learning would depend on the information processing flow up to the top of the hierarchy, namely the hippocampus. That structure is thought to underlie new episodic encoding, which is thought to be impaired in amnesic patients. However, the acquisition of new memories depending on “inferior” or downstream memory systems in the hierarchy would not require the hippocampus, at the cost of remaining “context-free” by contrast with “context-rich” memories. Episodic memories are considered “context-rich” in that their contents include the individual sensory components of an experience within their context

of processing. Semantic memories contents, however, miss the context to only include individual components of past experiences. Thus, semantic (or context-free) learning remains possible despite impaired episodic (context-rich) memory. Such proposals account for the findings in developmental amnesia and in some amnesic patients with damage limited to the hippocampus.

The strength of these accounts lied in the consistency between animal and human research, especially the cases of developmental amnesia, however not without exceptions.

First, recognition memory for item-location associations proved inconsistent across species. As acknowledged by Mishkin et al. (1997), parahippocampal, rather than hippocampal, damage in monkeys resulted in impaired object-place associations learning. By contrast, no evidence for parahippocampal damage could be found in the patients described by Vargha-Khadem et al. (1997), still they failed such task (as well as voice-face associative learning). Further work has not yet fully resolved these issues, suggesting at least in monkeys that memory for the context results from close interactions between the parahippocampal, perirhinal cortices and the hippocampus (Bachevalier, Nemanic, & Alvarado, 2015), along with a possible specific role for the hippocampus in object-place long-term memory binding (see Bachevalier & Nemanic, 2008; Belcher, Harrington, Malkova, & Mishkin, 2006; Malkova & Mishkin, 2003).

Second, neuropsychological evidence gathered in patients with selective semantic impairment also spoke against this model. Semantic dementia (Hodges, Patterson, Oxbury, & Funnell, 1992; Snowden, Goulding, & Neary, 1989) is a neurodegenerative condition where bilateral temporal poles undergo focal progressive atrophy, resulting in a typical cognitive profile of selective semantic impairments, with preserved day-to-day memory. Empirical evidence for preserved episodic learning (as assessed through recognition memory tasks) even for stimuli unidentifiable by the patients (Graham, Becker, & Hodges, 1997; Graham, Patterson, & Hodges, 1999; Graham et al., 2000; Simons et al., 2002; Simons, Graham, Galton, Patterson, & Hodges, 2001) is incompatible with core predictions of both the SPI model and the hierarchical view of the MTL. These frameworks indeed predict that impaired semantic memory – or damage to the parahippocampal gyrus – should lead to proportional impairments in semantic memory and episodic memory, independently of the hippocampal status. An evolution of the SPI model, named the Multiple Input Model (“MIM”, Graham, 2000) was then proposed,

involving a direct encoding route between the perceptual representation system and the episodic system, as depicted in **Figure 13**, and that is restricted to visual learning. Further work has extended the MIM to include the SPI proposal within other memory systems and sub-systems in an effort to provide a more comprehensive view of the concept of autobiographical memory (MNESIS model, Eustache & Desgranges, 2008; Eustache, Viard, & Desgranges, 2016). Noteworthy, a similar evolution of the SPI model, but involving a direct encoding route from PRS to episodic memory could be expected if the suggestive findings of Gagnepain, Lebreton, Desgranges, & Eustache, (2008) were replicated and extended to patients with selective semantic impairments.

In summary, the SPI model can be considered a content-based theory in that it assumes that e.g. semantic and episodic memories have fundamentally distinct properties. But it is also a process-based approach theory, in that each memory system is associated with a privileged kind of retrieval process, and because relationships between systems depend on the memory process considered. This model was built on strong neuropsychological grounds, and is supported by consistent findings regarding the anatomy of the MTL and from monkey research, which has eventually resulted in a framework guiding research in the last decades. Still, several modifications have been put forward to account for unpredicted findings both from a functional neuroanatomical and cognitive perspective. Endel Tulving essentially did not include these proposed updates to his framework, basically arguing that the episodic learning tasks used actually did not meet all criteria for episodic memory. All in all, such divergences may have led to a dead end, but other proposals, somehow departing from the episodic-semantic distinction, finally emerged in the early 2000's.

1.8.2. Content-based models

Given that recollection, as opposed to familiarity, involves the recall of perceptually absent information, it is considered a fundamentally associative process. Therefore, if one can relate a memory cue with some prior context of occurrence (context here is taken in a very broad sense, encompassing not only spatial and temporal features of an event, but also any thought, feeling, emotion unfolding during the event), the resulting memory will

necessarily includes *relations* between its components. Unsurprisingly, thus, several models have focused on the contents of memory: does encoding of relations between components of an experience rely on the same mechanisms and neural substrates as the encoding of its individual components?

1.8.2.1. Relational theory

The monitoring of eye movements in healthy subjects and amnesic patients while viewing colour images of real-world scenes has provided strong evidence for the existence of a relational encoding system (Ryan, Althoff, Whitlow, & Cohen, 2000). In controls, a second presentation of a visual scene in which an individual component has been removed or added by comparison with its initial viewing generated more fixations in the region where manipulations of relations among scene elements had occurred. This “relational manipulation effect” was found only when participants were not aware of the manipulation, and it was not found in amnesic patients (see *Figure 15*).



Figure 15. The relational manipulation effect. White crosses indicate eye fixations and black lines eye movements, for two different healthy subjects. On the left, the exact same scene has been presented before. On the right, the same scene was presented before but including two girls located within the black rectangle on the white path. The scene manipulation resulted in increasing fixations within the manipulated area, an effect no elicited in amnesic patients. (Taken from Ryan et al., 2000)

These findings and subsequent studies (Ryan & Cohen, 2003, 2004a, 2004b) led to the proposal that 1/ conscious access to stored memories may not be a defining feature of declarative memory and 2/ the hippocampus is essential for any learning task requiring the encoding of relations between distinct items, a process named relational memory binding (see also Cohen & Eichenbaum, 1993). Importantly, the hippocampus is assumed to store relational memory in a flexible way, as both the relations between items and individual items remain accessible separately from long-term memory. However, the individual components of an experience are supposed to be stored separately in the neocortex, the hippocampus being involved only in relational encoding through the binding process. A strong advantage of this view is that it explains how inferences can be made from memory. For example, provided that relational information $A + B$ and $B + C$ has been encoded, any further episode involving A will reactivate the relation with B , likewise presentation of B will reactivate the relation with C . Therefore, presentation of A and B will reactivate both relational information that share C in common, allowing the $A + C$ relation to be inferred. So a cue absent from the study phase (here, C) can nonetheless be reactivated thanks to the unique hippocampal computations, which is a defining feature of recollection. Such relational information may thus be stored, and during next encounters with either A , B or C , the corresponding individual representations will be reactivated via extra-hippocampal neocortical computations, while the hippocampus will allow the retrieval of the $A + B + C$ relational network (Moses & Ryan, 2006). Finally, it must be mentioned that within-domain item + item relations are supposed to take place without relational binding, as long as these individual elements can be processed as a unimodal perceptual “blend”, i.e. a unique element. A key prediction from that model is therefore that following hippocampal damage, relational inferences won’t be possible; however, the acquisition or maintenance of perceptual “blends” can take place, but these representations are considered “rigid” in that it cannot be updated when new related contexts occur. Similarly, relational information stored before amnesia should not be updated.

1.8.2.2. Conjunctive theory

This account, largely based on animal research with rats, shows some similarity with the relational theory: in both cases, the hippocampus is supposed to support associative processes that underlie the formation of representations composed of distinct elements (O'Reilly & Rudy, 2001; Rudy & O'Reilly, 1999). However, these representations called “conjunctive” in that model include both the relationships between individual elements of an experience, and the unique individual features of the event that differ from the individual elements (e.g. in the negative patterning problem, the representation “AB” must be learned as a unique entity, that is, distinct from “A” and “B” presented individually). Put this way, individual elements and its relationships within a unique conjunctive representation, once stored, cannot be retrieved independently, which is a key difference with the relational theory. To some extent, these conjunctive representations are close to the perceptual “blend” concept in the relational theory. However, multiple conjunctive representations would be formed from different vantage points but for a single event, as well as individual elements representations. The process of pattern completion, uniquely associated with hippocampal computations, is thought to allowing incoming representations to be compared with stored representations. Pattern completion can achieve memory retrieval this way, even based on a partial cue. This account therefore keeps the idea of flexibility, which here emanates not from the relational encoding itself but from the pattern completion process that allows retrieval of the ad hoc conjunctive representation for the current behavioural goal (O'Reilly & Rudy, 2001). Finally, an important aspect of the conjunctive theory that differs from the relational theory is that hippocampal computations are supposed to allow the rapid encoding of conjunctive representations. However, the surrounding cortices also can support conjunctive representations encoding, but through extensive repetitions during a slow learning process. A strong prediction therefore is that damage to the hippocampus should prevent from rapid learning of associations: hippocampal amnesia should not obliterate associative learning, but it could take place only at a slow pace, incidentally, and in the service of specific situations like problem-solving tasks.

1.8.2.3. Binding In Context (BIC)

Based on an extensive review of available behavioural, neuropsychological and neuroimaging data in humans as well as animal research including single neurons recording in the MTL, Eichenbaum, Yonelinas, & Ranganath, (2007) proposed the “Binding In Context” (BIC) model. This model, like the previous content-based theories, explicitly states a functional dissociation within the MTL, between the hippocampus on the one hand, and surrounding rhinal cortices and parahippocampal cortex on the other hand. The BIC is a three-components model, where the perirhinal cortex and the lateral entorhinal cortex, because they receive most of the projections from the “What” pathway, encode individual items. The parahippocampal cortex and the medial entorhinal cortex, being the main targets of the “Where” pathway, encode the context associated with the item(s). A particular emphasis is put on the spatial aspects of the context, but leaving open the possibility that non-spatial features of the context (e.g. temporal) can be represented here too (see also Eichenbaum, 2013; Eichenbaum, 2004). Finally, the hippocampus is the structure where “where” and “what” information converges, allowing for the encoding of item - context associations. Importantly, the familiarity component of recognition memory is thought to arise from a matching computation between the representation of an individual input and a pre-existing representation, at the level of the perirhinal and lateral entorhinal cortices. Thus, familiarity-based judgment in recognition does not require hippocampal computations. However, as long as the task involves not only the item but the associated study context as well, recollection will depend on the hippocampus and parahippocampal cortex.

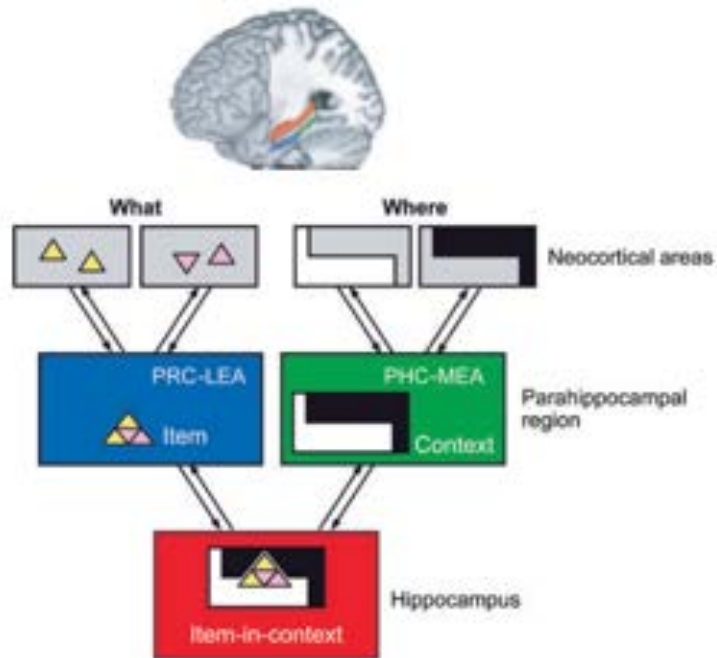


Figure 16. Binding In Context (BIC) model of recognition memory and the MTL, taken from Eichenbaum et al., 2007.

In accordance with the conjunctive theory, pattern completion is of great importance for recollection in the BIC model. When presented with a familiar item, it is processed up to the PRC and IERC, and the by-product may serve as a cue for pattern completion in the hippocampus. If successful (i.e. normal subject), this process may allow the reactivation of the activated pattern that occurred at study (i.e. during the last occurrence). Such activity, as an input to the parahippocampal cortex, will reactivate the corresponding context representation, thus leading to recollection. Therefore, at variance with the conjunctive theory, recollection-based retrieval depends not only on the hippocampus, but also on the PHC (see also Diana, Yonelinas, & Ranganath, 2007). Note that the BIC model also predicts that whenever a study context alone triggers a familiarity signal in the PHC, this could drive the reactivation of the corresponding hippocampal activation pattern, leading in turn to the retrieval of the associated item, again yielding recollection. From this perspective, it must be understood that the BIC model shares with the relational theory the idea that the hippocampus does not encode individual items, or event features, but rather it represents associations between items.

Finally, the BIC model also assumes that recollection can occur on the basis of PRC/IERC or PHC/mERC processing only, with no need of pattern completion, in situations where associations between items can be “unitized”, namely encoded as a single item (Murray

& Ranganath, 2007; Quamme, Yonelinas, & Norman, 2007; Yonelinas, 1999). While we have focused here on the MTL structures, further refinements of the BIC model will add distinctive roles of the dorsolateral and ventrolateral prefrontal cortices in contributing to the item-item associations and to the selection of the relevant features of the episode to increase the distinctiveness of the represented episodes (Ranganath, 2010).

1.8.2.4. The representational account (Davachi et al., 2006)

A closely related model has been proposed based on task-based functional neuroimaging (Davachi, 2006). This model, like the BIC model, argues that the hippocampus is responsible for the relational binding of the individual elements of an episode, including its context of occurrence. However, based on findings showing successful memory effects for individual items extending posteriorly to the perirhinal cortex, encompassing portions of the PHC, this model suggests that a single relational vs. item contrast does not fully account for the MTL involvement in declarative learning. Instead, the model proposed that while the hippocampus is responsible for domain-general episodic encoding, the PRC and PHC would be critical for domain-specific encoding. Based on the robust findings of a differential response of the PRC and PHC to objects and scenes, respectively, the representational account states that recollection for object-related features could be achieved through PRC computations, while recollection of scene-related features could be achieved through PHC computations (see Staresina, Duncan, & Davachi, 2011). The model therefore predicts that the respective contributions of distinct MTL structures to recollection or familiarity-based retrieval may, to some extent, depend on the representational domain of studies events. However, relational encoding across domains (i.e., domain-general) requires hippocampal processing.

1.8.2.5. Posterior-Medial / Anterior Temporal (PMAT) framework

This theoretical framework results from an extensive review of anatomical and functional connectivity studies of the MTL, and aimed at accounting for mental functions extending beyond declarative learning (Ranganath & Ritchey, 2012; Reagh & Ranganath, 2018; Ritchey, Libby, & Ranganath, 2015). We will briefly summarize the important aspects of the framework that are directly relevant for declarative memory learning.

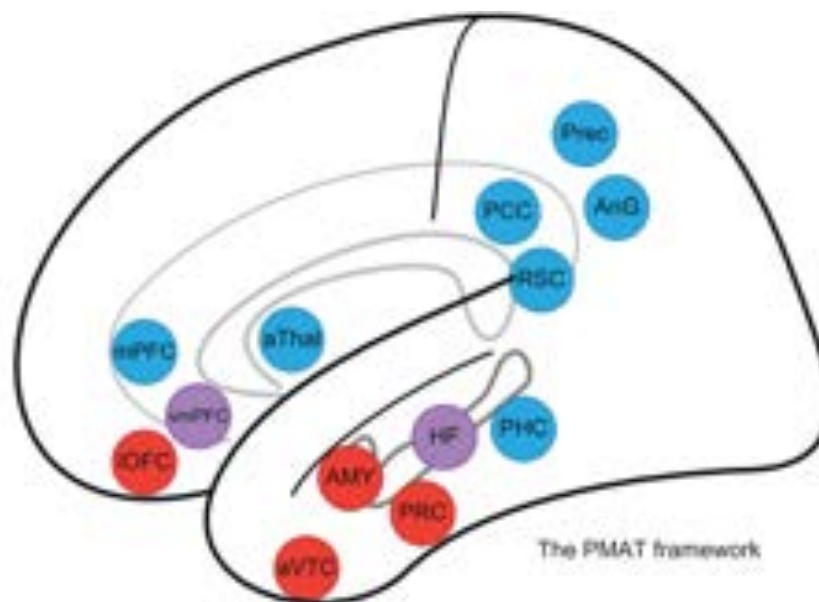


Figure 17. The PMAT framework, taken from Ritchey et al., 2015. Blue circles depict the Postero-Medial network, red circles the Anterior Temporal network, and purple circles represent possible area of integration of the information processed in both networks. [Prec=Precuneus; AnG=Angular Gyrus; PCC=Posterior Cingulate Cortex; RSC=RetroSplenial Cortex; PHC=ParaHippocampal Cortex; aThal=anterior nuclei of the Thalamus; mPFC=medial PreFrontal Cortex; IOFC=lateral OrbitoFrontal Cortex; aVTC=anterior Ventral Temporal Cortex; AMY=Amygdala; PRC=PeriRhinal Cortex; HF=Hippocampal Formation; vmPFC=ventromedial PreFrontal Cortex]

The PMAT framework was intended to integrate neocortical areas involved in memory-guided behaviour to the existing models focusing on the MTL contributions and its connections with the dorsal and ventral streams only. It proposes that the two large-scale networks depicted in Figure 17 are differentially involved in learning mechanisms: the PM network would be responsible for “the processing and the long-term storage of learned contexts in the form of situation models” (Ritchey et al., 2015, p.47). The AT network would be in charge of the “processing and long-term storage of previously learned items

in the form of concepts” (Ritchey et al., 2015, p.47). As a consequence of these distinct contents, the AT would mainly support familiarity-based recognition while the PM would be associated with recollection-based recognition memory.

Both networks would share a common purpose that is extracting statistical regularities of the environment, which make of these functionally-interconnected regions core learning structures, according to the definition of learning we have developed before (see “The problem of learning and memory” section p. 17 and followings). However, the memory contents that each network deals with would extend prior suggestions: the PM would essentially process and store associations between contexts, while the AT would do so for individual components of episodes. We further quote Reagh & Ranganath (2018) to clarify the respective contributions of these networks:

“Walking through a building, visual context information represented by PHC might be used to orient oneself relative to one’s knowledge of the topology of the building, accessed via a spatial situation model supported by activated representations in extra-MTL PM cortical areas, such as retrosplenial cortex, posterior cingulate, and precuneus. Upon encountering a familiar person in the room, activation of the corresponding PRC representation of the person’s face can be linked with knowledge about the person’s traits, via activation of representations in AT network areas, such as the amygdala and temporopolar, orbito-frontal, and insular cortex.”

Reagh & Ranganath, 2018, p. 70

A highly relevant aspect of the model for the present purposes is that it allows addressing the complexity of how prior experiences could guide behaviour, and contributing to new learning. For example, stored conceptual knowledge retrieved through the temporal poles and the PRC can provide top-down input to the visual ventral stream, thus providing a comparison space where predictions can be confronted to actual processing, which generates a prediction error signal helping to flexibly guide behaviour, and encoding new episodes simultaneously. Similarly, the PMAT framework provides insights into how memory “schemas” could be stored and used in behaviour. Semantic knowledge resulting from associations between items would be supported by the AT while semantic knowledge resulting from associations between contexts would be supported by the PM, a *schema* being activated via the convergence between both representations. This idea is in line with models highlighting the role of hippocampal-vmPFC interactions in schema-dependent learning (Van Kesteren, Ruitter, Fernández, & Henson, 2012, see Chapter VI). These schemas, or their item-based vs. context-based

components in the AT vs PM networks, respectively, are further assumed to provide a scaffold on which new episodes can be encoded.

Moreover, the model allows to accounting for findings linking extra-MTL regions to familiarity and recollection. For example, familiarity for faces has been associated with anterior lateral temporal cortex (Leveroni et al., 2000), and the role of the parietal cortex in autobiographical memory retrieval is well acknowledged (e.g. Cabeza, 2008; for a review of the involvement of the ventral posterior parietal cortex in qualitative recollection, see Moscovitch, Cabeza, Winocur, & Nadel, 2016).

1.8.2.6. Summary of content-based models

These models, exception made of the PMAT framework, do not specifically address the question of how prior knowledge influences episodic learning. Some predictions can nonetheless be made.

1. *The Relational* theory predicts that during encoding, pre-existing representations associated with the memoranda, when present, will be activated through hippocampus-dependent relational binding. Only within-domain pre-existing representations can be reactivated on the basis of neocortical processing. Thus, hippocampal damage should result in at least a decrease or an absence of prior knowledge effect on memory formation
2. Similarly, the *Conjunctive theory* predicts that prior knowledge activation critically depends on pattern completion, which is supposedly taking place in the hippocampus, so that again, memory should not benefit from prior knowledge at encoding in case of hippocampal damage. However, at variance with the Relational theory, the Conjunctive theory predicts that learning of conjunctions remains possible after hippocampal damage, at the cost of intensive repetitions and at a slow rate.
3. Activation of prior knowledge for relevant stimuli is also expected to depend on pattern completion in the hippocampus, within *the BIC framework*. However, a critical role for the PRC is outlined, which provides a kind of “comparison space” between incoming information and past experience, resulting in a prediction error signalling. In the

case where pre-existing representations are available, the PRC detects familiarity, and as long as the task does not involve contextual retrieval or source monitoring, accurate recognition can be provided without hippocampal computations. Thus, the model may be compatible with the prediction that studying stimuli with pre-existing representations should trigger familiarity and reactivation of past contextual encounters (based on pattern completion and PHC activation), thus enriching the memory trace and making it more distinctive. This may result in improved recognition memory for the item, with no clear prediction regarding familiarity or recollection. While this provides a more comprehensive account for potential prior knowledge effect, it still predicts that hippocampal damage, as it would impair pattern completion, should result in the absence of memory gain due to prior knowledge. The BIC model however suggests one exception, namely unitization. In the case where the item and its context can be processed as a single item, then further associative recognition can be based on familiarity. Note that this should be independent from prior knowledge effect: unitized item-context combinations should lead to accurate recognition, even after hippocampal damage, whether or not the combination is associated with pre-existing representations. But it may be the case that prior knowledge promotes unitization: in such instances, according to the BIC model, successful recognition would not result from prior knowledge itself but from unitization, and should be achieved only on the basis of familiarity, not recollection.

4. Finally, one core prediction added by *the PMAT framework* is that, consistently with other theories presented in Chapter VII, medial, orbital prefrontal cortices together with the temporal pole, the amygdala and the PRC should be of great matter for prior knowledge activation. It therefore predicts that, beyond the role of the hippocampus, the functional interplay between these regions and the hippocampus is critical for detection and use of prior knowledge in new learning.

1.8.3. Process-based models

1.8.3.1. Aggleton's model: hippocampal systems and the dual process model of recognition memory

Based on animal research in monkeys investigating the MTL connections, and more specifically the hippocampal projections, Aggleton (2012) highlights four distinct efferent systems: the extended-hippocampal system; the rostral hippocampal system; the reciprocal hippocampal-parahippocampal system; and the parahippocampal-prefrontal system (see Figure 18).

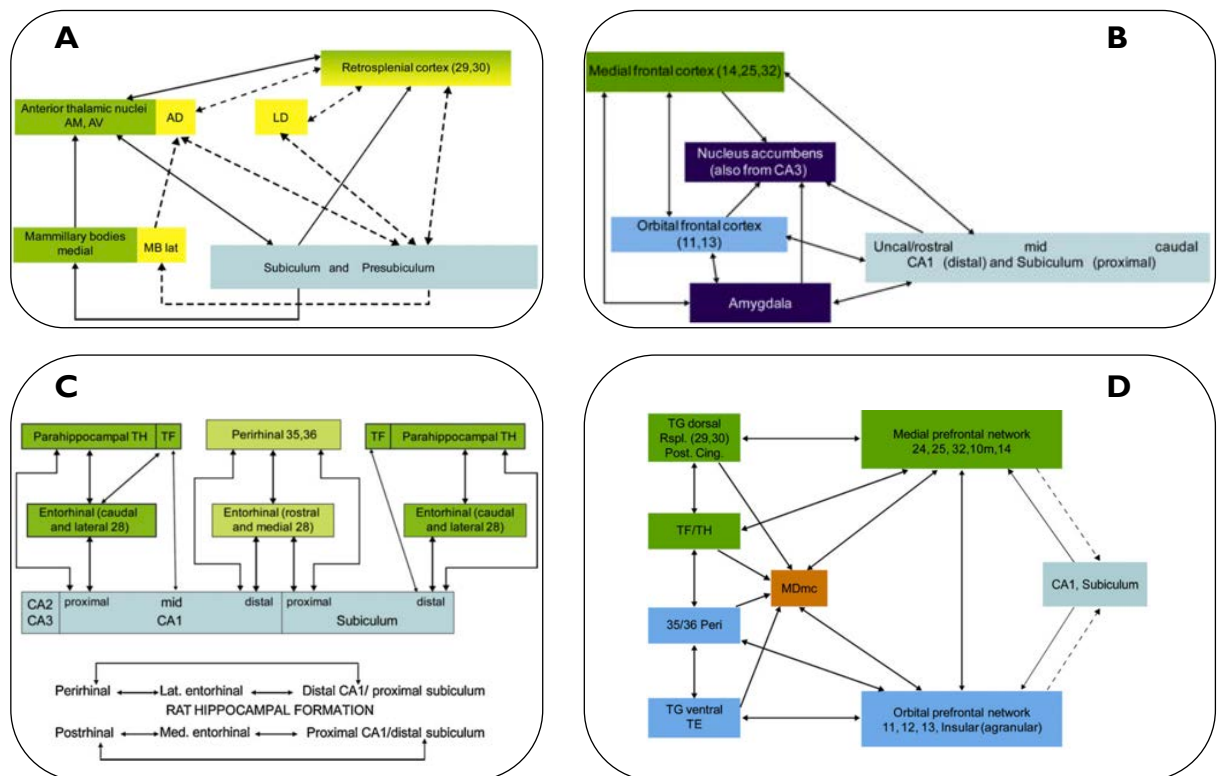


Figure 18. The four functional MTL systems (Aggleton, 2012). (A) The Extended Hippocampal System; (B) the Rostral Hippocampal System; (C) the Reciprocal Hippocampal-Parahippocampal System; (D) the Parahippocampal-Prefrontal System. (Adapted from Aggleton, 2012)

- The *Extended Hippocampal System* connects the subiculum to the anterior thalamic nuclei via the fornix, mammillary bodies and the mamillo-thalamic tract,

and the retrosplenial cortex. This system is thought to underlie recollection-based recognition memory and thus, would support episodic memory formation. One reason why the recollective experience may stem from this system is that hippocampal efferents to the mammillary bodies, thalamus and retrosplenial cortex are organized in a way favouring the maintenance of information segregation, until convergence that could occur in the thalamus. Thus, high-resolution representations inputs to the subiculum could be maintained as separated through separated streams of information within this system, making it well tuned to support the formation of context-rich memories (i.e. involving multiple associations between elements).

- The *Parahippocampal-Prefrontal System* includes the dense reciprocal connections between the parahippocampal region and various prefrontal cortex areas, as well as the medial dorsal nucleus of the thalamus and structures of the basal forebrain. This system is further divided in two networks, the “orbital prefrontal network” featuring connections with the perirhinal cortex and the “medial prefrontal network” corresponding to the connections with the parahippocampal cortex. The first network would support familiarity-based retrieval, while the roles of the second are less clear. One possibility is that it contributes indirectly to strategic aspects of retrieval, on the ground of the parahippocampal connections with the hippocampus.
- The *Rostral Hippocampal System* connects the CA1 subfield and the subiculum to medial and orbital prefrontal areas, as well as to the amygdala and nucleus accumbens. Rather than being involved directly in new learning, this system would be responsible for the modulation of memory formation depending on the emotional and motivational (reward values) stimuli or tasks contents. Thus, this system would be critical for memory formation of events including social and affective features.
- The *Reciprocal Hippocampal-Parahippocampal System* features the bidirectional connections between the parahippocampal region and the hippocampus, highlighting as previous models the relative segregation between the perirhinal and the parahippocampal cortices connections. While the former would be involved in the representations of item-based information, the latter would be responsible for representing context-based information. Here, the Aggleton view

is not distinct from the BIC model, however he importantly refers to the “gatekeeper” hypothesis for the perirhinal cortex on which we will come back later (Chapter VI) since it is of relevance for the present thesis.

1.8.3.2. Domain dichotomy model

This model was originally proposed in 2007 and later refined in 2010 (Mayes et al., 2007; Montaldi & Mayes, 2010) by the Manchester group. Basically, the model was grounded on particular recognition memory tasks tapping associative recognition performance, which is at odds with the models presented above. The idea is that declarative memories are inherently associative, and that three kinds of associations can be distinguished: intra-item, within-domain inter-items, and between-domains inter-items associations. It follows that distinct MTL regions will be devoted to distinct encoding processes allowing the representation of these distinct kinds of associations. Since the model has mainly put forward the recognition memory processes (Familiarity, Recollection) as supporting different associations, we considered it as a process-, rather than content-based model. Moreover, declarative memories can only be accessed through recall, which is also considered an associative process: in recognition memory tasks, a cue may allow the association with perceptually absent information, but related to the encoding situation. This is an instance of recall (cued recall), and defines recollection-based retrieval in this model. However, familiarity-based retrieval is not considered an instance of recall. Thus, this model has no ambiguity regarding the related concepts of episodic vs. semantic memories and recollection vs. familiarity. Only recollection can allow retrieval of episodic or semantic memories, while familiarity is leading to nothing more than a “feeling” of memory (Mayes et al., 2007, p. 126).

The domain-dichotomy model, like the BIC account, strongly relies on pattern completion and pattern separation processes derived from computational models (Norman & O'Reilly, 2003) to further characterize the respective roles of the PRC and HPC. Pattern separation allows to creating distinct memory representations from very similar inputs, and it takes place in the hippocampus. This separation process supposedly enables cued recall – pattern completion – at recognition, and this is how the hippocampus may binds

together between-domains items, and more generally any association between context and an existing representation. The resulting hippocampal representations are highly flexible, allowing the recall of both its individual components and their relations, in a similar view with the relational theory. By contrast, the perirhinal cortex would not be suited to perform pattern separation and pattern completion, instead being biased towards generalization. Generalization here refers to the extraction of common features (or components) across several inputs. In rapid learning tasks (i.e. one-trial learning recognition tasks), generalization would therefore fail to support recollection, instead underlying familiarity-based retrieval. Note, however, that the extent to which the PRC supports familiarity for associations is dependent on the degree to which individual components of the association converges in this structure. For example, if the components of a between-domains association actually involve neural processing sufficiently close in the ventral pathway space, then it could converge within the PRC and be retrieved on the basis of familiarity. This also could be the case when the orienting task at encoding explicitly facilitates a direct link between the components of an association (i.e., unitization), even if they belong to different domains.

Finally, it is important to note that the original formulation of the Domain Dichotomy (DD) model did not address the role of the PHC. This was done somewhat later in the CRAFT model (Convergence, Recollection And Familiarity Theory, Montaldi & Mayes, 2010), which proposes that the PHC would be specifically involved in familiarity for the context, whereas the PRC remains critical for objects/items familiarity. Overall, the Domain Dichotomy and CRAFT models have strong connections with the relational, conjunctive, and BIC content-based theories: the hippocampus uniquely represents associations that are dependent on pattern separation processes, while surrounding cortices can represent single objects, or items, with a proposed distinction between context (PHC) and items (PRC). However, it differs from all these theories in that the focus is put on how distinct recognition processes operate, rather than how distinct representations support these processes. Furthermore, at variance with the conjunctive theory, DD and CRAFT assume that flexibility of hippocampal memories arises from the possibility to recall its individual components. Finally, DD and CRAFT models strongly disagree with the BIC model with respect to the role of the PHC, which supports familiarity processes here, while in the BIC model it is involved in recollection.

1.8.3.3. The Complementary Learning System (CLS) computational model

Acknowledging that some functional specialization is most likely within the MTL, Norman & O'Reilly (2003) also make the point that simple dichotomies, either process- or content-based (i.e. recollection vs. familiarity; item- vs. associative memory) fail to account for the variable recognition memory impairments observed after MTL damage. The authors thus propose a computational model that is mapped onto the specific computational properties (i.e. neural processes) of the parahippocampal gyrus on the one hand, and the hippocampus on the other hand. This model is grounded on the general principle of the CLS (McClelland, McNaughton, & O'Reilly, 1995; O'Reilly & Rudy, 2001), namely that rapid learning of specific events relies on the hippocampus while the neocortex can support a slow learning, by detecting environmental regularities. However, it was dedicated to the explanation of recognition memory performance.

The parahippocampal region is assumed to be responsible for slow learning, because these structures are thought to be involved in memory-based generalization, only possible after numerous learning trials. Thus, the computations performed here would mainly be the detection of statistical regularities across events and items, to allow similar stimuli (or events, or events' features) to be represented similarly. With time, this would result in the representation of commonalities, that is to say representing common knowledge structures across multiple inputs. In the CLS framework, the core function of the parahippocampal gyrus is the building of "knowledge" structures represented in the neocortex. These structures then allow generalization, which basically corresponds to our ability to infer properties to new stimuli based on prior knowledge, in as much as the novel input has some similarities with stored representations. In the model, these cortical computations support familiarity-based recognition. The reason is that the representations built in the parahippocampal region (and especially the PRC) become sharper with repetitions: after a sufficient number of trials, the PRC can represent e.g. objects with a high level of sharpness, making these representations distinct enough to be discriminated from novel inputs. In that case, a single signal detection theory is sufficient to account for recognition performance. However, whenever high discriminative demands are placed on recognition (e.g. high similarity between targets and foils), the parahippocampal computations would not allow sufficient accuracy. These

subhippocampal computations would thus be responsible for objects / items or context representations, in a similar way to the BIC model.

By contrast, the main computation performed in the hippocampus is pattern separation, a process whereby similar inputs can nonetheless trigger orthogonal representations. This is a mandatory mechanism to avoid the “catastrophic interference” that would be associated with familiarity-signal alone. In other words, if generalization were the only driving force, then processing of any single stimulus would result in “overwriting” prior representations. On the contrary, pattern separation allows for the unique recollective experience that characterizes episodic memory (i.e. recollection-based recognition). Pattern separation supports the rapid encoding of neocortical patterns of activity (e.g. multiple sensory inputs while an event unfolds) so that when presenting with partial cues later on, the recall of the event is made possible through pattern completion.

Kumaran, Hassabis, & McClelland, (2016) and Kumaran & McClelland, (2012) have notably updated the CLS framework in way that is relevant to the present work. An important modification is that this new model (REcurrency and Episodic Memory Results in GEneralization, REMERGE) allows for rapid neocortical learning to occur, but only in situations where the sensory input is consistent with prior knowledge (in the form of memory schemas, see Chapter VI). In these cases, prior knowledge at encoding would result in accelerated system consolidation (Fernández & Morris, 2018a; Wang & Morris, 2010; see also Packard et al., 2017; Tibon, Cooper, & Greve, 2017).

1.8.3.4. Summary of process-based models

The process approach models acknowledge the idea of a functional dissociation with the MTL, distinguishing between familiarity and recollection. These models consistently put forward the PRC as a critical structure for familiarity, while the hippocampus is considered the key structure for recollection. Similarly, all these models highlight the role of pattern separation and pattern completion processes as critical for the building of new

memories, and especially for recollection, thus contributing to moving the field from psychologically defined processes (i.e. recollection and familiarity) to computationally defined processes (i.e. pattern separation vs. pattern completion). Some differences must be outlined.

First, the Aggleton view integrates larger scale MTL-neocortical networks as important for these processes, while the other models mainly focus on the MTL structures. Second, the DD and CRAFT models only explicitly predicts that familiarity-based recognition can support rapid learning of associations, provided that either 1/ intra-items associations; 2/ within-domain inter-items (e.g. face-face) associations or 3/ between-domain items under specific task instructions emphasizing unitization, are considered. Third, the REMERGE model importantly adds a situation where rapid learning could occur, namely when incoming information is consistent with prior knowledge.

Altogether, some of the process-based models of recognition memory therefore predict that new learning may be supported by extra-hippocampal neocortical structures at a fast rate, under certain circumstances. Models then diverge on these circumstances, but one can speculate that unitization and congruence with prior knowledge would be critical factors for such learning to occur.

1.8.4. Representational-hierarchical models

We will only shortly here describe the more recent and innovative accounts for the role of the MTL in learning. Accumulated evidence in the last two decades has demonstrated that the MTL, including the hippocampus, was also involved in perception and short-term or working memory tasks, thus casting doubt on the idea of a unique specialization in long-term memory (for review, see e.g. Yonelinas, 2013). This has led several authors to new theoretical approaches where mnemonic and perceptual functions of the MTL are no longer segregated. Since these theories assume that the MTL is no longer a functional entity devoted to declarative learning, and that memory itself cannot be fully separated from other elementary cognitive processes, we decided not to report it with other contents- or processes-based models.

The dominant model here is the perceptual-mnemonic or representational-hierarchical view (Rosemary A. Cowell, Bussey, & Saksida, 2010; Elisabeth A. Murray, Bussey, & Saksida, 2007). Along with prior proposals (e.g. the BIC model, see also Mishkin et al., 1997), this view acknowledges the hierarchical organization of the MTL, but considers that learning and memory, rather than being a cognitive function *per se*, would result from the dynamic interactions between high- and low-level perceptual representations distributed widely in the brain (Graham, Barense, & Lee, 2010). Structures of the MTL also are considered to have specific processing properties, according to a hierarchical-representational principle. This principle states that, along the visual ventral pathway, information processing is incrementally integrated up to the PRC, and finally to the hippocampus, resulting in a gradient of complexity in the representations built from caudal to rostral region. Thus, while the “earliest” structures would deal with building representations of items features, and these representations would become more and more integrated, finally reaching the PRC where the “entity” could be represented, namely the set of features and properties of a stimuli embedded within a single, unique “conjunctive” representation (see *Figure 19*). This complex representation would serve as an input to the hippocampus, in charge of binding together these representations with their spatial relationships (e.g. Barense et al., 2012).

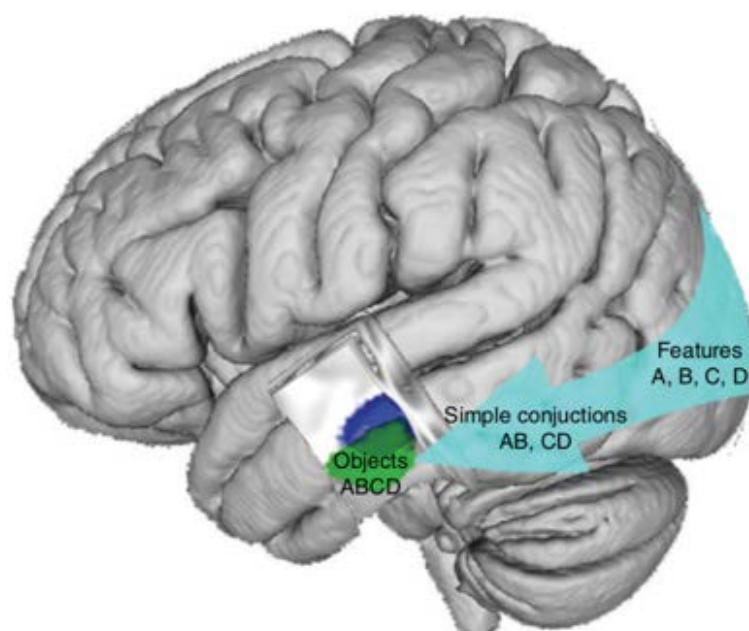


Figure 19. Illustration of the representational-hierarchical view (taken from Douglas & Lee, 2015).

This model therefore highlights how distinct tasks – including memory tasks – may place distinct demands regarding representational complexity. For example, *perceptual* discrimination between conceptually similar but perceptually dissimilar objects would place little demand on visual discrimination, so that it could be successfully preformed by caudal structures. By contrast, either perceptual discrimination or recognition memory for highly similar objects – both conceptually and perceptually – may require the perirhinal cortex to be involved, or the hippocampus depending on e.g. background contextual features similarity. This is a radically different view because typical reasoning in terms of “encoding, storage and retrieval” ever since Sir Arthur Melton (e.g., Melton, 1963) no longer holds here. In an elegant study in rats for example, Bartko, Cowell, Winters, Bussey, & Saksida, (2010) have shown increased sensibility to interference in an animal model of amnesia could be explained inclusively by impaired encoding and storage and retrieval. After postrhinal cortex damage, encoding and storage are impaired because the maintenance of the most complex representation of a stimulus is not possible, only lower levels of representational complexity can be achieved. If the memory task further requires the resolution of ambiguities between foils and targets that are similar, then retrieval will be impaired as well, because the cue processing is not sufficient to resolve the ambiguity, and because ad hoc stored representation is no longer available. Thus, the typical interference effect explaining amnesia can be considered as a direct by-product of impaired representations at some level of the ventral pathway, as long as the location of the lesion is incompatible with the representational demands of the task, irrespectively of whether perception or memory are involved. Note that regarding recognition memory, this theoretical view does not map recollection or familiarity-based retrieval processes on specific MTL structures. Each structure can theoretically contribute to both processes, depending on the representational demands of the task. However, given that the hippocampus is thought to encode the spatial relationships between complex item representations, the model predicts that recall or recognition tasks requiring the maintenance and retrieval of complex episodes including critical spatial components, which often matches with recollective experiences, will depend on the hippocampus. With that respect, a highly related theoretical perspective for the role of the hippocampus is the scene construction theory (Hassabis & Maguire, 2007, 2009; Maguire & Mullally, 2013), which argues that the core hippocampal function would be to build mental scenes, a scene being defined by an ensemble of at least three distinct entities sharing spatial relationships within a 3D mental image.

Finally, the relevance of the representational account for the present work can be illustrated with the following example. Consider two distinct situations, one where you meet a new colleague at work, and the other where you meet a friend of yours at work. In both situations, extensive prior knowledge about the context is available, while pre-existing representations about the person are available only for your friend. Due to this difference, it is expected that a higher-level representation would be achieved for the “friend at work” than for the “new colleague at work” event. This is because the background context (work setting) and the face trigger familiarity, so you need further representational processing to separate prior representations of your friend (i.e. meeting in different contexts than at your work) from that particular event. By contrast, the new colleague face does not yield familiarity, against a very familiar background. This face is therefore perceived as highly distinctive (see also “isolation effect”, Hunt & Lamb, 2001) and a lower-level representation should be built. Here, prior knowledge may therefore have distinct influences on further retrieval. If asked to simply make a judgement of prior occurrence on the faces of your friend or of the new colleague, low-level representations in the ventral stream should do the job, and therefore no impact of prior knowledge is expected. However, if the test involves face-context combinations as stimuli, with the context held constant (i.e. the work setting), but varying the faces (targets friends’ faces and new friends’ faces, target new colleague’s face and new unknown faces) the situation would be quite different and prior knowledge would play a role. This is because the target friend’s face had been represented at a higher level in the hierarchy, thus allowing discrimination between this particular face-context association and distractor combinations involving the same context (work) but a different friend’s face. However, for the unknown face, a lower (i.e. less integrated) representation of the association should make it harder to discriminate the target from combinations involving the same context but with new unknown faces. Following this logic, prior knowledge influence on recognition memory should therefore depend on the available cues at test.

1.8.5. Summary of recognition memory models and relevance for the present work

Current influential theoretical accounts for recognition memory vary greatly regarding the influence of prior knowledge on episodic learning. Most of these models do not explicitly address the issue, but some consistent predictions can be emphasized, beyond the differences between these theories:

- Content-based, like process-based, models predict that the hippocampus is critical for the reactivation of prior knowledge associated with the memoranda. It follows that any condition that changes hippocampal processing (like in the case of hippocampal amnesia, or even in aging) should affect any learning situation requiring prior knowledge reactivation.

- It follows that in most situations hippocampal damage should result in the absence or at least significant lessening, of prior knowledge influence on episodic learning.

- Prior knowledge detection (i.e. assessment of the congruency of the sensory input with pre-existing representations) depends on an extended MTL-neocortical network, mainly involving medial prefrontal structures regarding congruency with prior conceptual knowledge.

- Some of the models predict that, under specific circumstances, new learning can take place outside the hippocampus. Such learning can be achieved rapidly either when the memoranda is congruent with prior knowledge, or in cases where unitization can occur (namely, when elements of an experience can be processed as a single entity). Prior knowledge could be one factor promoting unitization (e.g. processing the association between a famous singer and a concert stage as a single, highly integrated representation, vs. the association “your neighbour unexpectedly met in a concert hall”). However, in such cases, further memory could only be based on familiarity according to some frameworks (e.g., BIC).

- Finally, the representational account would predict that prior knowledge influence will entirely depends on the representational demands at retrieval, with low demands supposedly immune to prior knowledge effect, and high demands sensitive to it.

Importantly, the process approaches to recognition memory leads to a conceptual shift in our approach to memory that is highly relevant for the present work. These models put forward the interactions between memory processes, rather memory systems. In that perspective, a new proposal is to consider *knowledge* systems rather than *memory* systems, and to use the term “memory” only by reference to memory recollection, or “remembering” (see Craik & Lockhart, 1972; Lockhart & Craik, 1990; Nadel, 2008). Thus, multiple knowledge system would represent distinct pre-existing representations

supported by specific neural routes (i.e. knowing what, knowing where, knowing where, knowing how, knowing valence, Nadel, 2008). This range of knowledge could differentially influence the reconstructive processes of memory (remembering), depending on the task goals and demands. From this point of view and considering our definition of learning (see pp. 18-24), learning would have little to do with memory (the act of remembering) but rather with how we extract regularities from our environment to build new knowledge, i.e. new bricks for further memory. Given that all the models described above consider that the extraction of regularities across experiences is not hippocampus-dependent, but rather depends on the parahippocampal gyrus and connected structures, we will be especially interested in how knowledge acquisition and influence may stem from computational processing in these structures (see Expts 1 & 4).

In summary, the process-based models may lead to a paradigm shift in memory research, considering that prior knowledge is the key factor driving further memory. Processes like unitization or congruency detection may be decisive in further remembering, either by allowing hippocampus-independent learning or by complementing the rapid, hippocampal-dependent, episodic learning.

Chapter II

A historical sketch for the episodic – semantic distinction: evidence from experimental psychology

“The Swiss psychologist Claparede (1911), discussing the feelings of familiarity in recognition, contrasted two kinds of mental connections: those established between representations, and those established between representations and the self. He suggested that the activation of connections of the first kind does not produce any feelings of familiarity or recognition, and that only those 'between the perception and the feeling of me-ness' are capable of doing so (1911, p. 63).” Cited in Tulving, 1983, p.17



Figure 20. Portrait of Edouard Claparède, retrieved from <https://www.notrehistoire.ch/medias/51989>

At the time Ebbinghaus started to investigate his own learning abilities, learning and memory were highly related to the concept of knowledge. That is, **learning was mainly about the acquisition of knowledge, which, in turn, was associated with the idea of intelligence.** This is not surprising since Greek philosophers defined “intelligence” as “the activity allowing the acquisition of science” (e.g. Speusippus in “Definitions”, a list of definitions for the terms used in the early work from the inescapable Plato). However, at

variance with famous pioneers of experimental psychology like Wundt or Titchener, and despite of the common use of introspection (in that Ebbinghaus had for single subject himself), he fundamentally sought for the mathematical rules guiding learning and memory. Thus, the aim was not to characterize the individual structures responsible for learning, but rather to find out the fundamental rules underlying memory processing. Ninety years later, the “Levels-of-processing framework” paper (Craik & Lockhart, 1972) - with more than 12200 citations ever since (GoogleScholar) - summarizes this processing approach: “[...] *it is the qualitative nature of the task, the kind of operations carried out on the items, that determines retention*” (cited in Roediger, Gallo, & Geraci, 2002). Beyond the processing approaches though, structuralism remains a very strong framework in memory research. The episodic-semantic dichotomy (Tulving, 1972) was interestingly first on stage the very same year, reaching above 7700 citations ever since (GoogleScholar), and remains widely accepted in the community, at least as an unavoidable heuristic. The idea of multiple memory systems pushed into the background the assimilation of learning and memory to the concept of intelligence, or of conceptual knowledge inherited from Plato. Instead, memory is conceptualized as the set of processes allowing to encode, store and retrieve information within different memory stores hosting memory representations with distinct properties, thus making the synthesis between structural and processing approaches (Tulving, 1995). Let us start with a reminder of how this idea came up in the late 1960’s.

II.1. What do we learn in list-learning paradigms?

In the late 1950’s and at the beginning of the 1960, namely at the fall of the “verbal learning” era, and at the very beginning of the “information processing” era (Tulving, 2001), it is worth noting that **researchers were investigating learning, without any mention of memory**. However, and essentially because memory students were well aware of the lack of ecological validity of word-lists learning experiments, they **started to think about the words in terms of to-be-remembered events, rather than individual items**. The rationale for this is that when subjects recall a word they have just heard, they do not inform the experimenter about how well they know this particular word (i.e. meaning, spelling); rather, and accordingly with the task instructions, they recall the

encoding episode, and one specific moment within the study episode when a given word was displayed (Tulving, 1983). In another words, **research moved from “verbal learning” to “event memory”**.

Endel Tulving started to develop the idea of episodic memory because he realized that “event memory” had to be dissociated from the kind of memory described in the early attempts towards theorizing how language operates. The term “semantic memory” was used after Quillian (1966) to designate the set of processes involved in the understanding of language, i.e. the meaning of words and sentences. This was because the psychology of language acknowledged the necessary role of memory in knowledge about words meaning and, more generally, in the use of language. Nonetheless, it seemed obvious that these language theories - e.g. about the structure of knowledge, (Collins & Quillian, 1969; Collins & Quillian, 1972) - could bring little if any insight into the problem of event memory. Thus, **the idea of episodic memory emerged in a sense from an epistemological issue: the psychology of recalling “mini-events” in a typical word-list learning paradigm and the psychology of recalling the meaning of a given concept to comprehend language could not be confounded**. The attempts towards such a distinction resulted in the Chapter 10 entitled “Episodic and semantic memory” from the book “Organization of memory” edited in 1972, a Chapter that has been cited almost 7800 times (Google Scholar).

We further consider empirical evidence from experimental psychology supporting the episodic-semantic distinction.

II.2. Experimental dissociations in the psychology of learning

The distinction proposed between episodic and semantic memory as functionally distinct memory systems takes its root in experimental psychology. Until the end of the 1980's, much of the relevant evidence took the form of experimental dissociations. ***If one single variable is found to alter performance in an episodic memory task, but not in a semantic memory task, or vice-versa, then a dissociation occurs, presumably supportive of the episodic-semantic distinction.*** A classical example can be found in paired associates experiments (see Tulving, 1983). Consider the learning of the pair A-B, until the subject accurately responds B when cued with A (cued recall task). Consider now the response B'

as the most likely response of a subject when asked to provide the first thing in mind when prompted with A (free association task). Along the episodic-semantic distinction hypothesis, learning of the association between A and B is typically requiring the episodic memory system: it is about learning the particular study event when and where A was paired with B. By contrast, the free association task (e.g. a category fluency task) would more likely rely upon the semantic memory system. While repeated study of A-B will result in the gradual acquisition of the association, this will have no impact on the free association A-B'. In the meantime, repetition of the A cue in a free association task will unlikely result in different responses than B'. This is an instance of dissociation where a single variable (repetition) alters performance in an episodic, but not semantic task.

After the 1972 proposal from Tulving, a series of experiments were conducted to look for such dissociations. These studies share a common a priori view about what is an "episodic" memory and a "semantic task"; based on this, manipulation of the materials (almost always words); or manipulation of the encoding task; or manipulation of "brain states" (Tulving 1983) e.g. through hypnosis were used to look for dissociations. We will further report some of these experiments because, ***while designed to address the question of whether episodic and semantic are separate memory systems (or "stores"), their findings and the methodological efforts achieved to dissociate both memory systems consistently illustrate the close relationship between semantic and episodic memory functioning in healthy subjects.*** It is therefore surprising to note that, over thirty years later, research remains essentially focused on one or the other of these systems rather than on their interactions.

So-called "semantic" tasks varied greatly and included - among others: judgments of sentences' accuracy (sentence verification tasks), lexical decision tasks with priming effects, perceptual recognition (i.e. perceptual identification), free associations, vocabulary, spelling, judgment of word frequencies. "Episodic" tasks varied less, essentially being free recall or Old/New recognition tasks.

Shoben, Wescourt, & Smith, (1978) (Expt. 2) contrasted performance of healthy subjects in a sentence verification task and in a sentence recognition task. In the first phase, subjects had to decide as fast as possible whether statements like "Tigers have stripes" or "Donkeys have wings" are true or false. In the second phase, subjects were asked to discriminate from memory the sentences presented in the verification task from lure sentences. The two phases were separated by several days. The authors manipulated two

variables: relatedness and fanning. The former referred to as the degree of semantic relationship between the subject (i.e. “Tigers”) and the predicate terms of the target statements. For example, “Tigers have stripes” corresponds to a high degree of relatedness while “Tigers have thighs” corresponds to a low degree of relatedness. The latter was defined as the number of different statements per subject, or per predicate. For example, if the following statements were presented at study “Donkeys have wings”, “Donkeys are grey”, “Donkeys like carrots”, it was considered as a “3-Fan” condition. These independent variables were hypothesized to have a differential influence on the sentence verification and sentence recognition tasks. Relatedness was found to alter reaction time during the former task (slower for high relatedness), but not the latter. Conversely, Fanning affected reaction time during recognition (increase), but not verification. The authors proposed that their finding of a double dissociation was consistent with the distinction between an episodic and a semantic memory system.

A similar experimental design contrasted a lexical decision task (Expt. 1) with an item recognition task (Expt. 4) (McKoon & Ratcliff, 1979). Critically, priming effects were manipulated in both task, namely the finding that upon fast successive presentations of individual items, if the n-1 item shares some kind of relationship (perceptual, semantic) with the n item, then a fastening of processing will be observed for the n item. After studying a list of pairs of words, subjects had to make a lexical decision on words, some from the study list and others not, or a word recognition task. The independent variables were the nature of the relationship between the prime and the target items in both tasks. In addition with a control condition where the prime and the target did not share any evident relationship, the association between the prime and the target could be “episodic”, “semantic”, or “episodic and semantic”. In the episodic condition, the n-1 item and the n item corresponded to a study pair. In the semantic condition, the n-1 item and the n item were semantically related (e.g. “green-grass”). Finally, in the “episodic and semantic” condition, the n-1 and the n items were semantically related and corresponded to a study pair. The reasoning was that if episodic and semantic are distinct memory stores, then semantic priming should not occur during recognition memory, but it should be the case during lexical decision task. Conversely, “episodic” priming should occur during recognition, but not lexical decision. To make it clear, we can take the example of the study pair “City - Grass” at study. If the pair “Green - Grass” follows it at test, this would be an instance of “semantic association” only, because while the first word has

not been studied, it is highly semantically associated with the second one. In turn, if “City - Grass” was to be studied and again presented at test, this counts as an instance of “episodic association”, since prior study has led to the episodic association between the two words, without any semantic relationships. Finally, if the pair “Green - Grass” is studied and followed at test by “Green - Grass” would be an instance of “episodic and semantic association”. The findings revealed that while in the lexical decision task, response times were similar across the prime-target associations conditions, it did during the recognition task, with faster responses corresponding to the “episodic and semantic” condition, and slower responses to the “semantic” condition. Tulving again took this as consistent with the distinction between separate semantic and episodic stores: the manipulation of one single variable at test (i.e. the kinds of prime-target associations) seems to uniquely affect an episodic, but not a semantic task.

Similar dissociations were reported by Herrmann & Harwood, (1980), who focused on response time analysis during a recognition test. During the test, subjects were showed word pairs of three types: two “old” words, two “new” words and mixed pairs, i.e. composed of a new and an old word. Subjects had to identify the correct type of pair by reference with a study phase. During study, subjects explicitly learned lists of words, each list made of words from a single category. At test, the authors varied two independent variables: the semantic variable corresponded to category belongingness of the test pairs (Same vs. Different category), and the episodic variable - called “relatedness” - referred to whether the words in the test pairs belonged to a studied category or not. The authors focused on the response times for the “new” pairs, and found an interaction between the semantic and episodic variables, resulting from a slower response time for words pertaining to distinct category, but only when these categories had been studied. When it was not the case, the semantic variable did not alter response times. The logic behind the interpretation was as follows. When asked to make recognition memory decision during about two items (presented simultaneously in this experiment), the response time will be influenced by the intrinsic organization of the store where the information is represented. If the items from a pair are closely represented in that store, then one item should prime the other, resulting in fastening of the decision. In the “related” condition, the finding of faster responses when the words belong to the same category reflects such mutual priming. The key issue is to establish whether this priming effect results from the organizational properties of a single store or from distinct organizational properties

from distinct (episodic vs. semantic) stores? Put simply, imagine one had studied a list of tools' names (e.g. screwdriver - hammer - pliers - paintbrush) and a list of vehicles' names (truck - car - bike - underground). At test, let's consider the following new pairs, both related to the study categories: "train - plane" and "boat - drill". The authors found that response time for the latter was slower than for the former. Is this due to the semantic pre-experimental organization of these items, or is this related to their episodic organization resulting from the study of these categories during learning? Since the authors found that in the unrelated condition (i.e. when the category of test words was different from the categories presented at study), response times were similar when the words in a pair belonged to same or different categories, they concluded that episodic, not semantic, organization was responsible for response time modulation in the related condition. The interpretation therefore supported the episodic-semantic distinction, since an "episodic variable" (test words' category relatedness with studied words), but not a "semantic variable" (same vs. different category belongingness of the words in the test pairs), alters performance in the same recognition task.

Finally, episodic recognition and perceptual recognition of words were contrasted after manipulating the encoding instructions, so that attention of the subjects was oriented towards the words visual appearance (capital typing or not), auditory features (rhyming with a given word or not), or its meaning (Jacoby & Dallas, 1981, Expt. 1). In the episodic recognition task, the target words were mixed with distractors and subjects had to decide whether the word was "Old" (i.e. displayed at study) or "New". In the perceptual recognition, the same set of Old and New words were used, and the items were visually flashed for 35ms. Subjects had to say what the word was. The results showed that encoding instructions influenced test accuracy in the episodic recognition task only, and not in the perceptual recognition task. In other words, the occurrence of an event (i.e. studying a word) can have independent effects on a supposedly episodic task (episodic recognition) and on a supposedly semantic task (word identification, called perceptual recognition in the experiment). Tulving, (1983, 1984a, 1984b) interpreted this as evidence for distinct memory stores.

Note that other experimental studies have been considered as supportive of the episodic-semantic distinction, but are less relevant here because they are not as representative of the episodic-semantic interactions as the one detailed above. We must however mention them shortly: among 33 memory measures, only low correlations between supposedly

“episodic” and “semantic” performance was found (Underwood, Boruch, & Malmi, 1978); using hypnose-induced amnesia, it was found that post-amnesia recall of word lists learned during the hypnotic state was severely impaired, but not free association performance using target words from the studies lists (Kihlstrom, Evans, Orne & Orne, 1980, Expt. 1).

II.3. Distinction vs. collaboration?

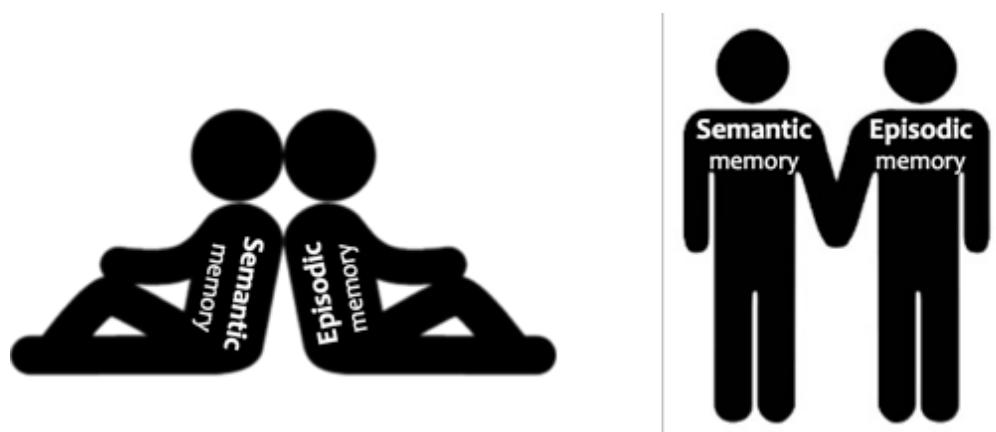


Figure 21. Is the episodic semantic distinction necessary considering massive evidence of collaboration?

A short summary of these findings actually highlights that **semantic variables affect episodic performance either at encoding or at retrieval**, a finding consistent with the Levels-Of-Processing account (“LOP”, Craik & Lockhart, 1972), stating that deeper processing at encoding (e.g. semantic processing) results in higher subsequent memory. The most typical finding is perhaps the one from Jacoby and Dallas (1981, Expt. 1), where a semantic orienting task at encoding (i.e. processing the meaning of target words) yields a 72% increase in recognition accuracy by comparison with a physical orienting task (i.e. is the word typed in capitals?). At retrieval, semantic priming also increases response latencies by 19% by comparison with episodic priming (McKoon and Ratcliff, 1979, Expts. 1 & 4). Conversely, other studies contrasting recognition (i.e. episodic) and identification (i.e. semantic) tasks have shown that studying a word increases the performance in a later semantic task - suggesting that episodic memory affects semantic memory as well - but, the benefit does not correlate with further probability of recognizing this word

(Jacoby & Witherspoon, 1982). Importantly, **such independence between the influences on a study event on further semantic vs. episodic tasks lacks generalization.** For example, when pseudowords are used, prior study yields to a positive correlation between further recognition and identification performance (Jacoby & Whitherspoon, 1982).

Most critically, the **interpretations favouring the hypothesis of separate semantic and episodic stores had been challenged on several grounds.** For example, it has been pointed out that “perceptual recognition” tasks (namely, identification of stimuli - almost always words - after very short presentation) cannot be considered as a typical semantic task, since procedural and / or lexical memories are involved (McKoon, Ratcliff, & Dell, 1986). Similarly, lexical decision tasks cannot be considered as optimal proxies for semantic memory, and dissociations between lexical decision performance and semantic performance have been reported (Blazely, Coltheart, & Casey, 2005). Even when the tasks used to gather dissociations seem to carry more clear-cut construct validity for semantic vs. episodic memory, like in sentence verification vs. sentence recognition tasks (Shoben et al. 1978), it is not clear how multiple stores would better account for the results than a single memory store. The findings that high relatedness items were processed more slowly than low relatedness items in the verification task, while no relatedness effect was observed in the recognition task, is interpreted as evidence for the fact that semantic information is used in the former task, but not in the later. As such, this could perfectly fit with the idea that both prior occurrence and semantic knowledge can be represented in a single memory store (Anderson & Ross, 1980; McCloskey & Santee, 1981). Moreover, the idea that in this experiment, semantic information at retrieval (i.e. words relatedness in the sentence) does not affect episodic recognition is a rather isolated result among **the wealth of studies reporting that semantic information generally improves further memory** (Piaget, 1929; Bartlett, 1932; Bransford & Johnson, 1972; Brod, Werkle-Bergner, & Shing, 2013; Craik & Tulving, 1975; Klatzky & Forrest, 1984; Lewis & Anderson, 1976; Reggev, Sharoni, & Maril, 2017; Schulman, 1974).

An interim summary of the evidence from experimental psychology in the early years of the episodic-semantic distinction therefore could be found in the following quote: “[...] *Tulving’s depiction of semantic and episodic memory has had obvious heuristic value. But in Elements he argues that it has more; that it*

represents a distinction between two systems of memory with the potential for independent function. Unfortunately, the evidence for dual-systems approach (...) is far from unequivocal.” (Klatzky, 1984)

A particular ambivalence lies in the interpretations made by Tulving of two of the above-mentioned experiments.

First, to estimate priming in lexical decision, McKoon & Ratcliff, (1979) used the condition where the target words were absent from the study list, to avoid episodic contamination on the priming effect. On the contrary, Tulving (1983) uses the condition where target words were part of the study list. Under the former condition, the response times for primed words do vary along with the kind of prime-target relationship (i.e. semantic, episodic or mixed), just like it does in the recognition task. Under the latter condition though, response times for primed words are not influenced by the priming conditions (see McKoon et al., 1986; Ratcliff & McKoon, 1986). Finding of episodic priming in lexical decision task in subsequent experiments (McKoon & Ratcliff, 1986) had further supported the unitary view (see also Neely & Durgunoğlu, 1985), and suggested that the distinction between semantic and episodic priming found in lexical decision vs. recognition could be accounted for by hypothesizing distinct retrieval processes without requiring the dual semantic-episodic view. **As early as in the late 1970's, this pointed out that subtle effects of semantic information in subsequent learning could occur or not, depending on the nature of the retrieval processes involved.**

Second, the finding that the orienting task at encoding boosted episodic recognition leaving unaffected perceptual recognition (Jacoby & Dallas, 1981) is also interpreted as an instance of a dissociation between semantic and episodic memories (Tulving, 1983, 1984). A careful examination of the authors' discussion however suggests otherwise. Even if one considers “perceptual recognition” as a semantic memory task, the authors acknowledge the contradictions between their results and the finding of McKoon & Ratcliff (1979), and asked (p. 336): **“How is memory for specific occurrences of an item related to more general memory of that item?”**. Rather than considering that general memory and memory for a specific occurrence could rely on separate stores, the authors put forward the recent evidence for two distinct basis for recognition memory. On the one hand, relative perceptual fluency can lead to the awareness that the item has been experienced

before. On the other hand, elaboration of the item's context can be achieved at retrieval to provide evidence of prior encounter during the study phase (the study event). The idea here is that the latter basis for recognition would undergo semantic influences (like the ones resulting from levels of processing manipulations at encoding), while the former would involve processes more similar to perceptual recognition, thus being not sensitive to semantic elaboration at encoding. This proposal had the advantage of reconciling divergent findings, and being compatible with the ideas from Atkinson & Juola, (1974) and Mandler, (1980) that recognition memory may not rely on a unitary process.

II.4. Summary

To sum up the above elements, this brief historical sketch of empirical evidence derived from experimental psychology for the episodic-semantic distinction reveals its frailty. The proposed distinction has in fact a still in-use obvious heuristic value, but evidence has not clearly tipped the scale in favour of separate stores. **What emerges, however, is that pre-experimental associations have a strong influence on further learning, either during encoding or retrieval.** However, the mechanisms underlying this influence are not specified. Interestingly, these series of experiments have also **put forward the value of recognition memory tasks to probe episodic learning, and its relationships with semantic memory.** Furthermore, it is noteworthy that not only recognition memory tasks started to be a standard in the psychology of memory at that time, but also that debates between structure- and process-based approaches have witnessed the birth of dual-processes models of recognition memory. In other words, the search for dissociations between semantic and episodic memory stores has promoted the idea that the judgment of prior occurrence may have two distinct basis: a sense of prior exposure based on perceptual fluency on the one hand, and an elaborative retrieval process allowing to re-instantiate the study event on the other hand.

Chapter III

A historical sketch for the episodic – semantic distinction: evidence from neuropsychology



Figure 22. Neuropsychological era of memory research. Free adaptation of the butcher-in-the-bus phenomenon

III.1. Early years: selective semantic memory impairments

It is worth noting that more than two decades of research were needed after the seminal description of the patient HM (Scoville & Milner, 1957) to finally get a formal proposal about preserved and impaired memories in amnesia following bilateral damage to the MTL. It took exactly 23 years for the first occurrence of “declarative” memory to appear in the famous Science paper from Neil Cohen and Larry Squire, cited over 2800 times ever since (Cohen & Squire, 1980). In the meantime however, the idea of a distinction between episodic and semantic memories was mainly grounded on findings from experimental psychology and theoretical arguments, but still lacked robust empirical evidence in neuropsychology. Consider that in 1984, one of the comments of the Behavioural & Brain Sciences paper of Endel Tulving was entitled “*Episodic versus Semantic Memory: A distinction whose time has come – and gone?*” (Hintzmann, p. 240). Still, neuropsychology

since HM has proved very powerful in identifying core brain regions as responsible for unique cognitive computations, thus highlighting the relative independency between some mental functions, and memory was of no exception.

It is to Elizabeth Warrington that we owe the pioneer work identifying semantic memory as a potential separate entity from episodic memory. **In 1975, she described three patients who seemed to be selectively impaired at understanding the meaning of visual objects and words, despite an overall preservation of reading and talking skills as well as general intellectual efficiency (E. K. Warrington, 1975).** Of special interest was the patient AB, who failed to define concrete words but could do so for abstract words. In response to the word “Macaroni”, AB said he had “no idea” of what this word would mean. Meanwhile, when prompted with the word “Soul”, his answer was “Your basic interior element” (Warrington, 1979, p.16). Warrington contrasted such neuropsychological profiles with their apparently normal day-to-day memory: *“Yet these patients were not at all like amnesic patients with a global amnesia for all on-going events. Unlike an amnesic patient they were all well-orientated in time and place; their conversation was not so repetitive and they were able to refer forwards and backwards to detailed events of importance in their lives.”* (Warrington, 1975, p. 650). This allowed the author to suggest a distinction between semantic and “event”, or episodic, memories. However, as she acknowledged, **the patients AB and EM were severely impaired in verbal recall tasks as well as in recognition memory tests involving verbal, or non verbal, materials**, where they scored even below the level of global amnesic patients (exception made of recognition memory for paintings). Thus, **one could hardly consider these case reports as an instance of dissociation between preserved event memory despite impaired semantic memory.**

Remarkably, she noted that during paired-associates learning tasks, amnesic patients could benefit from semantic associations between the words in a pair (e.g. fruit – apple) to improve cued recall. However, she also observed that when the verbal association did not refer to obvious semantic categories (e.g. green – grass), this no longer helped the patients. Thus, shortly after Tulving's proposal (1972), a thorough neuropsychological approach had already suggested that, when pre-existing representations (presumably in semantic memory) were available at encoding, this could benefit episodic learning. Such empirical evidence strengthened the idea of an episodic – semantic distinction, but also highlighted the close interactions between these memories.

Later work demonstrating **category-specific impairments** in patients with herpes simplex encephalitis (Warrington & Shallice, 1984), and the first description of semantic dementia, a degenerative condition that selectively targets semantic memory (Snowden et al., 1989) brought **more convincing evidence that impairments of semantic memory could occur despite leaving episodic memory intact.**

What was missing, however, was the demonstration of normal semantic learning despite abolished episodic learning.

III.2. Does evidence for preserved semantic testing in amnesia speak for the episodic semantic distinction?

In the early 1980's, several neuropsychological studies have investigated whether amnesic patients could succeed in various semantic tasks. For example, Wilson & Baddeley, (1988) reported the case of the densely amnesic patient KJ who performed in the fully normal range in vocabulary or verbal fluency tasks, even reaching controls' speed in semantic categorization tasks, and being at ceiling in complex lexical semantic tasks like the Mill Hill vocabulary test. The authors underline however that such tasks heavily rely upon memories acquired along repeated exposures, mostly occurring before the onset of amnesia. **Therefore, new learning tasks and semantic tasks differ in multiple aspects:** the age of the memory trace, the massed vs. distributed practice leading to the traces, and the moment of their acquisition, i.e. before (semantic) or after

(episodic) the onset of amnesia. **Each of these variables, or some combination, could therefore explain the apparent dissociation between semantic and episodic memory performance**, at variance with the hypothesis of separate memory stores.

Moreover, evidence gathered in amnesic patients that, when prompted with the first letters of target words, memory is improved despite amnesia (Warrington & Weiskrantz, 1968) does not imply preserved semantic memory, rather being an instance of priming, relying on preserved procedural learning.

Thus, **in the early 1980's, most of the neuropsychological studies reporting dissociations between semantic and episodic memory performance actually contrasted learning of post-onset events with retrieval of pre-onset knowledge, or involved "semantic" tasks that could be solved based on priming processes** (e.g. Damasio, Eslinger, Damasio, Van Hoesen, & Cornell, 1985; Nebes, Martin, & Horn, 1984; Schacter, 1983; Warrington & Weiskrantz, 1968). Besides, refinements in autobiographical memory testing in the late 1980's resulted in the finding of highly inter-correlated scores of episodic-like and semantic-like memories in amnesic patients and controls (Kopelman, Wilson, & Baddeley, 1989). This added little evidence in favour of the episodic-semantic distinction, and led to the conclusion that the acquisition of episodic and semantic information depends on a common memory system largely supported by the medial temporal lobes (Gabrieli, Cohen, & Corkin, 1988).

In summary, while strong evidence has led to a wide agreement for the procedural/declarative distinction, early evidence for dissociations in amnesic patients between semantic and episodic tasks was not sufficient to support the view of episodic and semantic memories as separate systems from a biological point of view.

III.3. A major step forward: patients TC and KC

In two landmark studies reporting on the case of patient TC, a young girl who suffered herpes simplex encephalitis aged 9, Wood, Ebert & Kinsbourne (1982) (see Wood, Brown, & Felton, 1989 for the follow-up case report) have brought evidence for substantial post-onset learning despite dense amnesia. **Patient TC's IQ rose from below 50 1-year post-onset to 83 at the age of 16, while remaining severely amnesic in everyday life as well as when tested with various psychometric tools.** The authors used tasks of reading, language and math academic achievement and found clear improvements both before

and after amnesia occurred. This was the **first convincing data suggesting that some form of declarative, anterograde, learning may take place despite severe amnesia**, which was a reminder of previous work showing that amnesic patients diagnosed with Korsakoff's syndrome could learn the Fibonacci suite and retain it for weeks (Wood et al., 1982).

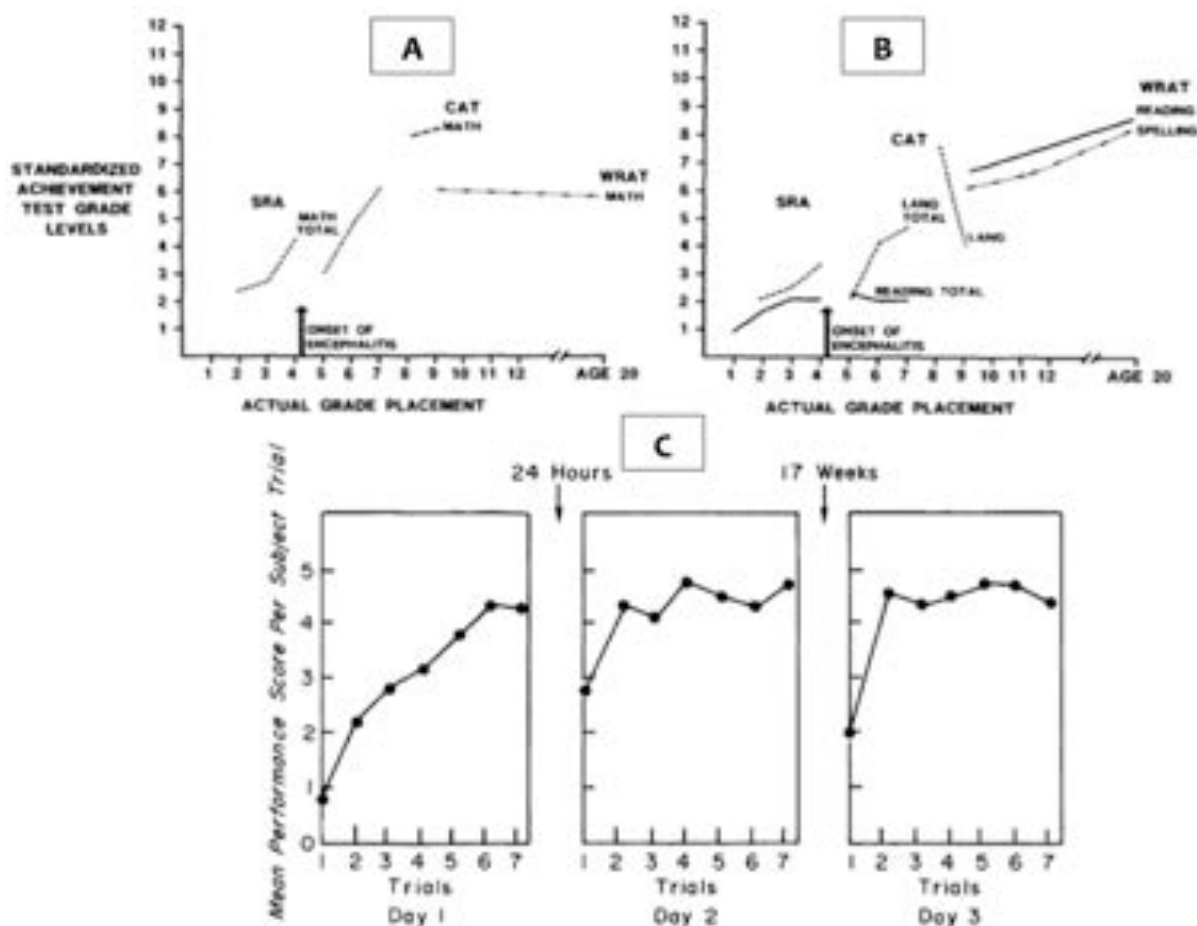


Figure 23. (A) & (B): Evidence for post-onset declarative learning in the amnesic patient TC., adapted from Wood et al., 1989. (C) Evidence for learning and retention of the Fibonacci suite in 6 amnesic patients with Korsakoff's syndrome (taken from Wood et al., 1982, p. 173).

However, a second look at the data also revealed that **TC was capable of some residual episodic learning**, as suggested by her far from floor performance during the Rey Auditory Verbal Learning Test (see Squire & Zola, 1998, and Figure 24).

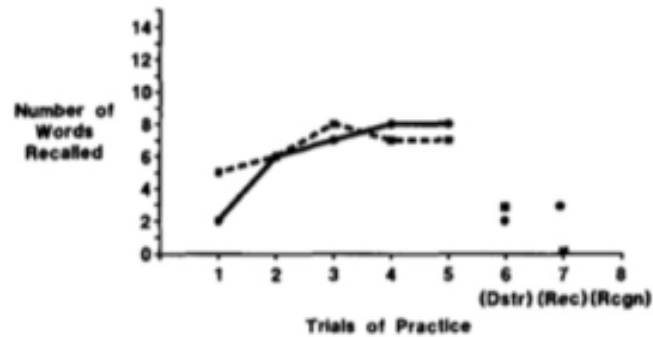


Figure 24. Residual declarative learning in the patient TC, grounding Squire & Zola’s (1998) critique against the episodic-semantic distinction, taken from Wood et al. (1989), p. 84. Solid line depicts results for the Rey Auditory Verbal Learning Task, the dotted line is for card presentation of the same words.

Moreover, tests of academic achievements tells us little on how a given grade level has been reached, leaving opened the possibility that, with enough time and repetitions, and relying upon her residual declarative learning abilities, patient TC had gradually improved her academic skills. This, again, is conceivable without assuming two separate learning systems.

In 1983, Morris Moscovitch had his attention drew upon a patient who was “just like HM” due to traumatic brain injury (Rosenbaum et al., 2005, p. 991). It was the beginning of a long series of publications featuring patient KC, who probably became the most important amnesic patient in the theory built by Endel Tulving. This patient, KC, had suffered two traumatic brain injuries with apparently no serious sequels at age 16 and 20. But in 1951, aged 30, a motorcycle accident was responsible for a severe and devastating traumatic brain injury. This accident left him densely amnesic, one single anecdote being sufficient to illustrate this point: “Each time he is told of September 11, he expresses the same horror and disbelief as someone hearing of the news for the very first time.” (Rosenbaum et al., 2005, p. 994).

A series of experiments were successful in demonstrating that KC could acquire new declarative memories. **When asked to learn target words in response to definitions, KC managed to reach 100% retention at 6 weeks (Glisky, Schacter & Tulving, 1986a); perhaps more impressive, patient KC could successfully learn basic programming skills using 6 previously unknown commands and maintained this learning to a fair level several months later (Glisky, Schacter & Tulving, 1986b),** and he was also found to significantly acquire new relationships between familiar words, or humoristic definitions for familiar

words and to maintain these acquisitions up to 30 months post learning (Tulving & Hayman, 1993; Tulving, Hayman, & Macdonald, 1991). Importantly, KC did not ever show any sign of recollection for the learning episodes. Critically, as part of the experiments involving learning of new relationships between familiar words, Tulving et al. (1991) found that the ability to recognize a target word did not predict how well the word could be recalled on the basis of a fragment serving as a probe (i.e. stem completion, word priming); conversely, priming scores did not predict recognition. Such a stochastic independence (Tulving & Hayman, 1993) between priming performance and declarative learning was taken as evidence against the idea that procedural learning would have supported new learning in KC.

These data provided **compelling evidence that new declarative learning could occur despite profound amnesia, and the proposal of a distinction between semantic and episodic memories could easily account for these findings**. Amnesia could therefore be understood as a dramatic loss of episodic, but not semantic, memory, instead of a selective impairment of declarative memory. Building up on his earlier proposals, Endel Tulving therefore strongly based his SPI model (Tulving, 1995) on these observations. Beyond the case of patient KC, other case reports had brought convincing pieces of evidence. Hirst, Johnson, Phelps, & Volpe, (1988) and Hirst, Phelps, et al., (1988) reported on patient CS who eventually progressed similarly to her husband in learning French, and two patients (AG and GS) were successfully taught new concepts (Van der Linden, Meulemans, & Lorrain, 1994). Still, **it remained unclear why some amnesic patients seemed to acquire new semantic memories while others could not**.

One must mention here that, in the late 1970's and up to the early 1990, several authors have proposed that among the factors explaining these discrepancies, prior knowledge or "meaningfulness" might be relevant (Warrington, 1979; Glisky et al., 1986a; Tulving et al., 1991; Van der Linden et al., 1994; see also Kitchener, Hodges, & McCarthy, 1998). The idea here is that when the material involves stimuli for which pre-existing knowledge (i.e. pre-onset) is available, amnesic patients could more easily update their semantic knowledge and thus acquire the corresponding new fact. However, when such prior knowledge is absent, patients would have to learn entirely new associations, which would not be possible. This account could indeed explain why Gabrieli et al. (1988), by using rather uncommon items (e.g. anchorite), did not find semantic acquisition

in the patient HM while Hirst et al. (1988) or Glisky et al. (1986a) did. The French vocabulary was partly acquired before amnesia in the case of patient CS, and so were computer words for the patient KC. Yet, by successfully teaching new concepts to two amnesic patients, using stimuli largely unfamiliar to the patients, Van der Linden et al. (1994) suggested that this may not be the main factor involved, pointing towards the use of the vanishing cue method instead.

Apart from Tulving's studies with patient KC, and some other cases of amnesia (e.g. Hirst et al., 1988; Van der Linden et al., 1994, patients AG and GS; Van der Linden, Brédart, Depoorter, & Coyette, 1996, patient AC), other research groups failed to find evidence for preserved semantic learning in amnesia. Patients EP and GP, with extensive damage to the whole MTL, were found unable to recall or recognize information about famous people or events from the post-onset period (Bayley & Squire, 2005). In case of patient EP, intensive repetition of stimuli across 24 learning sessions (vs. only 2 sessions required in controls) failed to provide evidence for new context-free learning. Even when damage was limited to the hippocampal formation, five other patients performed at chance level when asked to make a "Living / Deceased" judgment on famous names (Manns, Hopkins, Squire, & Diego, 2003).

More generally, when preserved semantic learning was reported in amnesia, such learning was usually 1) slower than controls; 2) achieved through extensive, repeated exposure to the to-be-learned material (Stark, Stark, & Gordon, 2005); 3) resulting from dedicated learning techniques such as vanishing cues or errorless learning. These features of semantic learning in amnesia led some authors to suggest that it should not be considered as declarative in nature, but rather relies upon perceptual learning processes (Bayley & Squire, 2002), thus accounting for the hyper specificity and rigid features of these memories, as acknowledged earlier (Glisky et al., 1986b).

Moreover, evidence for preserved semantic learning in amnesic patients can be interpreted in favour of a dissociation within declarative memory if and only if no evidence for residual episodic-like learning can be found, as stated above (Squire & Zola, 1998). At variance with this, several cases display residual recall abilities. For example, patient PS with damage thought to be limited to the hippocampal formation obtained a general memory index of 90 (Wechsler Memory Scale-Revised), clearly denoting considerable residual abilities for episodic learning (Verfaellie, Koseff, & Alexander, 2000). Likewise, patients AG and GS scored above 30/48 at the Free and Cued Selective

Reminding Test (immediate free + cued recall, Van der Linden et al., 1994), and patient CS obtained a general memory index of 88, together with far from floor associative learning abilities (Randt Memory Test, see Hirst et al., 1988, Table 1.). In such cases, preserved “semantic” learning could actually be the result of those residual aptitudes, though requiring more time and efforts than in controls. Indeed, each and every studies showing semantic learning in amnesic patients within controlled experimental designs involved very intensive learning protocols: consider for example that after 22 learning sessions, once or twice per week, patient KC at the best could recall about 50% of the 64 sentences of the memoranda (Tulving et al., 1991).

Altogether, these criticisms remained strong, **and late in the 1990’s there was still no agreement about whether patients with hippocampal amnesia could acquire new semantic information** (Mortimer Mishkin, Vargha-Khadem, & Gadian, 1998; Squire & Zola, 1998; Endel Tulving & Markowitsch, 1998). Another important limitation was that, until the early 1990’s, medical imaging techniques did not allow fine quantifications and localizations of the patients’ lesions. Thus, the hypothesis that semantic and episodic memories would rely on separate anatomo-functional systems, although appealing, remained far from compelling.

III.4. The syndrome of “developmental amnesia”: robust evidence for the episodic-semantic distinction

A brief summary of the neuropsychological evidence for the episodic-semantic distinction until the late 1990’s could be as follows. After bilateral damage to the medial temporal lobe, patients are severely impaired in declarative learning, but show preserved procedural learning. However, some patients, under conditions that remain unclear, but at the cost of intensive training and repeated stimulus exposures, and through dedicated learning techniques, seem to acquire new factual knowledge. In an even more limited number of cases, and probably in one unique patient (i.e., patient CS, Hirst et al., 1988), new knowledge acquisition was reported to occur at the same rate than in controls. Note however, that there was here one unique control subject who happened to be patient CS’s husband.

This is the context where Faraneh Vargha-Khadem and coworkers published their famous Science paper in 1997. Their key findings were the following:

- Three children with brain injury limited to the hippocampus that occurred at birth, at 4- or at 9-years old, displayed global amnesia
- All three obtained normal or subnormal IQs, and attained mainstream school with low-average to average levels of factual knowledge
- All three presented with preserved recognition memory for single items and for pairs of items as long as they belonged to the same domain (i.e. recognition memory for pairs of faces and pairs of non words was preserved, but not for mixed pairs combining faces and voices, or objects and places)

That publication was followed by other reports of patients with “developmental amnesia” (Bindschaedler, Peter-Favre, Maeder, Hirsbrunner, & Clarke, 2011; Brizzolara, Casalini, Montanaro, & Posteraro, 2003; D’Angelo, Kacollja, Rabin, Rosenbaum, & Ryan, 2015; Gadian et al., 2000; John M Gardiner, Brandt, Baddeley, Vargha-Khadem, & Mishkin, 2008; Guillery-Girard, Martins, Parisot-Carbuccia, & Eustache, 2004; Martins, Guillery-Girard, Jambaqué, Dulac, & Eustache, 2006; Picard et al., 2013; R S Rosenbaum et al., 2011; Vargha-Khadem et al., 2003; Vicari et al., 2007). Consistently across reports, bilateral damage apparently restricted to the hippocampus was observed, together with anterograde amnesia, contrasting with low average to average IQ and factual knowledge abilities.

The simple fact that these children and young adults have been reported with average IQ was thus the strongest piece of evidence for:

- the existence of semantic acquisition despite global amnesia
- the existence of a learning pathway largely independent from the hippocampus, albeit allowing new declarative learning

Obviously, the episodic memory theory of Tulving, and his recent SPI model predicting that semantic learning can occur without episodic memory, and that semantic retrieval can also take place without episodic memory, was the best candidate to account for these neuropsychological finding. This landmark study has thus moved the field from the declarative memory theory to the still in use era of the semantic – episodic distinction.

III.5. Critical influence of monkey research on the findings from Vargha-Khadem et al.

To account for the cognitive profile of developmental amnesia patients, it is important to acknowledge the contribution of animal – and especially monkeys – literature. At the time patient HM was described, little was known about the extent of his damage within the MTL. Nonetheless, researchers aimed at finding an animal model of amnesia that only could provide a detailed anatomical account for the findings of impaired declarative learning, leaving intact procedural learning.

The initial lesion studies of the hippocampus in monkeys actually failed to replicate the devastating effects found in humans (Meunier & Barbeau, 2013). It was not until 1978 that, using the delayed nonmatching-to-sample (DNMS) procedure combined with large ablation of the MTL in monkeys, a deficit in recognition memory was found that reproduced the impairments showed in HM (Milner, 1972; Mishkin, 1978). However, which structure within the MTL was responsible for the deficit remained unclear, until 1993. That year, Meunier et al. showed that selective damage to the rhinal cortices (namely, the perirhinal and entorhinal cortices) while sparing the hippocampus sufficed to replicate the severe impairments observed by Mishkin (1978) after aspiration of the inner MTL structures, i.e. amygdalo-hippocampectomy (Meunier et al., 1993). The reason, as shown in *Figure 25*, was that such aspiration necessarily implied the resection of the rhinal cortices.



Figure 25. Illustration of the anatomical constraints within the MTL, depicting the reason why the aspiration of the amygdala and the hippocampus (Mishkin, 1978) implies the removal of the rhinal cortices. Taken from Meunier and Barbeau, 2013.

Conversely, when Murray & Mishkin, (1998) performed toxic lesions restricted to the amygdala and hippocampus, but sparing the rhinal cortices, the monkeys behaved normally at the DNMS. This very brief reminder of over 40 years in animal research demonstrates that, at the time of the first description of patients with developmental amnesia, it became plausible that due to its position at the top of the MTL hierarchical structure, the hippocampus may be only involved in memory tasks requiring the highest level of information integration. This fitted with the observation of preserved recognition for items, and within-domain pairs, but impaired recognition for pairs of items belonging to distinct domains, (e.g. object-places) in developmental amnesia (Vargha-Khadem et al., 1997).

III.6. No getting away from facts: the missing piece for the episodic theory puzzle

If the cases of developmental amnesia are to provide definitive evidence for the episodic-semantic distinction, it therefore implies that:

- Acquisition of new semantic knowledge does not rely on highly integrated processes, but rather on single-item or item-item associative learning
- Acquisition of new semantic knowledge can occur at normal pace outside the hippocampus

We argue that these predictions have not been verified, on several grounds of evidence.

First, lesion studies – including case reports of developmental amnesia - have mostly focused on discriminating patients with damage strictly limited to the hippocampal formation or to the whole MTL. However, episodic learning is thought to depend on the so-called “extended hippocampal system” that includes the hippocampus, fornix, mammillary bodies, mammillo-thalamic tract, anterior nuclei of the thalamus as well as retrosplenial cortex (Aggleton et al., 2010). Indeed, damage to any part of that system has been shown to result in amnesia, with particular vulnerability of episodic memories (Aggleton & Saunders, 1997; Vann & Nelson, 2015). Therefore, in **case reports of damage restricted to the hippocampal formation one cannot rule out the possibility that preserved semantic learning may also occur through the functional preservation of some intact components of the extended hippocampal system.** Moreover, in principle, one hardly conceive how semantic knowledge like “we used to eat cookies and drinking fruit juice after playing soccer with my friends during the whole period of my primary school” may have been acquired without contribution of highly integrated processes, that should depend on the extended hippocampal system. Evidence is therefore still lacking that could clarify this point.

Second, that patients with developmental amnesia **score in the low average to average range in semantic tests that almost invariably assess formal academic knowledge** (i.e. subtests of the Wechsler Adult Intelligence Scale, Mill Hill vocabulary test, etc.) cannot be taken as strong evidence for normal semantic memory. More thorough assessments of semantic knowledge always elicit performances in the low-to-normal range (Bindschaedler et al., 2011; Brizzolara et al., 2003; Martins et al., 2006) or, in some cases, impaired performances (e.g., Patient KF, Martins et al., 2006; Patient CL, Vicari et al.,

2007; Patient Jocelyn, Picard et al., 2013). Moreover, recent findings in the patient HC suggest that her semantic knowledge structure may differ from that of healthy individuals (Blumenthal et al., 2017; D'Angelo, Rosenbaum, & Ryan, 2016). Thus, to make a strong case for semantic preservation, **what is needed is the demonstration of an at least fully normal range (but see below) of performance across multiple semantic assessments, encompassing distinct input modalities.**

Third, **evidence for a normal rate of semantic acquisition is missing in amnesic patients.**

As mentioned above, for adult-onset cases with evidence of semantic acquisition, it occurred at a great cost in terms of efforts, repetition, dedicated learning techniques, which certainly do not match controls' way of learning. Moreover, when assessed thoroughly, semantic knowledge was sometimes impaired, and / or abnormally organized. Given that most, if not all cases of developmental amnesia have shown some non-negligible residual learning abilities (e.g. words list learning, recall of Rey figure, see Squire & Zola, 1998), one cannot rule out the possibility the slow and effortful learning, supported by these residual abilities, can take place. Evidence for new declarative, or explicit, learning at the same speed of controls and in the absence of detectable residual episodic memory is therefore still missing, to the best of our knowledge.

Fourth and last, there is some **circularity in reasoning when comparisons between semantic and episodic performance are made to test the hypothesis of separate semantic and episodic memories.** As an example, let's consider the case report of RS, a 49-years old man who was tested 13 years after a subarachnoid haemorrhage leaving him densely amnesic (Kitchener et al., 1998). The authors provide an impressive amount of tests results and found that post-morbid knowledge was invariably impaired by comparison with controls (famous faces, famous names, famous events, vocabulary). However, because RS was found to be very deeply amnesic, with no detectable residual episodic abilities, and because his performance in post-morbid knowledge tests was above chance, the authors concluded: *"We argue that our patient, R.S., has provided irrefutable evidence that new semantic information may be acquired in the absence of any significant anterograde episodic memory."* However, their results also showed that RS performed at chance level when asked to judge whether names of personally known people met since the onset of amnesia were familiar to him or not. The authors argued that this strengthens the idea of undetectable episodic learning in RS. **It is unclear to us**

why familiarity judgments about famous names of people who came to prominence after the onset of amnesia is considered as a semantic test, while familiarity judgment about the names of people met after the stroke is considered as an episodic test. Moreover, the idea that above-chance (but still impaired) performance in semantic memory tests is unexpected given the total absence of episodic learning implies that we have some method to estimate the level of semantic knowledge given episodic performance. Unfortunately, this is not the case, and it probably does not make sense within the multiple memory systems framework, where semantic and episodic memories are supposed to have fully distinct properties. Thus, **evidence for residual semantic knowledge in patients with dense amnesia does not imply separate memory systems**, because we do not know whether or not the small amount of preserved semantic knowledge is *commensurate* with their general recall and recognition abilities. Neuropsychological evidence for the semantic – episodic distinction would thus be convincing only if an amnesic patient with no detectable episodic learning, as assessed through typical learning tests, would present with high-average or even superior level of performance in semantic knowledge tests. This might be the only cognitive profile circumventing the inescapable circularity of the episodic – semantic comparison.

III.6. Consequences for the theoretical framework behind the present work

Of course, since the present work aimed at further characterizing how prior knowledge associated with the memoranda may influence new learning, the above considerations regarding the “episodic-semantic distinction” are of great matter. If separate biological entities were to be considered as supporting episodic and semantic memory stores, then it makes sense to consider that our question relates to how semantic knowledge alters episodic learning within a multiple-memory systems theoretical framework (e.g. SPI, Tulving, 1995). On the contrary, if evidence for separate stores were lacking, then the same question would have to be addressed in a different theoretical framework. Candidates could be theories based on (see section 1.8 for more details):

- memory **processes**, rather than systems (e.g. the question here would be how familiarity-based retrieval influence recollection-based retrieval, (Aggleton & Brown, 1999; A P Yonelinas, 2002)

- memory **contents**, rather than systems (e.g. influence of context-free on the acquisition of context-rich memories, Mishkin et al., 1998; or influence of conjunctive memory traces on the acquisition of relational memories, Eichenbaum, 2007)
- hierarchical **representations**, rather than systems (e.g. within the perceptual/mnemonic view of the MTL functions (Baxter, 2009; Murray & Wise, 2004), the question would be how intermediate levels of processing impacts the acquisition of memories depending on the highest levels of processing?)

Below we summarize Chapter III and argue for a choice among these alternatives.

III.7. Summary

Over 50 years of neuropsychological case studies of amnesia have brought strong empirical evidence for the dissociation between severely impaired learning of new events or episodes, and preserved performance in semantic memory tasks. Neuropsychology has also established that the medial temporal lobes are responsible for successful learning of new facts and events, termed declarative memory. Converging data from case reports also points toward considerable residual abilities to learn new factual knowledge after apparently selective bilateral hippocampal damage, at least when injury occurs early in life. However, available evidence does not support the idea that these preserved learning abilities can occur normally outside the hippocampal system, nor that patients can reach a fully normal range of semantic knowledge if assessed thoroughly. Our claim here is therefore that neuropsychological evidence for the episodic memory theory remains incomplete. Moreover, pioneer neuropsychological studies had suggested that among the factors predicting whether or not an amnesic patient would acquire new declarative memories, the use of meaningless vs. meaningful (i.e. carrying pre-experimental knowledge or not) stimuli could be of great matter. Yet, this has remained largely speculative, and the most consistent factor has been the use of dedicated learning techniques such as the vanishing cues method, yielding very slow and gradual learning over countless repetitions.

Finally, the processing approaches to learning and memory, that assumes the idea of dual processes underlying recognition memory, are by far the most widely accepted conception. Considering our point that evidence for fully separate memory stores is

missing, the present work will therefore refer to these process-based models, rather than on the content-based or representational accounts. Thus, the question we further address in this thesis could be better expressed as “how does memory retrieval influence new declarative learning?”

Chapter IV

How prior knowledge and new learning have long been married: a historical sketch of the semantic-episodic interactions

IV.1. Prior knowledge influences on new learning and Behaviourism

It is worth noting that the problem of the relationships between prior knowledge and new learning has in fact long been addressed in psychology, though most often implicitly. Coming back to the golden era of Behaviourism, the amount of data accumulated with early paired-associates learning paradigm witnesses this fact (for review, see Kausler, 1974 cited in Bower, 2000). As mentioned above, in serial learning experiments, Ebbinghaus himself used - actually invented - nonsense syllables purposely, to avoid variations regarding the familiarity of the to-be-learned items. At the same period, Mary Calkins (1894, cited in Bower, 2000) introduced the paired-associates learning design, using words or pictured objects, a method that came to be favoured by later behaviourists. In their theory, the idea is that along with repetitions of the encoding trials, a gradually increased associative strength is supposed to be built up (so called S-R habit) until the subject can either recall or recognize e.g. the second associate when prompted with the first. However, the rate of acquisition for this new association was thought to depend on prior associative strengths, both within the pair and between each pair's component and the rest of the items in the pair's list. For example, if one would have to learn the following associations [*cat - dog*]; [*bone - mice*]; [*tail - leach*], the behaviourist approach would consider that successful learning will require each of these 3 association strengths to become stronger than any prior association. In the present example, given that, say, (cat-mice) may have a stronger pre-existing association than the target (cat - dog), it is expected that prior knowledge would result in confusions in early responses. Similarly, because pre-existing associations of a given strength might be available for (dog-leach), this would interfere with the strengthening of the target pair (cat-dog) along learning trials. In the first case, pre-existing associations are considered (in terms of S-R strength), and the second case evokes "generalizations" (in terms of overall association strength between each of the items taken individually). Importantly, both cases underline the consideration of pre-existing associations as major factors of (the rate of) new

learning. **Interestingly, these early behaviourist theories considered that, within a paired associates learning task, prior knowledge could either facilitate or hinder new learning.** In the following pairs [*cat - mice*]; [*dog - bone*]; [*tail - leash*], high prior associative strength for the first pairs is supposed to improve learning, while the low associative strength of the last pair is also supposed to facilitate learning, because this association has only little prior associative strength with the other items, and the one pre-existing (i.e. tail - dog; leash - dog; tail - bone; leash - bone; ...) are supposedly far weaker than pre-existing associations between [*dog & bone*], and [*cat & mice*], respectively. We will come back later on the more recently accumulated neural and behavioural evidence for an ambiguous role of pre-existing associations on subsequent memory formation. In contradiction with the behaviourist approach, available evidence highlights the role of distinct levels of processing at encoding, as well as distinct consolidation pathways and retrieval processes. However, **recent developments in the field of neurosciences share a common starting point with these early behaviourist theories: how can we explain that improved learning can be observed for information that is either congruent or incongruent with prior schemas?** (e.g. Fernández & Morris, 2018b; Greve, Cooper, Tibon, & Henson, 2019; Van Kesteren et al., 2012).

IV.2. The Psychology of Expertise and the Chunking Theory

A traditional field of psychology has long been the investigation of what make experts - and specifically domain-specific knowledge experts (Schneider, Körkel, & Weinert, 1989) - so good in their domain. Probably because of the involvement of strategy and problem-solving skills, highly related to the idea of intelligence, the chess game was of particular interest for psychologists.

“(…) Pareillement, on rencontre des joueurs d’échec qui, les yeux fermés, la tête contre le mur, conduisent une partie d’échecs. On a numéroté les pions et les cases; à chaque coup de l’adversaire, on leur nomme la pièce déplacée et la nouvelle case qu’elle occupe; ils commandent eux-mêmes le mouvement de leurs propres pièces, et continuent ainsi pendant plusieurs heures (…) il est clair qu’à chaque coup la figure de l’échiquier tout entier, avec l’ordonnance des diverses pièces, leur est présente, comme dans un miroir intérieur, sans quoi ils ne pourraient prévoir les suites probables du coup qu’ils viennent de subir et du coup qu’ils vont commander.”

Hippolyte Taine, De l’intelligence, [1870, pp. 81-82](#)

[English translation:

Similarly, on can meet chess players who, with their eyes closed, their heads against the wall, lead a game of chess. Numbered pawns and boxes; at each move of the adversary, they are called the displaced piece and the new box which it occupies; they themselves control the movement of their own pieces, and thus continue for several hours (…) it is clear that at each move the figure of the whole chessboard, with the order of the various pieces, is theirs present, as in an interior mirror, without which they could not foresee the probable consequences of the blow they have just suffered and the blow they will command.]

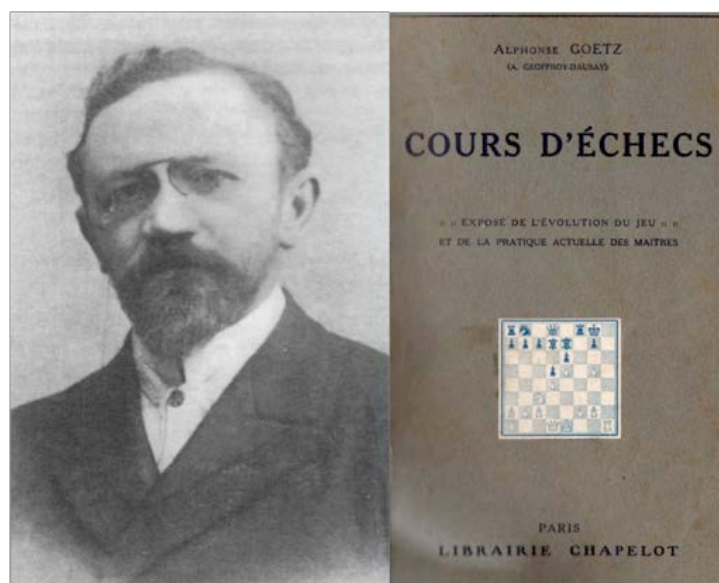


Figure 26. Alphonse Goetz, a famous chess master who inspired Alfred Binet's pioneer studies on experts' memory.

Back in 1891, Alfred Binet was inspired by this observation of the french philosopher when he heard about Alphonse Goetz, a young chess player who had played eight chess games simultaneously blindfolded. He started a large, worldwide survey to the attention of chess players who considered themselves as being able to play the chess game blindfolded (Binet, 1894). For the anecdote, Alfred Binet achieved this by publishing an ad in a magazine specialized in chess (“La Stratégie”), illustrating that great pioneers already took advantage of ancient “social networks”, well before Amazon Mechanical Turk©! He was particularly interested in Alphonse Goetz’s statement that he did not need any form of “visual memory” to successfully play multiple chess games blindfolded, apparently being able to accurately recall the 336 last moves in the middle of a game. This survey along with multiple chess masters interviews led Alfred Binet to underline the critical role of what he called “erudition”, and what we would probably label now “semantic memory” or “schemas” on chess players memory for the on going game. In that, Binet was among the first psychologists to put forward the importance of old memories in new learning. He gives a very clear illustration of the role of “erudition” in the following quote:

“Qu’un ignorant essaye de retenir une partie dont il entend annoncer les coups, quelle que soit la sûreté de sa mémoire, on peut être certain d’avance qu’il n’y parviendra pas (...) C’est précisément parce qu’il ne comprendra pas le sens des coups qu’il aura tant de peine à les retenir; il est dans la même situation d’esprit qu’un illettré qui voudrait se souvenir d’une ligne imprimée, de manière à reproduire fidèlement la lettre qu’il ne comprend pas; pour nous, il suffit de jeter un simple coup d’oeil sur la ligne, et nous retenons toutes les lettres qui la composent. Pourquoi? Parce que nous comprenons le sens des mots: les mots (...) [sont] des signes d’idées visibles pour notre esprit; et la suggestion d’idées qu’ils provoquent sert à les retenir. C’est là un curieux paradoxe de la mémoire; on allège le poids de sa charge en l’augmentant” (Binet, 1894, p. 204)

[English translation:

That an ignorant tries to memorize a game for which he is called all the moves, whatever the security of his memory, one can be certain in advance that he will not succeed (...) It is precisely because he will not understand the meaning of the moves that he will have so much trouble withholding them; he is in the same

situation of mind as an illiterate who would like to remember a printed line, so as to faithfully reproduce the letter he does not understand; for us, it is enough to take a simple glance on the line, and we retain all the letters which compose it. Why? Because we understand the meaning of words: words (...) [are] signs of visible ideas for our mind; and the suggestion of ideas they provoke serves to retain them. This is a curious paradox of memory; you reduce the weight of your load by increasing it.]

Following this consideration, Binet gives multiple examples of famous strategies and techniques, or well-known sequences of moves all referring to great chess players, often named after prestigious battles. Chess masters consistently reported how this makes each game unique, in that it evokes a single “storyline”. **Binet therefore suggests that “erudition” makes the build up of this storyline possible, by the constant matching between the last moves and prior knowledge about the game. As we will further report, this remarkable work from Binet can be considered as a genius intuition on what would become the Levels-Of-Processing framework, developed almost 80 years later** (Craik & Lockhart, 1972). Another key lesson from the series of studies from Binet, not only about chess masters but also about prodigy calculators, is **the attempt towards a taxonomy of learning and memory, e.g. with the suggested distinction between “la mémoire des idées” and “la mémoire des sensations”**. The former would correspond to memory schemas as introduced by Jean Piaget (1923) and popularized by Frederic Bartlett (1932) about 30 years later, or more broadly to semantic memory. The latter would fit with episodic-like memory contents, which can be quite large and impressive in the short run like in prodigy calculators, but rapidly fades away (e.g. Ebbinghaus, 1885).

As a pioneer in the psychology of expertise, Alfred Binet therefore has put forward the richness of the study of expertise in the understanding of learning and memory. This has opened a long experimental tradition, for which more recent findings are highly relevant in showing how existing knowledge and new learning deeply interact.

The most famous study in the field again used the chess game as a method, but focusing on short-term rather than long-term memory, like in the Binet’s reports. The authors (Chase & Simon, 1973a) replicated earlier findings from De Groot, (1978) when contrasting short-term memory performance for chess positions from chess masters vs.

novices. The participants had 5 seconds to memorize chess positions on a chessboard. Then, an immediate recall test asked subjects to reconstruct as fast and as accurately as possible the chessboard as it was displayed at study. Two main types of chess positions were used: first, game positions were recorded from chess books and magazine; second, random positions were generated by randomly replacing the pieces on the board from their original positions in real games. Chess masters were able to recall four times more positions than novice when real games positions were used (i.e. averaged positions recall = 16 vs. 4), while no expertise advantage was found for random games. Moreover, measurements of time intervals between the recall of each piece's position provided an experimental basis for identifying the boundaries of perceptual "chunks", namely ensembles of 3 to 5 positions on the chess that were perceived by chess masters as one information unit. This was taken as **evidence favouring the "chunking" hypothesis to account for the effect of expertise on memory: while short-term memory has the same capacity limits in experts and novices, experts would automatically chunk together meaningful patterns of piece's positions, thus resulting in some kind of compression of the information to be held in short-term memory.** Support for this view came from the findings that 1) estimates of chunks size was larger in chess masters than novices; 2) the number of chunks was higher in experts; and 3) when considering the number and the size of chunks given the number of pieces accurately recalled by experts, the overall quantity of information held in short-term memory did not exceed the memory span (Chase & Simon, 1973a; Miller, 1956).

Thus, convergent findings provided experimental evidence for the beneficial role of accumulated prior knowledge (Binet would have say "erudition") on new learning and memory. Importantly, these studies started to outline how expertise might lead to better memory. First, superior memory abilities are not responsible for the effect, given that experts behave like novice when asked to learn random chess positions. Second, short-term memory capacities do not differ due to expertise, rather the format of the chess board representation may differ, with the explicit idea from the title of Chase & Simon's study ("Perception in Chess") that an idiosyncratic visual perception, or encoding, of the chess board discriminates experts from novice. Here, the memory advantage would therefore result from the interaction between prior knowledge and visual encoding. The regularities of similar pieces' positions patterns across thousands of games played by chess masters are hypothesized to automatically bias new chessboards perception

towards the identification of pre-existing patterns. These patterns are considered “meaningful”, as earlier proposed by Alfred Binet, because it is implicitly assumed that experts can identify - i.e. recognize - their prior occurrence across past games. In other words, a large amount of prior domain-specific knowledge (here, chess game knowledge) would lead to the detection of prior occurrences, making the memoranda more meaningful, more likely than a small amount of prior knowledge. In turn, this knowledge from long-term memory could provide the basis for circumventing the limits of short-term memory capacity during new learning, through the process of chunking (De Groot, 1978; Gobet et al., 2001; Miller, George, 1956).

This account for the benefits of pre-existing long-term memories on subsequent learning (known as the “chunking theory”) illustrates how the psychology of expertise has informed us on the physiological relationships between knowing and remembering in the service of normal learning. However, a critical point in Chase and Simon’s views is that during new learning, once information is encoded as chunks, it is stored in short-term memory. More recent studies actually suggest that this may not be the case, and that long-term memory storage should host these chunks instead. According to this view, the immediate recall task developed by de Groot (1946/65) would therefore involve not only short-term, or working memory, but also long-term memory processes in experts. By contrast, the same task in novices would mainly tap on working memory alone. Moreover, the idea of linear relationships between the amount of chunks available from long-term memory and new learning performance has also been disproved, as we further below.

IV.3. The limits of the chunking theory

The original chunking theory as developed by Chase and Simon (1973b) makes the assumptions that information encoded as a chunk is stored in short-term, or working memory, thus explaining how chess masters can recall four times more positions than novice in their immediate recall task. Given the acknowledged temporary nature of storage in working memory, this implies that any interfering task right before recall, preventing the subject from active maintenance and rehearsal, should yield a drop in experts’ memory later on. To take only the example of the chess game, such experiments

have been performed and results disproved this aspect of the chunk theory: only a marginal performance drop in recall was observed (Charness, 1976; see also Glanzer, Dorfman & Kaplan, 1981; Glanzer, Fisher & Dorfman, 1984 for similar findings with different materials). Further evidence showing that chess masters can remember two chess positions with similar accuracy as they can recall one again speaks for the mandatory involvement of long-term memory (Cooke, Atlas, Lane & Berger, 1993). These findings were interpreted as reflecting **the involvement of long-term memory storage in the exceptional memory performance of experts** (Ericsson & Kintsch, 1995; Gobet, 2000; Gobet & Simon, 1996a).

As mentioned above, a straightforward prediction from the chunking theory is that the more chunks - or prior knowledge - is available from long-term memory, the more one should store chunks within short-term memory by reference to the actual perception, during a learning task for example. Put simply, more chunks, more memory for the domain-specific memoranda. This represents a big challenge since computer simulations have led to estimates ranging from 10,000 to 300,000 chunks stored in long-term memory to achieve a chess master level (Simon & Gilmarin, 1973; Gobet & Simon, 2000). It becomes hard, therefore, to understand how short-term memory and its limited capacity could on its own host the complex combinatorial computations required for, say, playing 6 chess games blindfolded. Moreover, a review of chess board memory experiments revealed that even for random positions, experts kept some superiority over novice players (Gobet & Simon, 1996b), again suggesting that short-term memory capacity optimization through chunking may not suffice to account for the effect.

Moreover, the organization of the individual elements of information within a chunk has remained elusive. In the example of the chess game, Chase and Simon (1973b) have acknowledged that chunks in chess masters may hold together by “more abstract relations” than the observed bindings based on mutual defense, proximity, attack or pieces’ colors and types (p. 80).

Interestingly, earliest attempts to characterize the organization of knowledge are contemporary of the chess’s studies. For example, individual conceptual nodes, inter-related according to distinct properties, would form a hierarchical network as proposed by Collins & Quillian (1969).

Moreover, beyond the domain of chess game, several studies using the expert-novice paradigm have **confirmed the superiority of experts for the acquisition of new memories regarding their expertise domain, across a wide range of domains:** baseball, soccer, american football, dinosaurs, famous films sagas, cars, music, odors, etc. and even...beer! (Allard, Grahams & Paarsalu, 1980; Frey & Adesman, 1976; Herzmann & Curran, 2011; Long & Prat, 2002; McKeithen, Reitman, Rueter, & Hirtle, 1981; Schneider, Körkel, & Weinert, 1990; Spilich, Vesonder, Chiesi, & Voss, 1979). **It seems unlikely that such a variety of expertise domains fit with the chunking theory,** for at least one simple reason, namely that learning e.g. new dinosaurs would hardly benefit from prior “chunk”-like knowledge stored in long-term memory. While chunking is a plausible hypothesis for domains of knowledge highly dependent on serial learning, like typically in the chess game or, to some extent, in musical expertise, where time and space are prominent features of the memoranda, one hardly sees how it could be the case for beer expertise.

Here, subsequent investigations have focused on the organizational structure of prior knowledge rather than the amount of prior knowledge available to experts. For example, in a quite unusual case study, the organizational structure of knowledge about dinosaurs was assessed in a 4-years old boy (Chi & Koeske, 1983), thus contrasting two sets of 20 items based on the mother’s rating of her son’s knowledge and on their frequency of occurrence in the child’s book. The authors then compared the two semantic networks mappings (maps derived from spreading activations models, i.e. Collins & Loftus, (1975) on a series of independent criteria used to estimate the respective structures of knowledge. The main result was that the internal “cohesiveness” accurately differentiated these mappings and also discriminated memory performance one year later, when the boy was asked to recognize and name the dinosaurs presented (accuracy was 10% vs. 55%, for low- vs. high-cohesiveness sets, respectively). **At variance with the chunking hypothesis, such findings** (see also e.g. Gobbo & Chi, 1986) **suggest that the influence of prior knowledge on subsequent learning and memory is not a simple function of the amount of knowledge available, but also depends on the organizational structure of prior knowledge.**

Subsequent studies have also put forward **the importance of a particular kind of prior knowledge** corresponding, in the case of chess, to “abstract description of a chess position based on tactical and strategic considerations” (Cooke et al., 1993). This kind of knowledge, referred to as “high-level knowledge” (Frey & Adesman, 1976; Goldin, 1978),

actually corresponds to conceptual knowledge. It contrasts with the perceptual knowledge assumed to underlie chunks: in the original chunk theory as well as in more recent accounts like the template theory (Gobet & Simon, 1996b), chunks are presumably stored in long-term memory as spatial patterns of pieces' positions resulting from their regularity of occurrence across thousands of games. Such knowledge does not involve conceptual processing, instead being dependent on repeated perceptual processing only.

Yet, it has been shown that when instructed to encode chess positions at a superficial level, which presumably constrains players to rely only on perceptual chunks, their memory advantage at recall over novices is eliminated (Lane & Robertson, 1979). **Thus, not only perceptual chunks but also meaningful encoding should be involved in the expertise effect on memory, and one candidate for understanding what makes encoding "meaningful" is the hypothesis of "high-level knowledge", i.e. conceptual or semantic knowledge associated with the domain of expertise.**

To test this idea, an elegant experiment asked chess experts to learn and recall chess positions, but they were provided with a verbal description of the chess position (corresponding to the high-level knowledge specific to this game, e.g. "Sicilian-Dragon with opposite-side castling; White is attacking the kingside, Black the Queenside") either before or after the study phase (Cooke et al., 1993). Moreover, the chess position was displayed gradually, by revealing during 5 seconds subsets of 4 pieces randomly picked up from the whole chessboard. Then each subset was erased and replaced by the following set. This procedure allowed to greatly minimizing the use of perceptual chunks, due to gradual exposition of random positions, which were unlikely to yield pattern recognition. The authors further reasoned that if high-level knowledge retrieval is involved early in the perception and encoding of the chess board, then the condition where the verbal description is presented before study should benefit further recall more than when it is presented post-study.

The results fitted these expectations, providing the first direct evidence that conceptual (i.e. semantic) knowledge retrieved from long-term memory at encoding contributes the expertise effect. A recent study (Lane & Chang, 2018) further confirmed this idea by showing a strong correlation between chess high-level knowledge and chess positions memory, and especially finding that even after controlling for chess experience (the main factor underlying the number of perceptual chunks available), chess knowledge accounted for 16% of the between-subjects variance of memory scores.

To sum up, while the chunking theory partly accounts for the effect of expertise on memory, evidence supports the idea that chunking benefits arise from long-term memory effects. **Prior knowledge retrieved from long-term memory seems to fasten new long-term memory encoding, beyond short-term memory effects.** Moreover, the amount of prior knowledge is not the sole factor playing a role, since the organizational structure of knowledge has proven critical, as well as its nature: not only perceptual, but conceptual knowledge is required to fully account for the superior memory of experts.

IV.4. Does prior knowledge associated with expertise alter perception or memory?

As mentioned above, the range of domain-specific knowledge giving rise to superior memory for these domains is impressive. To give just a few examples, baseball experts recall more information than novices from baseball texts (Spilich et al., 1979); texts narratives about soccer were better remembered and better understood by third-to-seventh graders children when they were experts in soccer knowledge, independently of their overall verbal aptitudes (Schneider et al., 1989); patients' case informations that are relevant for the reasoning leading to their diagnosis are better remembered by experts than novice physicians (Hassebrock, Johnson, Bullemer, Fox, & Moller, 1993); map reading experts display superior memory for topographic, but not planimetric, map information (Gilhooly, Wood, Kinnear, & Green, 1988), etc. (see Vicente & Wang, 1998, for an exhaustive list of 51 studies highlighting the expertise effect across 19 distinct domains). Thus, beyond the prototypical case of chess game in experimental psychology, some common factors should account for this effect.

While the chunking theory and its more recent instantiations have placed the emphasis on early effects on memory encoding, an alternative could be that experts may present with distinct early perceptual processes. In fact, it is acknowledged from experts / novices studies that early perceptual processing is affected by the degree of past experiences, and thus, prior knowledge. For example, the entry-level shift designates the fact that experts show a faster and more automatic identification of entities at the subordinate level when it belongs to their domain of expertise. Typically, if a novice has to name the picture of a robin under time constraints, the response will be a basic level name (i.e. "bird", see Rosch, Mervis, Gray, Johnson, & Boyes-Braem, 1976), however an

ornithologist will more likely answer “robin”, illustrating the so-called “entry-level shift” (Tanaka & Taylor, 1991). This shift is related to the acknowledged higher ability of experts in within-category discrimination tasks for their domain of expertise (Goldstone, 1998). For example, expert wine tasters are able to isolate independent perceptual features in wines that non-experts fail to identify (Melcher & Schooler, 1996). Another striking example is provided by Seitz (2017), showing that for non-experts, the discrimination between healthy and unhealthy bone tissue is almost impossible, still it is a critical aptitude developed by radiologists for accurate cancer diagnosis (see *Figure 27*).



Figure 27. Identical x-ray images in a case of bone cancer. Red circles highlight malignant features. Can you differentiate the malignant features from healthy tissue, or even identify these features on the left image? Taken from Seitz, 2017.

Goldstone (1998) has proposed that **two mechanisms involved in perceptual learning are particularly sensitive to expertise, namely *differentiation* and *unitization***. The former refers to the ability to discriminate similar percepts (see *Figure 27*) while the latter designates the integration of individual elements within a functional whole. Regarding unitization, the most famous example is probably holistic processing. In the case of familiar faces perception, inverting the face (presenting the face upside-down) leads to substantial loss in speed and accuracy, but this “inversion effect” does not occur for other objects (Tanaka & Gauthier, 1997; Rossion, 2008). Interestingly however, the inversion effect is found for highly practiced stimuli like in the case of visual expertise for a specific domain. A highly cited study showed that dog experts presented with a large

inversion cost for dog breed recognition, while inversion had no effect on recognition in novices (Diamond, Carey, Wilson, Whitaker, & Moses, 1986).

Regarding discrimination, some studies have started to investigate how prior knowledge may be beneficial for basic visual processes. For example, when objects for which we are experts are displayed in a visual scene, we may be able to scan a greater part of our visual field per eye fixation, resulting in expertise effects on the detection of favoured objects (Hershler & Hochstein, 2009). Moreover, when perceiving familiar objects, top-down processes can modify the physiological correlates of visual perception (ERPs) as early as 120 ms. post stimulus onset, which in turn has been shown to facilitate discrimination and recognition memory (Rahman & Sommer, 2008). **Very recent evidence has strongly supported a broader influence of semantic knowledge in early visual processing**, within a strikingly similar time windows (120 ms, see (Samaha, Boutonnet, Postle, & Lupyan, 2018).

In summary, **consistent evidence favours the influence of prior knowledge gathered through expertise on perceptual processes. Perceptual learning mechanisms, and especially differentiation and unitization, are optimized following extensive training, and very early stages of visual processing display expertise effects.** This optimization however remains specific to the objects belonging to the domain of expertise, in close relation with a large amount of conceptual knowledge in the field. As the perceptual optimization does not extend to other objects, memory enhancement resulting for expertise accordingly does not extend to memory for other, unrelated, memoranda (e.g. Evans et al., 2011, for a very convincing example). **One must therefore keep in mind that the learning advantage for items with prior knowledge may, at least partly, have resulted in differential perceptual processing in experts and novice, or for favoured vs. “normal” objects. Any experimental attempt to study the impact of prior knowledge on subsequent declarative learning should thus consider experimental designs that allow equalizing perceptual effects across prior knowledge conditions.** One way to achieve this, as we will further develop, is to use stimuli for which virtually all subjects have a high level of expertise, but that can – or not – lack prior knowledge. With that respect, human faces are obvious candidates.

IV.5. Does prior knowledge associated with expertise benefit memory independently of the testing format?

Literature on expertise has therefore showed that prior knowledge of multiple forms supports encoding processes, certainly facilitating elaborative encoding, and thus improving declarative learning within the domain of expertise. Another issue is whether expertise also alters how memory content is further retrieved. This has long remained unclear: numerous **reports with superior recall for the domain-specific materials of experts** (Anderson, 1981; Anderson & Pichert, 1978; Bower, Black, & Turner, 1979; Fass & Schumacher, 1981; Johnson & Kieras, 1983; Schneider et al., 1990; Spilich et al., 1979; Sulin & Dooling, 1974), **contrasted with either small or even absent benefits of expertise on recognition memory** (Alba & Hasher, 1983; Alba, Alexander, Hasher, & Caniglia, 1981; Moravcsik & Kintsch, 1993; Schneider et al., 1990; Summers, Horton, & Diehl, 1985). Such dissociation across studies could reflect a specific influence of expertise on recollection, while familiarity could remain unaffected. Indirect evidence for this idea is available across more recent studies that have confirmed the benefits of expertise on recognition memory, and under which conditions it could occur.

For example, it was shown that beer experts were better than novices in recognition memory for the beers tested, but not for beers discrimination (Valentin, Chollet, Beal, & Patris, 2007). This suggests that long-term-related memory processes, rather than fine-tuned perceptual processes, supported the expertise benefit. Moreover, the effect was tightly associated with expertise in that it was observed only for highly familiar beers, for which experts had been familiarized during their formal training, but not for unfamiliar ones. Here, a possibility raised by the skilled-memory theory from Chase & Ericsson (1981) is that experts may have built knowledge structures helping them to identify the discriminant features among different beers. Other authors have proposed that wine experts, for example, may form structures based on grapes varieties (Hughson, 2003), a somehow similar idea with the proposal that chess experts may build abstract relationships between prototypical patterns, further scaffolding long-term encoding and retrieval (Chase & Simon, 1973b). Recall would be greatly facilitated if these structures were identified at study, and available as retrieval cues (e.g. see the Constraint Attunement Hypothesis, Vicente & Wang, 1998). Convincing evidence for this hypothesis

has long been reported with baseball experts, whose recall of baseball texts was more accurate than novices, especially considering text's proposals that are highly related to the structure of a baseball's game (Spilich et al., 1979; see Schneider et al., 1990 for similar findings with soccer experts). Thus, experts' memory could be supported at retrieval by the availability of domain-specific structures of knowledge serving as additional retrieval cues.

Similar data from an elegant study emphasizes how retrieval processes involved in the expertise advantage may rely upon mental structures or "schemas" (Piaget, 1929; Bartlett, 1932) closely and uniquely associated with the domain considered. Eight taxi drivers from Helsinki and eight Helsinki's students serving as controls had to learn lists of streets names from the Finland capital. Taxi drivers proved better than students, but the effect was particularly large when the list order was congruent with the natural spatial constraints of the city (Kalakoski & Saariluoma, 2001). Even more convincing, the performance of taxi drivers seemed to linearly increase with the increase between the order of street names displayed at study and the realistic routes that could be driven (Expt. 1, see figure 1). These results converge in suggesting that superior memory retrieval for the domain of expertise can take the form of associative retrieval, namely of bound items and contexts, which is highly suggestive of recollection-like processes. Such results in recognition memory would however be dependent on the experts' ability to rely not only on their domain-specific knowledge, but also on the activation of relevant structures of knowledge at study, which may serve as additional retrieval cues at test.

In support of this idea, (Kawamura, Suzuki, & Morikawa, 2007) asked expert hikers and novice hikers from the Osaka area (Japan) to learn hiking trail pictures with high- or low-functionality features. Functionality referred to the presence of particular scene attributes implying specific actions (like crossing, wading, resting, climbing, etc.), which are of particular relevance for confirmed hikers. Strikingly, expert hikers provided more Hits and fewer False Alarms than novice hikers, but only for the "High-functionality" photos (see also Rawson & Van Overschelde, (2008), for similar findings with National Football League experts). **Thus, the recognition memory advantage observed in experts is not related to their better general knowledge of the hiking trails, but more specifically to the availability of knowledge structures** (e.g. detecting a particular feature on a trail pictures activate related knowledge about specific actions to be performed). Again, the

availability and use of these structures could **favour recollection-based rather than familiarity-based recognition memory.**

Nonetheless, due to their long training, experts have been processing the very same objects (be it beers, wine, base-ball, chess games, or whatever domain of expertise) across numerous similar but different contexts. This could lead to the expectation of decreased recollection of the specific context associated with the probe during recognition (e.g. Reder, Donavos, & Erickson, 2002). A common related effect is the mirror effect, whereby low-frequency words yield more Hits and fewer False Alarms than high-frequency words. The Source of Activation Confusion dual-process model theory of recognition (Reder et al., 2000) predicts that due to higher contextual competition for high-frequency words at retrieval, their accurate recognition can only be achieved through familiarity-based retrieval. Translating this to expertise, one could consider that high-frequency words mimic the domain-specific expertise for some class of objects (e.g. beer tastes), and thus recollection would be expected to decrease in experts for materials related to their domain of expertise, because of the large amount of contextual competition.

Studies aiming at explicitly testing whether expertise affects recollection, familiarity, or both retrieval processes are therefore warranted. Unfortunately, they are rather scarce.

In one such study, psychology students who were defined as “Star Trek experts” or novices on the basis of a Star Trek knowledge test were asked to learn either psychology chapters or Star Trek short stories (Long & Prat, 2002). Thus, all participants supposedly shared a common expertise for psychology texts but not for Star Trek stories. Recognition memory was assessed using Remember / Know procedures (Expt. 1) or Process Dissociation Procedure (Expt. 2). In both experiments, Recollection but not Familiarity estimates showed the expected Group X Material interaction. Similarly, car experts were compared with car novices on a recognition memory test for pictures of cars or birds (Herzmann & Curran, 2011). Estimates of recollection and familiarity were based on ROC curve analysis and on an adaptation of the Remember / Know procedure. The authors reported a consistent benefit of expertise on recollection estimates, leaving unaffected the core estimate of familiarity (Independent Remember Know familiarity estimate), but nonetheless benefiting the overall sensitivity measures (ability to

discriminate Old and New stimuli). At retrieval, ERP typically associated with familiarity (FN400) was not influenced by expertise. In the meantime, the electrophysiological correlate of recollection (i.e. parietal Old/New effect around 500 ms post onset) was found for all subjects with birds, and only for car experts for cars. Finally, a recent experiment addressed these issues albeit less directly (Bruett, Fang, Kamaraj, Haley, & Coutanche, 2018). Sport experts and novices were asked to perform an incidental encoding task. At study, they were presented with combinations of unknown faces and a written question. The question was designed to include information related or unrelated to sports expertise (e.g. “Panthers running back” vs “Indiana fire-fighter”). An Old/New judgment for faces was asked after while, and for each “Old” response, subjects were asked to recall as much information as they could that was associated to the face at study (i.e. information included in the question). The results showed similar Old/New accuracy for expert and novices, but the experts recalled more associated information than novices. Not only this study shows that expertise benefits memory even after incidental encoding, but it also implies that associative, but not item memory benefits expertise, extending prior findings with a very different approach. It further adds one instance where the expertise advantage is unlikely to be accounted for by perceptual processes differences.

Taken together, these findings seem to support a specific sensitivity of recollection, not familiarity, to prior knowledge associated with expertise. This might explain why earlier studies sometimes failed to find superior recognition memory in experts, as long as the tasks used only tapped Old/New judgments.

IV.6. Interim summary: contribution of the expert/novice paradigm

Research on experts’ memory has a long history in psychology, and it has now become a domain of investigation in cognitive neurosciences (see Hambrick, Campitelli & Macnamara, 2018 for a recent book on that topic). This domain has put forward some key ideas that continue illuminating the field:

- A critical factor explaining the superior domain-specific memory of experts is not simply the amount of domain-relevant knowledge, but ***rather the congruency between incoming information and the domain-relevant past experiences***. As we

will see in the Chapter VI, congruency with pre-existing schemas has gained considerable interest in contemporary research

- An impressive memory advantage in experts can be due to **chunking processes in short-term memory**, but a large part of the effect lies in **retrieval from long-term memory**
- What is retrieved from long-term memory that helps experts memory correspond to **abstract representations** that we now term **“semantic knowledge”**
- Explicit or incidental retrieval of this knowledge seems to yield a **specific increase in recollection-based recognition memory**, leaving familiarity unaffected

Nonetheless, beyond expertise effect on memory, it is clear that expertise also change early perceptual processing, notably by **improving differentiation** (and, thus, perceptual discrimination abilities) and **unitization** (perception of separated elements as a single entity) in the domain of expertise. Any investigation of the influence of prior knowledge on new learning therefore must take these “early” effects into account.

IV.7. Limits of the Expertise paradigm and plea for using faces as memoranda

While a huge literature with the expert-novice paradigm has shaped our understanding of how past experiences can influence declarative learning, some very basic observations still fall out of the range of the expertise paradigm. A famous example comes from instances of “one-shot learning”, which is a categorization problem usually referred to in the field of computer vision and machine learning algorithms development. Basically, “one-shot learning” corresponds to a durable modification of perception after one single exposure to a stimulus. Some illustrations are provided in *Figure 28* and *Figure 29*.



Figure 28. Once you have seen the cigar hidden in the bricks (A), you will never see this picture the same way. Besides, on a Bayesian perspective, the likelihood of perceiving a cigar among bricks will dramatically increase (i.e. from zero) in your visual system; (B) see the hidden face? Adapted from <https://michaelbach.de/>

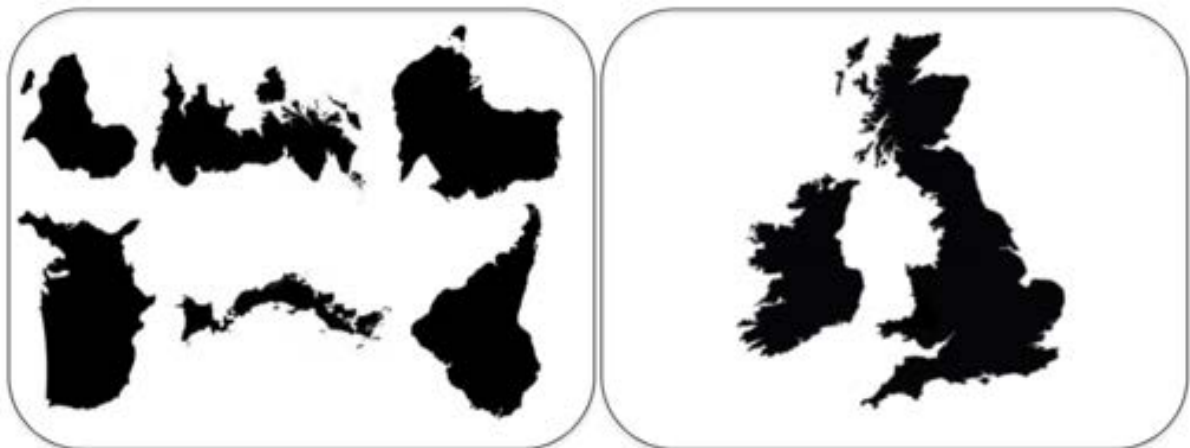


Figure 29. How past experiences influence perception (beyond expertise). On the left picture, very basic geographical knowledge allows to recognizing the United Kingdom and continents like Oceania, albeit quite slowly because of their incongruent presentation with prior knowledge. On the right picture, the very same prior knowledge prevents you from seeing immediately the Queen profile. (Adapted from <https://www.opticalspy.com/opticals/>)

As mentioned before, basic perceptual (e.g. expectations we have about a wall of bricks) or semantic (e.g. memory for the contour of the United Kingdom satellite map) knowledge therefore leads to strong changes in our encoding processes. Such changes are long lasting in the case of one-shot learning, and thus long-term modifications in the behaviour can occur in response to environmental regularities. In that case,

environmental regularities (think of the various and numerous bricks wall you have experienced) produce perceptual and semantic knowledge, and one single change in these regularities (top-down identification of one feature breaking prior expectations) will result in a new behaviour (e.g. always “seeing” the cigar in the wall). This is a clear instance of learning, highly dependent upon prior knowledge, which does not require any expertise. Thus, beyond the field of domain-specific expertise, everyday information processing provides situations where prior knowledge interact with memory encoding, for which the expert-novice paradigm is of little help.

Moreover, **the benefits of expertise on learning result from multiple sources, since expertise is typically associated with specific perceptual, procedural, but also declarative knowledge.** These kinds of knowledge are likely to differentially contribute domain-specific learning improvements, but at various degrees depending on the kind of expertise considered. For example, chess masters may build on their procedural, semantic and schemas-like knowledge to support improved learning of chess games, with little involvement of perceptual skills. Conversely, expert radiologists likely rely on their perceptual expertise to perform highly demanding visual discrimination tasks (see *Figure 27*), and maybe less on semantic knowledge. The expertise paradigm offers little opportunity to disentangle the contribution of each variable, and prevents from generalizing the observed effects to other domains.

Beyond domain-specific expertise, studying how prior knowledge may influence declarative learning may therefore take advantage of natural expertise for some class of stimuli. An obvious example is the case of memory for faces in humans. Because humans are likely to process their peer’s faces with overall similar levels of expertise, more can be expected from paradigms manipulating prior knowledge associated with faces to investigate its impact on learning. Put simply, using stimuli for which we all have the same level of expertise, and then controlling the amount and kind of prior knowledge associated to it, could circumvent the limitations of the expertise paradigm (see also above, section 5.4.).

This is one of the reasons why we have focused on declarative learning of faces across several experiments in the present thesis. In the next chapter, we will further describe available evidence for the influence of prior knowledge associated with expertise in the particular case of faces.

IV.8. Summary

The psychology of expertise has been particularly fruitful in demonstrating that **representations stored in long-term memory**, rather than short-term memory chunking alone, **enable impressive benefits on subsequent learning**. Research has brought evidence that both perceptual and conceptual representations, along with their particular organization in experts, would likely account for superior declarative learning, albeit restricted to the domain of expertise. Beyond the amount of knowledge available from experts' long-term memory, it seems that **successful retrieval during encoding, driven by congruency between sensory inputs and stored conceptual knowledge, may result in enhanced recollection-based memory**, leaving familiarity unaffected. Importantly, not only long-term memory but also early perceptual processes are under influence of prior knowledge resulting from expertise (e.g. leading to increase in both differentiation and unitization). Thus, moving forward to explore the impact of prior knowledge on declarative learning **requires to reducing the variability due to perceptual expertise**. A way to achieve this can be the use of materials for which there is little inter-individual variability in perceptual expertise, like faces.

Chapter V

“Expertise” influences declarative learning: the special case of faces

Beyond the hot recent debate about whether or not we are experts for unfamiliar faces (see Rossion, 2018; Young & Burton, 2018), it is widely acknowledged that as human beings, we are particularly good at recognizing our contemporaries. A recent report estimates that **we know – and recognize – on average 5,000 different faces** (Jenkins, Dowsett, & Burton, 2018). Moreover, **accurate recognition can be performed very fast, probably well below 400 ms** (Barragan-Jason, Besson, Ceccaldi, & Barbeau, 2013). The adaptive advantage of such impressive abilities in humans is obvious: everyday routines involve dense social interactions for most of us, and we need a very efficient system to guide our behaviour when encountering a peer. Recent research in psychiatry has demonstrated the **close relationships between faces learning and recognition on the one hand, and social inhibition and engagement in social interactions on the other hand** (Avery, VanDerKlok, Heckers, & Blackford, 2016; Corbett, Newsom, Key, Qualls, & Edmiston, 2014). In patients with early Alzheimer’s disease, for example, complaints regarding the inability to recognize and name the relatives are very common (e.g. see (Clare, Wilson, Breen, & Hodges, 1999)), thus highlighting the functional relevance of memory for faces.



Figure 30. The special case of faces. Stimuli used in experiments 3a, 3b, 4 & 5.

In keeping with our aim of studying the contribution of prior knowledge to declarative learning, faces are not only interesting because these stimuli allow equalizing levels of perceptual expertise, but also because of its functional and clinical relevance. What does prior studies tell us about the influence of prior knowledge on learning of faces? Studies so far can be divided in two categories. First, a series of experiments have capitalized on own-race or age effects to contrast learning of faces for which we have a superior level of expertise (e.g. faces of people of your own age) vs faces for which our expertise is normal (e.g. faces of distinct ages than yours). Second, many studies have contrasted famous and unknown faces to answer these questions, or similar manipulations meant to contrast novel faces with familiar faces. In both contexts, we would like to draw the reader's attention to the importance of these questions beyond the field of fundamental memory research. In the field of justice, for example, a deep understanding of the mechanisms responsible for eyewitness testimony is clearly mandatory when one considers that since 1989 in the U.S., about 70% of the 300 DNA-based exonerations of wrongfully convicted persons involved eyewitness misidentifications (Wixted, Mickes, Clark, Gronlund, & Roediger, 2015).

V.1. Manipulating the cross-race effects or the own-age bias

The “cross-race effect” (CRE) designates the finding of better recognition performance for own- vs. other-race faces (Chance, & Goldstein, 1996). Similarly, the “own-age bias” (OAB) refers to the finding of better recognition memory for faces of one's own age group than for faces of another age group (Anastasi & Rhodes, 2005; Rhodes & Anastasi, 2012). In either case, one can conveniently consider that the level of expertise for faces ranges from superior (for a cross-race or a different age face) to very superior for own-race and own-age faces. Thus, it seems clear that, even after equalizing the perceptual expertise factors (participants are all face experts, and all faces are unknown), some additional factor makes a difference.

Again here, some studies aimed at identifying whether superior recollection, familiarity, or both would account for the CRE or the OAB. For example, young Hispanic students were asked to learn Hispanic and African-American faces right before a recognition test phase (Marcon, Susa, & Meissner, Christian, 2009). During test, lure faces were repeated

across lags of various lengths, and participants were asked to respond “Old” only to faces presented at study (Expt. 1). The authors reported a mirror effect similar to the one mentioned above with words (see section 5.5.), that is, Hispanic students made more Hits and fewer False Alarms for Hispanic faces than for African-American faces, yielding the expected own-race effect. More interesting was the finding of a superior rate of repetition errors for other- than own-race faces. That is, Hispanic students falsely responded “Old” to repeated lures more often for African-American than Hispanic faces. Repetition errors can be accounted for by either a failure of recollection of prior presentation during the test, or by an increased familiarity incorrectly leading to Old judgments. Thus, the CRE on repetition errors could reflect either a superior recollection for own-race (lure) faces or an increased familiarity for other-race (lure) faces. Experiment 2 addressed these possibilities by using a Process Dissociation Procedure where the exclusion condition required subjects to respond “No” to repeated lures, while the inclusion condition asked for “Yes” responses for repeated lures. Results suggested a clear-cut CRE on recollect estimates, while familiarity estimates did not differ with faces’ races. Note however that Familiarity estimates reported (Table 3, p. 102) were apparently much higher for other- than own-race faces (0.44 vs 0.29), with similar dispersion (0.26 & 0.28, respectively), yielding a p value of 0.09. Thus, one possibility acknowledged by the authors is that prior knowledge based on visual expertise for own-race faces could increase recollection-based recognition, but in the meantime increase familiarity-based recognition memory for other-race faces, thus contributing to the observed CRE. In a similar vein, Horry, Wright, & Tredoux, (2010) combined a Remember / Know / Guess procedure for faces recognition memory with a source memory design, since each face was presented at study within one of four possible scene backgrounds. Again, the authors found consistent evidence for superior recollection estimates for the own-race faces, be it computed from the R/K/G procedure or based on the conditional source memory performance. However, regarding Familiarity, results were less consistent, depending on the metrics used and on the ethnicity of the participants. Accordingly, a very original study found that when faces are presented at study as belonging to either the same or different “personality” group than the subject’s, a same-group effect is observed for both recollection and familiarity estimates during further recognition, favouring the same group (Herzmann & Curran, 2013).

Studies investigating the OAB have reported similar results. Interestingly, one such study have found indirect evidence for increased recollection of own-age vs. other-age faces, but also found that the degree of exposure to same or different age faces modulated the OAB in the elderly. Thus, elderly with frequent contacts with persons of their age did present with an OAB during face recognition, while the effect disappeared, in elderly reporting much less frequent contacts with people of the same age (Wiese, Komes, & Schweinberger, 2012). The same research group has suggested that the lack of OAB in elderly would in fact be the result of impaired recollection with aging, so that recollection-based retrieval would be considered a pre-requisite for the OAB (Wolff, Wiese, & Schweinberger, 2012) (see *Figure 31*), making clearly the case for the influence of prior knowledge for faces on recollection, but failing to rule out a contribution of familiarity.

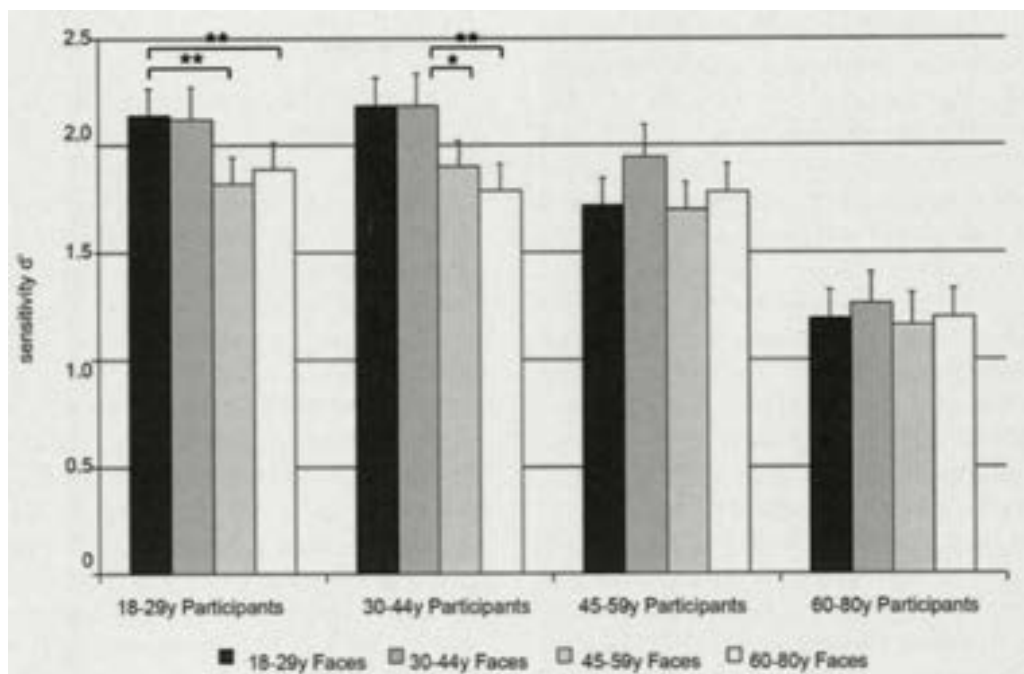


Figure 31. Findings from Wolff et al. (2012, p. 1072). The Own Age Bias in recognition memory is sensitive to aging.

Altogether, these findings point toward a **contribution of prior knowledge that seems to increase recollection-based recognition for faces, while the additional role of familiarity processes remains uncertain.**

V.2. Manipulating the familiarity of faces

Another approach to the same problem is to **directly manipulate the degree of prior knowledge associated with faces**, to further investigate whether and how it affects recognition memory processes. A pioneer study from had already established the superior recognition memory for famous over unknown faces, and provided highly relevant data regarding the cognitive substrates of such advantage (Klatzky & Forrest, 1984). The authors first reported evidence that better recognition for famous over unknown faces was not associated with better memory for the perceptual attributes of each study episode (i.e. faces features). For example, when correctly endorsing an Old famous face as “Old”, participants were not better at deciding whether the face was presented in the same orientation or not by reference to the study phase (Expt. 1). Similar results were found when subjects were questioned on ear or mouth details (Expt. 2). In a third experiment, subjects were explicitly asked to provide a fame judgement plus a category label at study. At test, they were administered a recognition test for labels and for faces. Here, it was observed that famous faces that were not labelled at study were still better recognized than non famous faces. Moreover, unlabelled famous faces were not better recognized than labelled ones. These findings along with earlier classic studies (e.g. Ellis, Shepherd, & Davies, 1979) prepared the grounds for the idea that famous and unknown faces would depend on distinct representations. For the current purposes, the important finding is that superior memory for faces associated with prior knowledge would seem to depend on the formation of an abstract representation of familiar faces distinct from the one for unknown faces, but not necessarily yielding superior recollection at test. In fact, **in showing the absence of fame advantage for memory of physical details, Klatzky & Forrest (1984) results could suggest increased familiarity, rather than recollection.**

Subsequent studies contrasting famous and unknown faces have unambiguously confirmed the superiority of famous faces regarding recognition memory. All of these studies have further investigated whether recollection, familiarity, or both processes would be influenced by faces' status. To do so, a Remember / Know paradigm has always been used (Bellana & Moscovitch, 2019; Liu, Grady, & Moscovitch, 2016; Reder et al., 2013b) but only two have combined this with a source memory design (Liu et al., 2016; Bellana & Moscovitch, 2019). A consistent increase in recollection estimates, but not in

familiarity estimates, was reported for famous faces. Besides, source memory (i.e. memory for faces-scenes or faces-colours associations) also was found more accurate for famous faces.

The story might be more complex, though, **since familiarity for faces does not result from fame only**. Faces of our relatives, for example, or faces of people we just met, also carry levels of familiarity. Is this kind of familiarity also associated with increased recollection?

In the only study contrasting famous faces with personally known faces and unknown faces (Trinkler, King, Doeller, Rugg, & Burgess, 2009), both kinds of faces with pre-experimental knowledge yielded increased recollection and decreased familiarity. However, and importantly, Leveroni et al., (2000) have contrasted famous faces with familiarized faces, that is, initially unknown faces that have been shown prior to the study phases. They found equivalent recognition memory accuracy for both kinds of familiar faces. This would suggest that **prior exposure, rather than knowledge resulting from semantic memory about a celebrity, could drive the effect, thus accounting for the absence of difference between personally known and famous faces** in the Trinkler et al. (2009) study as well. Unfortunately, we could not find research investigating this possibility further, which would involve entirely novel faces, familiarized faces and famous ones. Nonetheless, some studies have contrasted familiarized faces with famous ones, or familiarized faces with unknown ones, within Remember/Know paradigms. One such study remained inconclusive with that respect, because of a floor effect (d' of 0.38 and 0.58 for familiarized and famous faces, respectively). Yet, participants gave more Remember Hits for famous faces (Gimbel, Brewer, & Maril, 2017). Dennis, Turney, Webb, & Overman, (2015) contrasted familiarized faces with unknown ones, and found increased recollection and familiarity estimates for familiarized faces. Finally, when contrasting faces that are personally known to participants with unknown faces, Bird, Davies, Ward, & Burgess, (2011) consistently found increased recollection and familiarity for faces with prior knowledge, be it estimated from ROC curve or Remember / Know methods. This contrasted with the decreased familiarity observed for personally known vs. unknown faces in Trinkler et al. (2009, Fig. 2, p. 722).

Noteworthy, **much of these studies have used the Remember / Know paradigm, which has been put to question on several grounds**. Shortly, the assumption of independency between R and K answers has been strongly criticized (Dunn, 2004, 2008), which qualifies

the straightforward interpretations in terms of recollection vs. familiarity (see also Wais, Mickes, & Wixted, 2008). Moreover, findings of better source memory for items with pre-experimental knowledge are at odds with the report of increased recollection and familiarity based on ROCs analysis. Regarding source memory tasks, it has been suggested that **any variable known to affect item memory also affects item-context binding in long-term memory, namely source memory (Glanzer, Hilford, & Kim, 2004).** Among the variables tested, the authors showed that an encoding task focusing on the meaning of the stimuli rather than its physical features (i.e. deep vs shallow encoding) equally affects item and source memories. In other words, from a theoretical perspective, prior knowledge should yield increased recollection and familiarity rather than targeting one specific retrieval process. One possible explanation for this apparent contradiction could lie in the **distinct retrieval demands placed on recognition memory for familiar vs. unknown faces.** When making an Old/New judgment for a famous face, one must discriminate between past occurrences of this face outside the experimental setting and the recent occurrence of the face, during the experimental study phase. Facing unknown faces at test, such discrimination is no longer required, and unknown lure faces can be accurately rejected on the basis of the absence of familiarity. Correct rejection of a famous lure face cannot be achieved on the same basis. Thus, recognition of famous faces among famous foils is more biased toward recollection processes than is recognition of unknown faces among unknown lures. This could account at least partly for the consistent finding of increased recollection, and unchanged familiarity, for familiar faces. Experiments 3a & 3b in this thesis tried to circumvent these issues by contrasting familiarized faces with famous faces, and by using a source memory paradigm allowing to equalizing the retrieval demands at test.

To the best of our knowledge, so far only one theoretical account has been proposed for the finding of better recollection, not familiarity, for famous faces. (Reder et al., 2013) suggested that items with pre-existing representations at study would be less demanding in terms of working memory resources, thus being easier to bind with their context. Although this could explain some of the data, it remains unclear why both subjective recollection and familiarity (e.g. estimates from R/K tasks or ROC analysis of confidence ratings) can, on some occasions, be affected by prior knowledge.

Moreover, while the literature has mainly focused on retrieval processes, little is known on other potential targets processes for prior knowledge. For example, modifications of

short-term memory encoding due to prior knowledge has been highlighted (Curby, Glazek, & Gauthier, 2009; Jackson & Raymond, 2008).

Finally, **how and whether prior knowledge influences on learning are affected by aging remains largely uncovered**. This is rather surprising, given that elderly have accumulated a lot of knowledge of various types, and given that they keep a largely intact access to it, thus making of prior knowledge a potential compensatory candidate for the adverse effects of age on episodic learning (Umanath & March, 2014). Here, what we know is that recognition for personally known faces is impressively efficient in healthy aging (Bahrick, Hall, & Da Costa, 2008), which fits with prior findings of better performance for dated rather than contemporary famous faces (Bäckman & Herlitz, 1990; Lipinska, Backman, & Herlitz, 1992). This is remarkable since several studies have reported that elderly perform poorly in face recognition memory tests when compared with youngest subjects (Bartlett, Leslie, Tubbs, & Fulton, 1989; Boutet & Faubert, 2006; Crook & Larrabee, 1992; Smith & Winograd, 2006). Only one recent study successfully demonstrated that increased *congruency* with prior knowledge for face-name associations resulted in better memory for the association both in young and old subjects, with elderly subjects being more susceptible to the effect than their younger controls (Badham & Maylor, 2015). This added to **emerging evidence** from the same lab suggesting **that associative memory in elderly could disproportionately benefit from prior knowledge effect, in the form of congruent or high relatedness between words in word-pairs paradigms** (Badham, Hay, Foxon, Kaur, & Maylor, 2015). Predictions regarding the role of prior knowledge on further recognition derived from the models of recognition memory presented in the section 1.8 consistently put forward the role of the hippocampus, while sometimes acknowledging a possible parahippocampal learning pathway when relevant prior knowledge is present at encoding. Now, **given that aging typically yields decreases in hippocampal volumes** (see for review Raz & Rodrigue, 2006; Ries et al., 2008), **while leaving the parahippocampal gyrus much less affected** (and especially the perirhinal cortex, see Insausti et al., 1998), **a better understanding of how prior knowledge modulates memory formation in aging is therefore of utmost importance**. This is the core issue that we will address in Experiments 3a & 3b.

V.3. Summary

Altogether, available evidence therefore shows that **prior knowledge about faces available at encoding**, resulting either from multiple encounters all over the lifetime (like in the case of famous faces), from repeated exposures and real-life interactions (like in the case of personally known faces) or even from experimental familiarization prior to study, is a **powerful learning enhancer**. Although some divergences remain regarding familiarity-based retrieval, consistent findings have revealed the involvement of enhanced recollection-based processes. Thus, **prior knowledge may improve item declarative learning, but also item-context associative learning, although consistent evidence is still lacking**. The underlying cognitive substrates are largely unknown, but could involve differences in working memory resources, which might be under-recruited in the case of familiar faces, thus freeing up attentional resources for binding faces to their encoding context. We also **largely ignore whether this applies similarly in aging**, which is a striking gap in our knowledge since there is evidence pointing towards pre-existing knowledge as disproportionately enhancing memory in the elderly, and given the importance of memory for faces in social interactions.

Chapter VI

Neurocognitive accounts for the benefits of prior knowledge: advances and pitfalls

How do we understand the influence of prior knowledge on new learning? How do we account for the semantic-episodic interactions during learning? Is the structural approach to memory (i.e. multiple memory stores) favoured to account for these effects?

Below we review the most influential theoretical frameworks that are relevant to address these issues.

VI.1. The levels-of-processing framework

The basic ideas behind the levels-of-processing framework have come in sharp contrast with the structuralist view of learning and memory. Instead of considering that memory stores with distinct properties would determine the fate of our experiences, this framework suggested that sensory inputs are processed at different levels of a cognitive hierarchy. The resulting memory trace can therefore be thought of “simply as a record of those analysis that had been carried out primarily for the purposes of perception and comprehension” (Lockhart & Craik, 1990). This trace is assumed to be strengthened and thus more durable following “deeper” or semantic processing (that is, higher levels of processing in the cognitive hierarchy) than following “shallower” processing.

Interestingly, the observation that everyday cognition can be considered as relying on either perceptual or conceptual processing, and that experimental manipulation of the study orienting tasks towards either perceptual or conceptual processing yielded robust effects on subsequent remembering is a strong ground for this framework. Put simply, our natural cognitive processing of unfolding daily experiences seemed to result in a low (perceptual, shallow processing) or high (conceptual, deep processing) probability of memory formation. This observation matched apparently with the common sense in that not all of our experiences turn into long-term memories, but that events that are meaningful to us are more likely to do so. Further theoretical frameworks of e.g.

autobiographical memory have also put forward this idea in suggesting that only self-relevant memory processing may result in later conscious remembering (Conway, 2009).

The concept of “depth” of processing however needed refinements to accurately derive predictions from the levels-of-processing (LOP) framework, which states that the durability of a memory trace is a positive function of depth of processing (Craik & Lockhart, 1972; Craik & Tulving, 1975). The original formulation of the framework distinguished depth from elaboration, and further theoretical proposals have introduced key aspects of these concepts to understand how deeper processing might result in better retention.

First, **elaboration** was introduced to explain that, across multiple experiments when the orienting task at encoding took the form of “Yes/No” questions (i.e. for the item “BRUSH”: “Is the word print in small case?” or “Is the word something used for cleaning?”), participants showed better retention after “Yes” answers, whatever the “depth” of processing induced (Craik & Tulving, 1975). The interpretation of this finding was that when a statement is compatible with the item, it benefits encoding by virtue of the activation of multiple associated representations that in fact are congruent with the stimulus. This cannot be the case for “No” responses, i.e. in the case of “BRUSH”, the question “Does the word rhyme with cotton?” cannot trigger beneficial retrieval for further encoding of “BRUSH”. Elaboration can thus be considered as an enriching process – relying on retrieval – that benefits the memory trace. Noteworthy, in the example of Craik & Tulving (1975) experiments, beneficial elaboration is supposed to occur when the context (i.e. orienting question) and the memoranda (i.e. the target word) are in fact *congruent*. To some extent, the concept of elaboration is therefore closely related to the *congruency effect*, which is known to improve episodic memory formation (Maril et al., 2011; Schulman, 1974; Bernhard P. Staresina, Gray, & Davachi, 2009). In summary, one dimension behind the concept of processing “depth” is that information processed within a context that is congruent with prior knowledge associated with the memoranda will trigger beneficial retrieval processes resulting in enrichment of the memory trace, which in turn is more likely to be recalled. However, elaboration alone leads to the prediction that better retention will be observed after elaborative encoding, irrespectively of the qualitative nature of encoding (i.e. perceptual vs. conceptual encoding), which is not in line with the LOP proposals. In fact, “depth”

encompasses not only the concept of elaboration, but also the concept of “depth” itself that captures the qualitative nature of encoding processes.

Second, “*depth*” of processing itself refers to the basic assumption of a hierarchically organized cognitive system where sensory processing must precedes conceptual processing. Thus, the concept of depth actually corresponds to whether the item has been processed up to a semantic level or simply at a perceptual – sensory level. In fact, depth of processing is here highly related with the notion of distinctiveness, i.e. the deeper an item is processed, the more likely it is that associated prior knowledge has been associated with it, thus making it more distinctive and facilitating subsequent recall provided the presence of an appropriate cue (Bransford et al., 1979; Stein, 1978 cited in Lockhart & Craik, 1990).

Finally, a clear idea of how “elaboration” and “depth” are involved is given in Lockhart & Craik, (1990). Elaboration, as mentioned above, benefits later memory independently of processing depth. So why in the end elaboration of surface features (i.e. colour, texture, etc.) is not as beneficial as elaboration of deeper features (e.g. taxonomic or functional properties) for later memory? Considering distinctiveness, there is no reason why a complex scene picture would be less distinctive than a meaningless pattern of colours. In fact, the reason is that when the incoming stimulus “meets” existing knowledge (schematic knowledge, see below), it will form a unitary representation (i.e. “landscape”), whereas perceptual processing of a meaningless stimulus will result in the representation of unrelated, separated, elements.

The LOP framework thus states that during learning, stimuli processing can generate either shallow or deep encoding, i.e. it can be processed perceptually or conceptually, which will critically result in distinct degrees of distinctiveness. High distinctiveness will result from conceptual processing and thus yield a better encoding precision, along with a higher probability of retention. In the meantime, and regardless of “depth” itself, item – context congruency effects will trigger more or less elaborative encoding. Higher congruency would lead to higher elaborative encoding, thus to a richer memory trace that will be better integrated with existing knowledge and thus better retained.

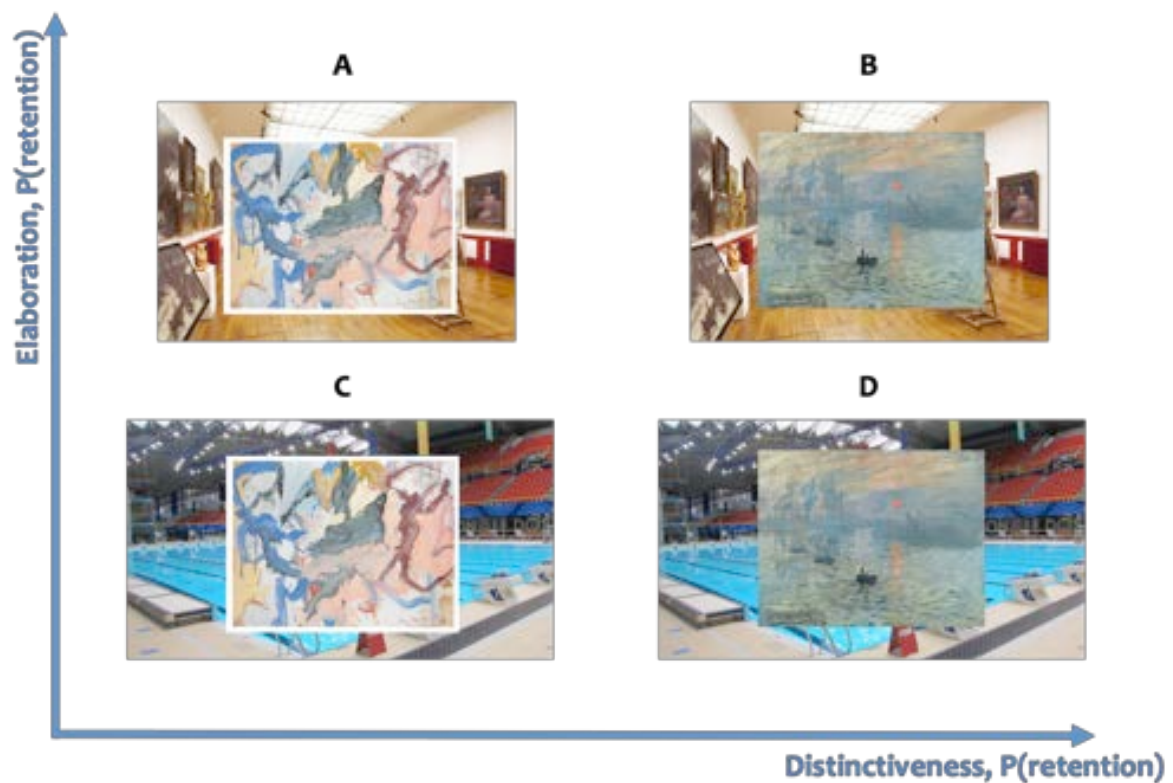


Figure 32. Memory for paintings. Illustration of the LOP framework core predictions. On the left are displayed pictures of a painting from Willem De Kooning from the “landscapes” series. On the right are displayed two pictures of a painting from Claude Monet, “Impression, soleil levant”. The LOP framework states that both distinctiveness (i.e. “depth” per se) and elaboration (i.e. congruency with the context) will determine memory formation. The painting from De Kooning is a meaningless colourful pattern that can yield high elaborative encoding if presented in a congruent (i.e. museum) rather than incongruent (swimming pool) context. However, the Monet painting will be encoded as a more distinctive trace due to its integration with pre-existing knowledge (i.e. it is a harbour landscape), while retaining elaborative processing as well if the context is congruent.

Finally, the framework originally makes no clear prediction regarding whether processing depth should benefit recollection-based, familiarity-based or both recognition processes. The clear prediction is that memory for items should be better (either tested through recall or recognition) following deeper encoding. One can also predict that given the relative independence between elaboration and distinctiveness, task features will be of great matter. For example, in words list learning paradigm using unrelated items, distinctiveness should be the key factor given that context remains constant, and thus helpless. By contrast, in associative memory tasks where item-context congruency is manipulated, both distinctiveness and elaboration will be critical. Finally, given that both recall and recognition are improved after deep encoding, one could speculate that both

familiarity and recollection-based recognition should benefit from higher levels of processing.

Limitations and pitfalls

A strong challenge to the LOP framework has come from studies showing that encoding-retrieval interactions, rather than the type of encoding operations alone, were a critical factor for successful learning. For example, Morris et al., (1977) found that when encoding and retrieval tasks tapped on similar processes, memory was better than in situations where encoding and retrieval tasks recruited distinct processes. Importantly, this pattern was true even when encoding tasks depended on rather “shallow” processing, like the judgment of whether or not a target word rhymed with a cue. Such findings have led to the influential “Transfer-Appropriate-Processing” (TAP) framework, which core assumption is that better retention will be observed to the extent that operations used during test “overlap or recapture the operations used during encoding” (Roediger et al., 2002). Thus, a pitfall of the LOP approach would be to account for within-subject variability in learning by focusing only on levels of processing at encoding. For example, if prior knowledge is manipulated at encoding like explained in the section V.2., i.e. varying the pre-experimental familiarity of faces used as memoranda, the nature of the test will be critical. In the case of recognition, asking subjects to recognize studied famous faces among unstudied famous faces will require source monitoring operations that may have not been present at encoding. By contrast, recognition of studied unknown faces among unstudied unknown faces will not trigger the same operations: familiarity judgments will be sufficient for the task goal. Thus, the interpretation of higher memory for famous faces as reflecting a deeper processing level may be incorrect here, since distinct demands and therefore distinct retrieval operations are placed at test for familiar vs. unknown stimuli (see also Poppenk, Köhler, & Moscovitch, 2010).

Finally, other limitations of the LOP framework is that it does not make explicit prediction on how prior knowledge may specifically impact the processes underlying recognition memory. Moreover, the predictions from the LOP regarding the supporting neural networks are hard to disentangle from other frameworks like the TAP. For example, if following the LOP memories are nothing more than the record of perceptual and / or

conceptual analyses that have been carried out at different levels, then one would expect an overlap between brain areas active at encoding and during test (e.g. Nyberg, 2002), at least for successful test trials. However, the same is expected in the TAP framework as long as encoding and retrieval operations are matched together.

VI.2. The Schema-Linked Interactions between Medial prefrontal and Medial Temporal lobes (SLIMM framework)

The concept of schema has a long story in psychology (Piaget, 1923; Bartlett, 1932) but has been under scrutiny in neurosciences comparatively recently. A schema can be defined as an associative knowledge structure, acquired along multiple episodes, which lacks of unit details and which is flexible (i.e. adaptable enough to integrate new episodes) (Ghosh & Gilboa, 2014). Psychology has long established that these knowledge structures are of great influence in new learning. Since new learning does not occur in a vacuum, our past experiences guide learning. Incoming events can be either congruent or incongruent with existing schema, which may result in distinct memory fates. For example, when learning a text reporting on the biography of a dictator, further recognition memory for the text item will differ depending on whether the text was presented as referring to Adolf Hitler or to a fictitious dictator (Gerald Martin) (Sulin & Dooling, 1974). When presented with recognition foils absent from the text, but highly related to Adolf Hitler (e.g. “He hated Jews”), these foils were much more likely to be accepted (i.e. considered as “Old”) when the passage was introduced as referring to Adolf Hitler than Gerald Martin. Similarly, in a famous series of experiments, Frederic Bartlett (1932) showed that along multiple successive reproductions from memory of an ambiguous stimulus, retrieval was progressively biased towards the most meaningful features identified in the memoranda, at the cost of reporting false memories.



Figure 33. The “portrait d’homme” series from Bartlett (1932), showing that successive reproductions from memory of an ambiguous stimulus increasingly resembles a prototypical face. (Taken from Carbon & Albrecht, 2012)

These pioneer experiments suggested that remembering is a constructive process that builds on pre-experimental knowledge: pre-existing memories, in the form of schemas, would serve as a scaffold for retrieval processes. More recent neuropsychological studies in amnesic patients and patients with semantic dementia have similarly suggested that semantic knowledge may provide a framework facilitating subsequent episodic learning (Greenberg & Verfaellie, 2010; Irish, Piguet, Staniloiu, & Szpunar, 2013). While this “scaffolding hypothesis” explained both the benefits associated with prior knowledge and the shortcomings due to biased retrieval (see also the concepts of accommodation and assimilation in Piaget’s schemata theory, 1926, 1929), further research has shown that schema could also benefit encoding and consolidation processes, not only retrieval (Fernández & Morris, 2018). Moreover, it is acknowledged ever since the 30’s that not only schema-congruent, but also schema incongruent information, may benefit memory formation (e.g. von Restorff, 1933). Finally, more recent research in rodents has showed that schema-congruent consolidation might be accelerated by comparison with schema-incongruent consolidation, revealing a putative fast and hippocampus-independent associative learning pathway (Tse et al., 2007, 2011) that critically involves areas of the medial prefrontal cortex. These considerations led to the proposal of the Schema-Linked Interactions between Medial prefrontal and Medial temporal lobe framework (SLIMM, Van Kesteren et al., 2012).

The SLIMM framework is an extension of the standard consolidation theory that considers how prior knowledge (in the form of semantic, or schematic, stored memories) will affect the formation of new, hippocampal-independent, neocortical representations. The role of the medial prefrontal cortex is to detect whether incoming information (i.e. an event) is congruent with existing knowledge. As a result, two consequences are described in the case of congruency. First, medial prefrontal cortex activity is supposed to increase linearly with congruency, which in turn will strengthen internal connections between existing neocortical representations (and thus, accelerate memory formation). Second, congruency detection and high medial prefrontal cortex activity will inhibit medial temporal lobe activity, thus bypassing its usual involvement in consolidation. In the case of incongruence detection however, mPFC activity is lowered, which reduces its direct influence on neocortical connections and releases its inhibitory influence on the MTL regions. This results in new binding processes that will go through the usual, slower, hippocampo-neocortical dependent, consolidation process.

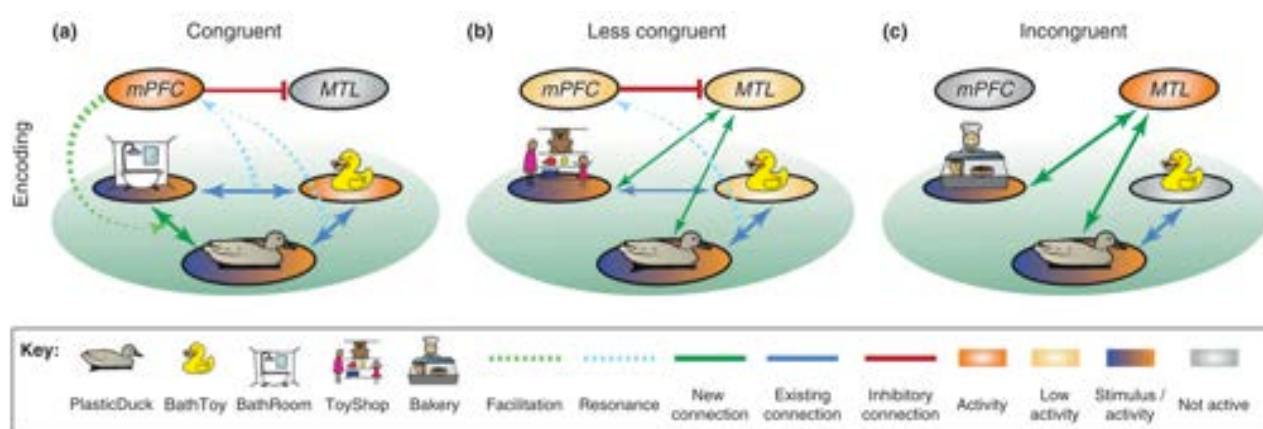


Figure 34. Illustration of the SLIMM framework predictions in the case of a) congruent (vision of a PlasticDuck model in your bathroom), b) less congruent (vision of a PlasticDuck model in a Toyshop), c) incongruent (vision of a PlasticDuck model in a Bakery). In the a) situation, mPFC detects congruency due to the existing knowledge relating your Bath Toy and the context, which strengthens direct connections between the “Bathroom” and “PlasticDuck model” neocortical representations, while inhibiting MTL activity. As a result, the consolidation of the new association “Bathroom” – “PlasticDuck model” is accelerated, with little involvement of the MTL. In the c) situation, incongruence releases mPFC inhibition on the MTL, which in turn binds together the new association “Bakery” and “PlasticDuck model” for further slow consolidation. In the b) situation, both MTL-dependent and mPFC-dependent processes are involved, reflecting the supposedly linear relationship between mPFC activity and congruency.

A strong advantage of the SLIMM framework is that it allows to reconciling theories highlighting novelty detection as a promoter of learning (see below) with theories

putting forward the role of existing knowledge in improving memory formation. This is achieved in the SLIMM theory through the predictive coding models of memory (Friston, 2005; Henson & Gagnepain, 2010). These proposals adopt a Bayesian perspective whereby new efficient learning will depend on a prediction error signal: more prediction error, more encoding. The SLIMM theory suggests that congruency detection supported by the mPFC could be achieved through similar principles. The idea is that the system must update prior expectations if the prediction error is large, so occurs learning. With this in mind, one can consider two apparently opposite situations: you encounter a familiar object in a familiar environment, or you encounter an unknown object in a novel environment. Let's take the example of the face of your favourite singer on stage during a concert, or an unknown individual met in a field maze you visit for the first time. In both situations, the prediction error is supposedly small, because seeing the face of your favourite singer fits prior probabilities given the context of the concert hall; likewise, prior probabilities of seeing an unknown individual in a field maze are rather flat so the prediction error will be similarly small. In both cases, subsequent memory will be unlikely, except if a helpful cue is provided for the famous singer event. So that events entirely novel, or associated with multiple prior knowledge can both result in poor memory. In the meantime, consider you meet your favourite singer in the field maze, now the prediction error is large and the further recall probability is high. This is not due to novelty of familiarity per se, but rather to the prediction error generated by the comparison between priors and actual likelihood of the presence of the specific object (here, your favourite singer). The SLIMM framework can therefore account for increased memory formation for both novel (incongruent) and familiar (congruent) incoming information.

Limitations and pitfalls

Two main limitations arise from that framework. First, the hypothesis of a linear relationship between mPFC activity and congruency can be tested only with a quantitative measure of congruency, which itself relies on a clear definition of a memory schema. While efforts have been made in that direction (Ghosh & Gilboa, 2014; Van Kesteren et al., 2013), a consensual definition has yet to be found (Fernandez & Morris, 2018), and so far much of available evidence has contrasted congruent with incongruent

stimuli (Bein, Reggev, & Maril, 2014; Van Kesteren, Rijpkema, Ruitter, & Fernández, 2010). Accordingly, some studies have used words pair relatedness as a proxy for schema congruency (e.g. Bein et al., 2014) while others have asked subjects to rate subjective congruency (Van Kesteren et al., 2013), making generalization unlikely regarding the role of prior knowledge in new learning. A critical issue here is to conceptually distinguish between semantic and schematic knowledge in future studies. Moreover, while mainly tested with associative memory paradigms and thus often focusing on recollection, the model does not explicitly make predictions regarding whether schema congruency may impact familiarity, recollection, or both recognition processes.

VI.3. The Novelty Encoding Hypothesis

While the LOP & SLIMM frameworks emphasize the beneficial role of prior knowledge in memory formation, the Novelty Encoding Hypothesis, at first sight, pleads for the exact opposite. This hypothesis was grounded on an impressive amount of evidence showing that human behaviour – and, to some extent, animals in general – favours the processing of novel over routine events (for review, see Reggev et al., 2017). Moreover, neurons responding selectively to novelty have consistently been found in animal research (e.g. Gabriel et al., 1988; Rolls, Cahusac, Feigenbaum, & Miyashita, 1993), always located in regions of the extended limbic system. Beyond the obvious adaptive advantage conferred by novelty preference, multiple studies have shown that novelty detection improves memory formation. For example, recognition memory is bettered for rare than frequent words (Glanzer & Adams, 1985; Kinsbourne & George, 1974), and more generally, memory is better for unexpected stimuli (Von Restorff, 1933). Furthermore, stimuli repetition has yielded robust findings of decreased neural signal in the medial temporal lobe and the visual ventral pathway (for review, see Grill-Spector, Henson, & Martin, 2006a; Kumaran & Maguire, 2009), reinforcing the idea that novelty detection is a key factor in memory encoding.

On such grounds was proposed the “Novelty Encoding Hypothesis” (Tulving & Kroll, 1995; Tulving, Markowitsch, Craik, Habib, & Houle, 1996). This theory suggests that novelty assessment of the incoming stimuli would represent the earliest stage of encoding, and that it should be supported by cortical and subcortical structures of the

limbic system, including the hippocampus. These early encoding computations would trigger additional elaborative processes (as proposed in the LOP framework), so that, keeping novelty constant, the probability of subsequent recognition or recall would remain a linear function of processing depth. However, the critical assumption in the model is that novelty detection is necessary to drive further encoding processes. Thus, if the usual orienting tasks are kept constant with respect to depth, memory for novel items will be superior to memory for familiar items.

Limitations and pitfalls

At first sight, such a proposal seems problematic given the widely acknowledged role of repetition in learning, since repeated items should trigger high familiarity and certainly no novelty signals, and thus should not lead to memory encoding in a strong version of the model. We believe that the definition of novelty and familiarity here is the key factor that can reconcile these contradictions. Behavioural evidence for the Novelty encoding hypothesis does not rely on the manipulation of absolute familiarity with the memoranda (like, e.g., pseudo-words vs. words or unknown vs. famous faces), but rather used relative familiarity. That is, what made an item novel was that its probability of occurrence during the study phase was low by comparison with familiar items (e.g. Tulving & Kroll, 1995). Thus, what is manipulated here is the context, rather than the absolute familiarity of the items. Another relevant example is the study conducted by Kishiyama & Yonelinas (2003) investigating the impact of novelty detection on recollection and familiarity. The authors found superior recollection and familiarity estimates (R/K paradigm) for novel vs. non-novel objects. Among 600 objects presented during study, 30 were considered non-novel because they were black thumbnail object images on a white background, while 30 were considered novels because they were coloured. The kind of novelty under scrutiny here is in fact entirely captured by the concept of distinctiveness, and therefore it is hard to generalize the findings to any kind of novelty.

Showing that the retrieval demands placed on recognition memory for “novel” vs. “familiar” items may differ widely has also challenged the Novelty encoding hypothesis. For example, in the Tulving & Kroll’s original study (1995), participants had to discriminate between familiar words those that were in the study phase, and had to avoid acceptance

of words presented in the familiarization phase but not in the studied phase. For novel words however, that were presented only once at study, distractors were words never presented in the experience. Therefore, as pointed out by Poppenk, Köhler, et al., (2010), the “novelty” advantage may well result from distinct discriminative demands at test, being actually unrelated to Novelty or Familiarity per se.

Altogether, the Novelty encoding Hypothesis has proven very influential in the field of neurosciences, but its generalization seems largely insufficient given that:

- only relative novelty is considered, thus ruling out the situations requiring processing of entirely unknown stimuli (e.g. pseudo-words, unknown faces or objects)
- novel and familiar conditions generally trigger different retrieval demands at test, preventing from any interpretation in terms of novelty effect *per se*
- the role of prior knowledge in the novelty assessment process, which is supposed to trigger memory encoding, is not specified despite its unavoidable involvement (i.e. how to conceive a novelty detection process without a comparison space with existing representations? See Kafkas & Montaldi, (2018) for the idea of distinct types of novelty depending on distinct pre-existing representations)

VI.4. The gatekeeper hypothesis

A theory related to the Novelty encoding hypothesis is the “gatekeeper hypothesis” (Fernández & Tendolkar, 2006), which proposes that the rhinal cortices (entorhinal and perirhinal cortices) plays a key role in both encoding and retrieval of declarative memories, based on their novelty or familiarity.

Considering that our encoding capacities per time unit are limited, the authors make the assumption that some operation must optimize learning by allocating our encoding resources towards novel, more than familiar, stimuli. This operation would further integrate both encoding and retrieval processes, because the “gatekeeper” responsible for it would be involved in encoding and familiarity detection.

The gatekeeper hypothesis is grounded on parallel evidence that the rhinal cortices are involved in novelty detection at encoding (Ranganath & Rainer, 2003) and in familiarity-based recognition memory for single items (Wais, 2008). fMRI and ERPs recording literature indeed demonstrate both an increased activity in the rhinal cortices at encoding for items remembered later at test, and conversely a decrease in activity is observed for Old relative to New items during recognition (Kafkas & Montaldi, 2018). These sub-hippocampal cortical areas are therefore well suited to perform both the encoding and retrieval operations required for the “gatekeeper”.

Based on these findings, it is proposed that at encoding, the rhinal cortices are tuned to detect novelty (and familiarity), in the form of an increased activity for novel items, and reduced activity for familiar (or repeated) stimuli. The model states that semantic coding is used to do so, based on the position of the rhinal cortices at the top of the ventral stream. Thus novel (unknown or unfamiliar) stimuli would trigger higher rhinal activity at encoding, which would allow more allocation of encoding resources, resulting in a more “vigorous” long-term encoding. By contrast, familiar stimuli at encoding would yield less activity in the rhinal cortex, limiting the resources devoted to encoding at the rhinal level, but signalling the need for further relational processing to the hippocampus.

The gatekeeper hypothesis thus makes strong predictions regarding the formation of long-term declarative memories. Unfamiliar, or unknown, stimuli generate the highest rhinal activity, which in turn increases the probability of hippocampal encoding. By contrast, familiar, or repeated, stimuli generate reduced rhinal activity, lowering the probability of hippocampal encoding and enhancing the feeling of familiarity. Similarly at retrieval, the rhinal cortices would support familiarity-based recognition for single familiar items, while unfamiliar items would gather additional recollection-based recognition processes dependent on the hippocampus. Importantly, the gatekeeper hypothesis considers that familiarity detection (i.e. a retrieval mechanism) and novelty detection (i.e. an encoding mechanism) are “two sides of the same coin” (see Kafkas & Montaldi, 2014, for a different view).

Limitations and pitfalls

The gatekeeper hypothesis focuses on the candidate mechanism and candidate neural structures that could support the necessary optimization of encoding processes. It therefore proposes a broad Novelty/Familiarity dichotomy but does not account for the role of context in the novelty/familiarity detection. Thus, the model predicts that a familiar item in a familiar context should have the same status than a familiar item in an unknown context, leading to decreased rhinal processing in both cases. However, while the former is quite likely (i.e. familiarity detection of my coffee mug on my office), the latter is not (i.e. familiarity detection of my coffee mug on my boss's office) (for discussion, see Reggev et al., 2017). Moreover, the model does not account for the benefits of prior knowledge in general, nor does it provide explanations for the findings of better memory for schema-congruent information.

VI.5. Are faces special?

Most of the studies underlying the above-cited models have used words, visual scenes, or object pictures as memoranda. However, as already mentioned, one of the oldest and most robust findings in memory literature is the expertise effect. Thus, as we argued in chapters IV & V, going one step further to account for prior knowledge influence on subsequent memory formation requires disentangling the effects due to expertise *per se* from the effects due to pre-existing representations. One way to achieve this goal is to 1/use materials for which there is little inter-individual variability; 2/use materials that allow to contrast stimuli with no prior representations with stimuli carrying various kinds of pre-existing representations. These conditions are not met with words (for which individual expertise cannot be controlled beyond the frequency metrics), nor with objects or scenes, which can hardly lack *any* pre-existing knowledge. One remaining candidate is therefore human faces: we all have similar expertise for faces of our contemporaries, and an unknown face judged truly unknown by a subject cannot carry any pre-experimental knowledge.

So are faces special with respect of prior theoretical accounts for the impact of prior knowledge on learning?

First, we are not aware of any study showing that novel faces are more memorable than familiar faces. Available data always report an advantage for familiar, or famous, faces. This could at first sight rule out the relevance of the novelty encoding hypothesis, and also suggest that the gatekeeper hypothesis does not apply to faces.

Second, albeit the literature is very limited, the nature of prior knowledge seems to be of little matter. Prior studies have shown an advantage for famous or personally known faces over unknown faces, but with no differences between famous and personally familiar faces or recently learned faces (Trinkler et al., 2009; Leveroni 2000). That is, one possibility is that prior exposure is the critical factor, independently of whether pre-experimental conceptual knowledge is available or not. However, this remains to be tested as no prior study directly contrasted novel faces with faces with distinct pre-existing knowledge (see below), and controlling for retrieval demands.

Third, and at variance with domain-general accounts of hippocampal processing, there is considerable neuropsychological evidence that recognition memory for faces is dependent on the hippocampus only when prior knowledge is available at encoding. For example, it has been reported that unknown faces recognition as probed in the Recognition Memory Test (Warrington, 1984) is selectively spared after damage restricted to the hippocampus (Bird & Burgess, 2008; Smith et al., 2014). This test however lacks validity for the assessment of face recognition since it was shown that even after masking all the faces features, 65% of healthy young participants could still score normally (Duchaine & Weidenfeld, 2003). Nonetheless, independent evidence with different faces memoranda appeared to confirm the sparing of unknown face recognition after hippocampal damage (Bird, Shallice, & Cipolotti, 2007; Carlesimo, Fadda, Turriziani, Tomaiuolo, & Caltagirone, 2001; Cipolotti et al., 2006; Smith et al., 2014; Taylor, Henson, & Graham, 2007; for review see Bird, 2017), even if one important remaining issue is whether recollection and familiarity, or only familiarity, is preserved (Aly, Knight, & Yonelinas, 2010; Bird & Burgess, 2008; Bird et al., 2007; Bird, Vargha-Khadem, & Burgess, 2008; Cipolotti et al., 2006). By contrast, recognition memory for famous faces – which, as already mentioned above, is superior to memory for unknown faces in controls – is

impaired after hippocampal damage (Smith et al., 2014). Prior knowledge about faces thus could drive hippocampal-dependent learning, but this remains poorly understood, as are the reasons why familiarity boosts recognition memory for faces.

One possibility suggested by Bird (2017) is related to the ideas of elaborative encoding discussed above (section VI.1.) and discriminative demands at retrieval (section V.2. and VI.3). The author suggests that superior memory for famous faces would result from the activation of related pre-existing knowledge at study, which may provide additional cues for later retrieval. Moreover, given that famous face recognition involves higher discriminative demands than for unknown faces (i.e. “did I see the face during the study phase?” vs. “did I ever see the face?”, respectively), the idea is that famous faces recognition would therefore likely involve relational processing and thus relies on the hippocampus. This proposal is in line with other material-specific views of MTL functioning (e.g. Davachi et al., 2006; Bird et al., 2007; see also Kafkas et al., 2017). It also broadly fits with the proposals that pattern completion is involved in the retrieval of conceptual knowledge associated with a stimulus, especially for across-domain knowledge (e.g. retrieval of the name, occupation, personality traits or usual contexts of occurrence for a famous face), like the BIC model. As long as superior memory for famous faces is thought to rely on associative processes involved both at encoding and during retrieval, and not taking place for unknown faces, then hippocampal processing should be critical.

However, the hypothesis that pre-existing representations for faces would trigger hippocampal-dependent computations for further memory does not fit with all the theoretical accounts presented above. For example, the CLS & the more recent REMERGE computational models, or the SLIMM framework, predict that when the incoming information is congruent with prior knowledge, rapid neocortical learning could take place, bypassing the hippocampal involvement. If correct, the recognition memory advantage of familiar over unknown faces should 1/not depend on the hippocampus and 2/should be more critically depending on congruency with past experiences, thus not only on prior exposures, but on the existence of stored (conceptual) knowledge structures.

Other theoretical accounts put forward the differential involvement of attentional and working memory resources in the processing of famous vs. unknown faces (Reder et al.,

2013a). Similarly, but considering how primed items show a memory advantage over unprimed items, (Gagnepain et al., 2008; Gagnepain et al., 2011) have proposed that primed stimuli during a study phase could free-up attentional resources, that could be reallocated to context processing (in a broad sense: physical background, but also thoughts, feelings, etc.). This would not be the case for unprimed items, for which a learning task requires to focus attentional resources on the stimulus. We believe that this could very well be applied to the familiar / unknown face distinction as well: at study, familiar faces but not unknown faces obviously benefit some priming effect.

Last, we have previously considered the concept of unitization, acknowledging that it could be promoted by pre-existing representations (see section 1.8 & Chapter IV). Several models suggest that unitized representations can be further recognized based on familiarity, with no involvement of the hippocampus. Turning to faces, this would predict that pre-experimental familiarity for faces could promote e.g. face-background unitization, which in turn could support familiarity-based recognition of this association for familiar, but not unknown, faces. Although there is no direct evidence for this to our knowledge, the findings from Reder et al., (2013a) and Liu et al., (2016) are consistent with better face-background associative memory for famous than unknown faces. However, a very recent study found increased recollection but unchanged familiarity for faces-colours combinations when faces were famous (Bellana & Moscovitch, 2019), thus suggesting that either the memory advantage did not result from unitization, or that a unitized memory had been retrieved through recollection processes.

VI.6. Summary

In summary, **several models of memory functioning have in common to consider how existing memories may interact with the on going learning processes.** Strikingly, these models can put forward **novelty** (i.e. absence of prior knowledge), **familiarity** (i.e. presence of prior knowledge) as critical learning enhancers, or **both**. These accounts however do not always provide clear definitions for novelty or familiarity (but see Bastin et al., 2018, regarding novelty), making these issues unclear. In that context, the use of faces as memoranda has brought fascinating insights into how prior knowledge may

influence learning, but leaving us with various and sometimes contradictory accounts. The main disagreements relate to **whether or not conceptual knowledge, rather than simple pre-exposures, is responsible for the effect; whether or not hippocampal-dependent processing is critical for the effect; and whether or not the effect rely on memory-specific processing or may be the result of other cognitive processes like those involved in working memory and selective attention.** Moreover, the extent to which **unitization** can be involved also remains unclear. Finally, we largely **ignore whether aging affects prior knowledge influences** on learning new episodes involving faces, despite the high relevance of such situations for everyday cognition.

Chapter VII

Objectives & Hypotheses

VII.1. Objectives

As a neuropsychologist for about 15 years, questions without answers have accumulated up to the point that this PhD represented an opportunity to simply contributing to the progress in knowledge. My goal was to bring new data for the refinements of the models highlighting that learning does not rely on a sequential and static series of cognitive processes involving distinct separated stores, but rather depends on highly interactive and dynamic processing where the concepts of encoding and retrieval largely overlap, in the service of everyday cognition.

Specifically, the starting point of the present work was the meeting with the patient KA, with developmental amnesia. It became shortly obvious that this patient had some extraordinary features, and especially that his ability to acquire and retain knowledge was in many cases not only fair, but well above expected levels given his condition. Beyond his *exceptional amount of semantic knowledge*, a striking feature was that this patient apparently could *normally acquire and retrieve new context-free memories only for meaningful*, not meaningless, materials. That is, **prior knowledge about the stimuli** seemed to critically drive his residual learning abilities.

Following on from the neuropsychological tradition, we have therefore **pursued two distinct but complementary experimental paths** in this thesis.

First, our objective was to **characterize as best as possible the preserved declarative learning and memory aptitudes** of patient KA. In the meantime, we aimed at gathering **as detailed anatomical information on his brain through cutting edge imaging techniques**, to enlighten which pattern of preserved and impaired learning processes can be observed in a case of developmental amnesia. Beyond the case of KA, our goal here was to *fill a considerable gap in the neuropsychology of human memory, namely the lack of demonstration that normal retrieval and acquisition of explicit memories could occur in*

amnesia. In other words, **are the models predicting the existence of a rapid learning pathway outside the hippocampal system correct?**

Second, following the findings of a material-specific effect in patient KA, our objective was to **test the idea that prior knowledge could play a role in declarative learning**. The second objective was therefore to identify whether novelty, prior exposure, or pre-experimental prior knowledge would be critical learning enhancers, and to gain further understanding of the underlying mechanisms.

VII.2. Hypotheses

We further present two sets of theoretically-driven hypotheses corresponding to the two research paths explored in this thesis: first, the issue of whether rapid explicit learning can occur outside the hippocampal system; second, the question of whether and how pre-existing knowledge at encoding influences learning in declarative memory.

1- Towards evidence for rapid neocortical explicit learning?

We reasoned that if, as speculated ever since the key publication from Vargha-Khadem et al., 1997, extra-hippocampal structures can support new explicit learning, then we should be able to:

- Demonstrate that, in case of virtually no residual episodic memory abilities, reaching a fully normal range of semantic knowledge is possible.
- Demonstrate that, in such case, acquisition and retrieval of explicit memories should be doable in the absence of any dedicated learning techniques or extensive repetitions.
- Demonstrate that no residual functional structures within the hippocampal system could account for the findings.

Moreover, following the processing approach to recognition memory, our hypothesis was that in a case of bilateral hippocampal damage, familiarity-based recognition should be preserved independently of any other variable (e.g. delay, type of materials). Such findings would lend support to the models predicting that non-hippocampal, neocortical pathways can underlie rapid explicit learning.

2- Towards evidence that pre-existing knowledge, not novelty, increases declarative learning?

Considering evidence that stimulus familiarity, rather than novelty, should increase learning; considering the theoretical proposals point towards hippocampus-independent learning pathways for stimuli congruent with existing knowledge, we further hypothesized that:

- Contrasting novelty and familiarity within the same task design should yield an advantage for familiar items in subsequent recognition, and this should apply for item and associative memory. Alternatively, models that put forward the role of novelty detection in long-term memory encoding would predict at least superior item recognition for novel materials.
- Conceptual, but not perceptual knowledge should benefit associative memory. This hypothesis follows from the levels-of-processing framework, putting the emphasis on elaborative semantic processing as yielding a higher likelihood for memory formation.
- The benefits of conceptual prior knowledge on item memory should be age-resistant. Rather than resulting from a specific theoretical framework, this hypothesis stems from emerging findings that elderly subjects may disproportionately benefit from prior knowledge at encoding, but this has never been explored with materials highly relevant to everyday cognition like the face-scene associations that we will use. Alternatively, it could be the case that higher discriminative demands at retrieval for familiar materials may prevent elderly from showing such benefit, due to the weakening of recollection-based processes with age.
- Following predictions from the ReMerge or the SLIMM frameworks, conceptual prior knowledge benefits should be observed at least for item memory even after hippocampal damage.
- Conversely, any condition yielding damage extending to the subhippocampal structures should prevent from benefiting conceptual prior knowledge.

Experimental Section

Experimental Section

Experiment 1: Patient KA, or making the case for normal explicit learning in amnesia

Scientific valorisation

Poster presented at the Memory Mechanisms in Machine & Man workshop, Albi, France, September 2015

Poster presented at the Joint meeting of the British Neuropsychological Society and the Société de Neuropsychologie de Langue Française, London, UK, March 2016

Oral communication, International Conference on Memory (ICOM 6), Budapest, Hungary, July 2016

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Highlights from Experiment 1

The series of experiments with patient KA provide the first evidence of efficient explicit learning despite severe amnesia following damage to the whole extended hippocampal system. The unique contribution of this case report, in our opinion, lies in the following findings:

- Patient KA has reached **normal-to-superior explicit knowledge** in several domains, and can have **access to knowledge about famous faces as fast** – and even faster – than controls.
- This occurred in the context of **close-to-floor recall performance**, while most of the recognition tasks were performed successfully, replicating prior findings in developmental amnesia.
- He was able to **acquire new explicit memories about objects as accurately as controls after one single exposure**, and again showed a normal speed at further retrieval in the context of a very constraining recognition paradigm. That is, **new learning in amnesia can occur without extensive training or dedicated learning techniques**.
- MRI findings in patient KA points towards the **possibility that neocortical structures outside the hippocampus, and especially the anterior parahippocampal gyrus, may have played a role in the preserved acquisition of knowledge**.
- Cortical thickness analyses and full MTL segmentation replicated through different methods brings evidence for **deep structural reorganization** of these structures after neonatal damage.

Importantly, we *do not take these findings as evidence for normal semantic memory vs. impaired episodic memory*, since we did not investigate e.g. the organization of semantic knowledge in KA. Rather, we believe that this case report brings **evidence for the existence of a set of learning processes resulting in new explicit memories that can further guide behaviour, outside the hippocampal system**.

Introduction

The first objective of this thesis was to test whether new explicit learning could occur despite severely compromised memory. The historical debate regarding the distinction between episodic and semantic memory takes its roots in experimental psychology, but the more convincing evidence has come from neuropsychological studies. Perhaps the most important study in the field was the one from Vargha-Khadem et al. (1997) who brought robust evidence that child and teenagers suffering amnesia following neonatal or early bilateral damage to the hippocampus have nonetheless reached low-to-normal levels of semantic knowledge. By contrast, adult-onset cases of amnesia have consistently been reported as unable to acquire new knowledge, or at the cost of very intensive and repeated learning sessions, in the context of dedicated and supervised learning techniques. Despite the huge impact of Vargha-Khadem et al. (1997) study, we ignore how these patients have acquired this fairly preserved level of knowledge. It remains to be shown that new knowledge can be acquired at a normal rate, and retrieved at the same speed as controls, if one is to look for conclusive evidence for independent learning pathways separating knowledge (or “semantic”) from event (or “episodic”) learning. This is the main issue we addressed in the following case study of patient KA, published in the journal *Hippocampus*.

RESEARCH ARTICLE

Superior explicit memory despite severe developmental amnesia: In-depth case study and neural correlates

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Abstract

The acquisition of new semantic memories is sometimes preserved in patients with hippocampal amnesia. Robust evidence for this comes from case reports of developmental amnesia suggesting that low-to-normal levels of semantic knowledge can be achieved despite compromised episodic learning. However, it is unclear whether this relative preservation of semantic memory results from normal acquisition and retrieval or from residual episodic memory, combined with effortful repetition. Furthermore, lesion studies have mainly focused on the hippocampus itself, and have seldom reported the state of structures in the extended hippocampal system. Preserved components of this system may therefore mediate residual episodic abilities, contributing to the apparent semantic preservation. We report an in-depth study of Patient KA, a 27-year-old man who had severe hypoxia at birth, in which we carefully explored his residual episodic learning abilities. We used novel speeded recognition paradigms to assess whether KA could explicitly acquire and retrieve new context-free memories. Despite a pattern of very severe amnesia, with a 44-point discrepancy between his intelligence and memory quotients, KA exhibited normal-to-superior levels of knowledge, even under strict time constraints. He also exhibited normal-to-superior recognition memory for new material, again under strict time constraints. Multinodal neuroimaging revealed an unusual pattern of selective atrophy within each component of the extended hippocampal system, contrasting with the preservation of anterior subhippocampal cortices. A cortical thickness analysis yielded a pattern of thinner but also thicker regional cortices, pointing toward specific temporal lobe reorganization following early injury. We thus report the first case of superior explicit learning and memory in a severe case of amnesia, raising important questions about how such knowledge can be acquired.

KEYWORDS

amnesia, new learning, recognition memory, RRID: SCR_009567, single case study

1 | INTRODUCTION

The formation of long-term declarative memories relies on medial temporal lobe (MTL) structures that include the hippocampus and entorhinal, perirhinal, and parahippocampal cortices. Many studies have demonstrated that the retrieval of facts or general knowledge acquired before the onset of amnesia can be preserved. For example, Patient HM performed normally when asked to retrieve lexical knowledge acquired before the onset of amnesia, across a wide variety of

tasks (Kavinger, Ullman, & Corkin, 2001). However, the question of whether amnesic patients can acquire new knowledge still remains debated.

Patients EP and GP, who both had extensive damage to the whole MTL, were unable to recall or recognize information about famous people or events from the post-onset period (Bayley and Squire, 2005). In the case of Patient EP, intensive repetition of stimuli across 24 learning sessions (controls only required two sessions) failed to yield any evidence of new learning. Even when damage was limited

to the hippocampal formation, five other patients performed at chance level when asked to make living/deceased judgments on famous names (Manns, Hopkins, Squire, & Diego, 2003). When new explicit learning is observed in amnesia, this learning is usually described as being (1) slower than in controls, (2) achieved through extensive, repeated exposure to the to-be-learned material (Stark, Stark, & Gordon, 2005), and (3) the result of dedicated learning techniques such as vanishing cues or errorless learning. These features of new knowledge acquisition in amnesia have led some authors to suggest that this kind of learning cannot be considered as declarative, as it relies upon perceptual learning processes (Bayley & Squire, 2002).

Even so, some researchers have found that patients with adult-onset amnesia can acquire a certain amount of new factual knowledge (e.g., Kitchener, Hodges, & McCarthy, 1998; O'Keefe, Kensinger, & Corkin, 2004; Stark *et al.*, 2005; Tulving, Hayman, & Macdonald, 1991; Van der Linden, Bédard, Depoorter, & Coyette, 1996; Verfaellie, Koseff, & Alexander, 2000; Westmacott & Moscovitch, 2001). More robust evidence for this acquisition has come from patients with developmental amnesia (DA). These patients (e.g., Bindshaedler, Peter-Favre, Maeder, Hirzbrunner, & Clarke, 2011; Brizzolara, Casalini, Montarano, & Postorano, 2002; D'Angelo, Kacolla, Rabin, Rosenbaum, & Ryan, 2015; Gardiner, Brandt, Badddeley, Vargha-Khadem, & Mishkin, 2008; Gulléry-Grand, Martins, Parisot-Carbuocia, & Eustache, 2004; Martins, Gulléry-Grand, Jambaqui, Dulac, & Eustache, 2006; Picard *et al.*, 2013; Vargha-Khadem *et al.*, 1997) consistently exhibit low-to-normal levels of knowledge acquisition. They usually have hippocampal atrophy but relatively preserved subhippocampal structures, leading to the suggestion that these structures support the acquisition of new context-free knowledge, such as vocabulary, concepts, semantic facts, and familiarity (i.e., whether stimuli have previously been encountered) (Mishkin, Vargha-Khadem, & Gadian, 1998). However, interpreting these findings as evidence for preserved semantic learning must be undertaken cautiously, for three main reasons.

First, the conclusion of preserved semantic learning is usually based on the results of tests measuring academic achievement or general knowledge, such as the Information, Vocabulary and Comprehension subtests of the Wechsler Adult Intelligence Scale (WAIS; Bindshaedler *et al.*, 2011; Brizzolara *et al.*, 2002; D'Angelo, Rosenbaum, & Ryan, 2016; Gadian *et al.*, 2001; Martins *et al.*, 2006; Picard *et al.*, 2013; Rosenbaum *et al.*, 2011; Vargha-Khadem *et al.*, 1997, 2003). It should be noted that more thorough assessments of semantic knowledge always elicit performances in the low-to-normal range (Bindshaedler *et al.*, 2011; Brizzolara *et al.*, 2003; Martins *et al.*, 2006) or, in some cases, impaired performances (e.g., Patient KF, Martin *et al.*, 2006; Patient CI, Vicari *et al.*, 2007; Patient Jocelyn, Picard *et al.*, 2013). However, just because some patients with DA perform the Vocabulary or Information subtest of the WAIS correctly does not mean that they have normal semantic memory. Recent findings suggest that their semantic knowledge structure differs from that of healthy individuals (Blumenthal *et al.*, 2017; D'Angelo *et al.*, 2016; Patient HC). There is also the question of whether these patients acquire new semantic knowledge in a similar way to healthy individuals, with available evidence suggesting that they do so at a slower pace (e.g., Gardiner *et al.*, 2008; Martins *et al.*, 2006). Furthermore, it is unclear at present whether patients with DA use semantic

knowledge as quickly and efficiently as controls. Time constraints need to be used at retrieval to assess this point properly, but to our knowledge this has yet to be done.

Second, a careful examination of published cases of adult-onset amnesia or DA suggests that some patients exhibit residual episodic learning abilities (e.g., Bindshaedler *et al.*, 2011; Brizzolara *et al.*, 2002; D'Angelo *et al.*, 2015; Martins *et al.*, 2006; Picard *et al.*, 2013; Vargha-Khadem *et al.*, 1997; Verfaellie *et al.*, 2000). For example, Patient PS, whose damage was thought to be limited to the hippocampal formation (Verfaellie *et al.*, 2000), achieved a general memory index of 90 (Wechsler Memory Scale-Revised; WMS-R), clearly denoting considerable residual abilities for episodic learning. In such cases, apparently preserved semantic learning may very well be the result of these residual episodic learning abilities, albeit requiring more time and effort than in controls (Squire & Zola, 1998).

Third, lesion studies have mostly focused on distinguishing between patients with damage limited to the hippocampal formation or else spread across the whole MTL. However, episodic learning is thought to depend on the so-called extended hippocampal system, which includes the hippocampus, fornix, mammillary bodies, mammillothalamic tract, anterior thalamic nuclei, and retrosplenial cortex (Aggleton, O'Mara, Vann, Wright, Tsanov, & Erichsen, 2010). Damage to any part of this system has been shown to result in anterograde amnesia, with context-rich memories being particularly vulnerable (Aggleton & Saunders, 1997; Vann & Nelson, 2015). Accordingly, a detailed investigation of each component of the extended hippocampal system is crucial if we are to draw any further inferences about the cognitive profiles of patients with amnesia. Interestingly, in DA, recent evidence has confirmed that damage is not limited to the hippocampal formation. Despite early evidence of abnormalities in the putamen, brainstem, thalamus, and/or retrosplenial cortex (Gadian *et al.*, 2000; Vargha-Khadem *et al.*, 2003), diencephalic abnormalities have only been reported comparatively recently (Bindshaedler *et al.*, 2011; Olsen *et al.*, 2013; Rosenbaum *et al.*, 2011, 2014). A group study has just confirmed that mammillary body atrophy is quite common (Dedeclol *et al.*, 2017), as is anterior thalamus atrophy. We now have substantial evidence suggesting that some parts of the so-called extended hippocampal system can be affected in DA. Thus, in case reports where damage is restricted to the hippocampal formation, we cannot rule out the possibility of residual explicit learning abilities, owing to the functional preservation of intact components of the extended hippocampal system.

Taken together, evidence of normal knowledge acquisition (i.e., as fast and as efficient as in controls) in amnesia is therefore still lacking. This needs to be demonstrated in cases of severe amnesia with extensive damage to the extended hippocampal system and no residual episodic ability. Here, we describe the case of a new patient with DA who displayed several novel and outstanding features. This patient had the extremely rare condition of selective damage to the whole of the extended hippocampal system. He was severely amnesic, with close to zero residual episodic ability, but displayed superior (i.e., significantly better than controls) abilities on many semantic memory tasks. Experiments involving speeded recognition memory paradigms yielded evidence that he could retrieve and acquire new knowledge as efficiently as controls. We also performed for the first

time in DA to our knowledge a cortical thickness analysis that revealed a pattern of thicker subhippocampal cortex, indicative of profound reorganization. This case study suggests that in some instances, and in conditions that remain to be fully elucidated, novel knowledge can be acquired up to a very good level in severe amnesia.

2 | CASE DESCRIPTION

KA is a right-handed male who was 27-years old at first testing, when he was referred to our memory clinic for persistent memory issues he and his family had had to face since he was a child. His only notable antecedent was severe neonatal hypoxia. KA was delivered prematurely at 32 weeks of gestation. He suffered from cardiac arrest and hypoxia at birth, requiring intubation and ventilation and a 40-day stay in the intensive neonatal care unit. His development thereafter was unremarkable, and his parents even reported precocious knowledge of the alphabet at Age 3, with a normal acquisition rate for language and motor abilities. We did not find any medical history in KA's family, his parents and his brother being free of any specific medical condition. All completed at least 12 years of education and reported normal socio-occupational integration.

However, very early on in his development, his parents also reported a series of everyday situations where KA obviously exhibited marked anterograde amnesia. When asked to perform two simple things, KA always forgot one, and at Age 4 years, his teachers worried about his inability to complete the activities he was instructed to perform. By Age 7 years, KA's learning disabilities had become a serious concern at school. Despite many consultations in different clinical settings, no clear diagnosis emerged. These difficulties persisted throughout secondary school, leading KA to repeat his first year, then to go to a vocational school where he failed to obtain his vocational diploma despite two attempts. In 2009, his mother heard about memory clinics, which is when KA was referred to us. KA is currently unemployed. He cannot live fully independently without the supervision of his parents for administrative tasks, but he can drive, orient himself in very familiar surroundings, and generally take care of himself. KA systematically records most events or thoughts in a notebook he always keeps with him, together with at least three pencils, just in case. In this notebook, he can write ideas shared in conversations he has just had, as well as the place where he left his sunglasses, or something he should think about the next day. Nonetheless, KA is known by his close relations to have an impressive amount of general knowledge.

3 | NEUROPSYCHOLOGICAL BACKGROUND

3.1 | General cognitive assessment

KA underwent various neuropsychological assessments between March 2009 and July 2015, without any noticeable change. To qualify KA's performance by reference to controls, we followed the recommendations from Strauss, Sherman & Spreen (2006). Thus, we used the term "Superior" for scores corresponding to point estimates

interval falling in the [0.950-0.979] percentile range, and "Very Superior" for scores falling above that range. As shown in Table 1, KA was found to have preserved cognitive abilities in virtually all domains, except memory. For the sake of clarity, every score has been converted to percentile ranks, based on published normative data. KA had a 44-point discrepancy between his memory and intelligence quotients (MQ and IQ derived from the Wechsler scales), scoring 53 and 97, respectively. After Patient HC (Hurley, Maguire, & Vargha-Khadem, 2011; Rosenbaum et al., 2011), this is the second greatest discrepancy between IQ and MQ ever to be reported in DA to our knowledge. An ecological assessment of memory was performed with the Rivermead Behavioral Memory Test. For the sake of comparison, results are provided in Table 2 alongside the values reported for two similar well-known cases: Patient Jon (Vargha-Khadem et al., 1997) and Patient HC (Rosenbaum et al., 2011). These data confirm severe anterograde amnesia in KA.

3.2 | Recall tests

We extensively tested KA's recall abilities across different modalities, to further investigate the severity of his amnesia. Across 11 different standardized recall tests and 30 corresponding scores, KA's mean percentile rank was 3.1. When we only considered delayed recall scores, performance dropped to a mean percentile rank of 0.1 (see Table 3).

3.3 | Recognition memory tests

Turning to recognition memory, we first administered five delayed matching-to-sample (DMS) tests, keeping the testing format constant while varying the types of stimuli. These tests were also administered to 19 male control participants matched with KA for age (mean = 29.3 years, SD = 3.2, range = 25-35), but with a slightly higher education level (mean = 14.8 years, SD = 2.1, range = 10-18).

First, we administered the DMS 48 test (Barbeau et al., 2004), which involves the incidental encoding of 48 colored pictures (16 abstract designs and 32 concrete pictures). After a 3-min break filled with a verbal fluency task, participants underwent a two-alternative forced-choice recognition task. After a 1-hr break, the same two-alternative forced-choice task was administered with new foils. Second, the same procedure was used with 16 concrete words, 16 abstract words and 16 pseudo words as stimuli (verbal version of the DMS 48) using a similar procedure (we used the Lexique database (New, 2006; New, Brysbaert, Veronis, & Pallier, 2007; <http://www.lexique.org/doc/Lexique.php>) to match words for frequency: median = 6.02 per million, [0.05-77.3]; number of letters: median = 7, [4-11]; number of syllables: median = 2, [1-4]; pseudo words were also matched to words for the number of letters: median = 6, [5-8]). Third, participants performed the Recognition Memory Test for Faces (Warrington, 1984).

Modified *t*-test procedures (Crawford & Garthwaite, 2002, 2007a; Crawford & Howell, 1998) revealed normal performances on all tasks (see Table 4) by KA, with the exception of the 1-hr delayed DMS 48 score, where KA failed on only two items, yielding overall accuracy of 96% (46/48).

TABLE 1 Neuropsychological background

Cognitive domains/tests	Raw scores	Percentile ranks
French national adult reading test		
Raw score, max = 40	21	
Estimated full scale IQ (mean = 100, SD = 15)	100	50
Estimated verbal IQ (mean = 100, SD = 15)	100	50
Estimated performance IQ (mean = 100, SD = 15)	101	50
Intelligence/WAIS, II		
List of subtests		
Vocabulary	36	50
Information	22	75
Comprehension	20	37
Similarities	23	63
Digit span	13	16
Letter number sequencing	8	9
Arithmetic	13	37
Picture completion	22	63
Digit symbol - coding	62	16
Block design	29	6
Matrix reasoning	22	63
Symbol search	29	25
Standard scores, mean = 100, SD = 15		
Verbal comprehension	105	63
Perceptual organization	93	32
Working memory	84	14
Processing speed	84	14
Memory/WMS II		
List of subtests—Raw scores		
Information and orientation	14	>56
Logical memory I	11	0.1
Face recognition	36	23
Verbal paired associates I	4	1
Family pictures I	8	0.1
Words list, first recall	9	23
Words list, Total recall	23	2
Letter number sequencing	8	9
Spatial memory	12	9
Mental control	35	93
Digit span	13	9
Logical memory II	1	0.1
Logical memory II, retention (N)	12.5	0.1
Face recognition II	39	50
Verbal paired associates II	0	0.1
Family pictures II	9	2
Words list II	0	0.1
Standard scores, mean = 100, SD = 15		
Verbal immediate recall	58	0.3
Verbal delayed recall	54	0.1
Visual immediate recall	67	1
Visual delayed recall	75	5
Delayed recognition	56	0.2

TABLE 1 (Continued)

Cognitive domains/tests	Raw scores	Percentile ranks
Working memory	77	6
Attention and executive functions		
Two and seven ruff selective attention test		
Speed	267	45
Efficiency	1.146	57
Verbal fluency		
Letter P	20	46
Letter R	20	59
Fruits category	16	35
Ruff figural fluency test		
Unique designs (raw score corrected for age and education)	74	21
Persistent errors ratio (raw score corrected for age and education)	0.086	48
Trial making test		
Part A (seconds)	33	72
Part B (seconds)	72	80
Hayling test		
Part A, total response time (seconds)	8,427	31
Part B, total response time (seconds)	8,130	—
Part B, raw score	0	80
Dual task interference paradigm		
Mu index	92.02	50

We further used two four-alternative forced-choice visual recognition memory tests (Doors test; Baddeley, Embley, & Nimmo-Smith, 1994) and the "Reconnaissance de dessins" subtest of the Batterie d'Efficiency Mnésique 144 (BEM 144; Signoret, 1991). The latter drawings recognition test involves explicit encoding of 24 abstract black-and-white drawings, displayed one at a time for 5 s. After a 15-min interval, participants had to identify each target drawing among three distractors. In both tests, Patient KA again performed within the fully normal range (see Table 4). Finally, since prior studies had suggested that the forced-choice test format may enhance recognition memory in amnesic patients compared with the old/new test format (Holdstock *et al.*, 2002), we administered the Face Recognition subtest of the WMS-III (Wechsler, 2001). Again, KA achieved normal scores for both immediate and delayed trials (see Table 4).

3.4 | Source memory

A common feature of anterograde amnesia is the inability to perform context-rich memory tasks, where both the item but also its context of acquisition must be correctly recalled. We therefore adapted the item versus visual spatial memory experiment (Wolk, Signoff, & Dekosky, 2008) to further investigate whether Patient KA exhibited any dissociation between item-only (i.e., context-free) and item-plus-context (i.e., context-rich) memory. During an explicit encoding phase, two living and two nonliving objects were displayed on a screen, each located in one of the four quadrants (labeled 1–4). Participants were explicitly asked to learn the association between the nonliving objects and their

TABLE 2 Overall memory and intelligence scores in patient KA vs patients Jon and HC

	KA April 27	Jon April 19	HC April 22
Briefcase Behavioural memory test			
Profile score	5	30	30
WAIS III (standard scores, mean = 100; SD = 15)			
Full-scale IQ	97	114	109
Verbal IQ	97	108	105
Performance IQ	98	120	113
WMS III (standard scores, mean = 100; SD = 15)			
Memory quotient (general memory)	53	93	49

location on the screen. 20 arrays of four pictures were successively presented in a self-paced manner. The recognition test started 3 min after the encoding phase. Participants were shown a total of 80 photographs of nonliving objects (40 studied, 40 novel). For each item, they were instructed to make an old/new judgment, and for each old response, the correct location of the item had to be retrieved by pressing the corresponding key. Signal detection theory (Snodgrass & Corwin, 1988) was applied to measure both discriminability (d' index; i.e., $[d(\text{Hits} - \alpha \text{False Alarms})]$) and bias (C index; i.e., $0.5 \times [d(\text{Hits} + \alpha \text{False Alarms})]$). Source memory was estimated by calculating the ratio of correct locations to hits. Patient KA and five healthy male controls underwent the experiment (mean age = 28.0 years, SD = 2.1; mean education level = 13.2 years, SD = 3.0), and modified t -test procedures were applied. KA performed normally in terms of accuracy (83%), and although his d' index was impaired, owing to a higher FAs rate; it remained at a reasonable level (Figure 1). However, KA massively failed to recall the locations of the targets, with a source memory score of just 25% (chance level = 25%; controls' median score = 90%).

4 | NEURORADIOLOGICAL FINDINGS

4.1 | MRI examination

Visual examination of MRI scans revealed severe bilateral atrophy of the hippocampus (see Figure 2a). We used the VolBrain system (Marjón & Coupé, 2016) to obtain gross volumetric information about the main brain structures. As recently described in a group of children who had sustained neonatal acute respiratory failure (Cooper *et al.*, 2015), we found a slightly lower cerebral white matter volume in KA, despite normal overall gray matter volume. The thalami and caudate nuclei, as well as the left nucleus accumbens, also showed reduced volumes, and severe bilateral hippocampal atrophy was confirmed (see Table 5). Visual comparison between a normal brain and KA's brain (see Figure 2b) further revealed that neither the body nor the columns of the fornix were clearly discernible, and only some vestiges of the crura were identifiable. Moreover, both the mammillary bodies and the mammillothalamic tract remained unidentifiable, which is an

extremely rare condition in the literature. Figure 2c illustrates additional bilateral atrophy of anterior thalamic nuclei.

4.2 | Hippocampal subfields

To further examine Patient KA's hippocampus, a dedicated high-resolution ($0.375 \times 0.375 \times 2$ mm) proton density-weighted MRI sequence was acquired on a 3T-scanner perpendicular to the long axis of the hippocampus. This sequence allowed us to segment the hippocampal subfields according to a protocol developed by La Joie *et al.* (2010) on the basis of anatomical atlases (Duvernoy, 2005; Harding, Halliday, & Kiri, 1998), successfully applied to neurodegenerative disorders (La Joie *et al.*, 2013), and which reliability has specifically been assessed recently (de Flores *et al.*, 2015). Three subfields (CA₁, subiculum, and other subfields, that is, CA₂₋₃-dentate gyrus) were traced along the head and body of the hippocampus, based on macroscopic landmarks and heuristic geometric rules (La Joie *et al.*, 2010). After normalizing for total intracranial volume, Patient KA's volumes were compared with those of a group of 20 healthy males who underwent the same MRI sequences, in the same scanner, and were matched for age (mean = 28.4 years, SD = 3.4), but were more educated than KA (mean education level = 14.5 years, SD = 3.0). In line with the VolBrain results, we found severe bilateral hippocampal volume loss (volume loss exceeding 55%, z score = -5.6), and further showed that volume loss was marked in every segmented subfield in both hemispheres, particularly in the CA₁ and subiculum (see Figure 3).

4.3 | Whole-brain cortical thickness

Finally, we performed a whole-brain cortical thickness analysis of Patient KA's brain, comparing it with 10 healthy male controls aged 19–36 years (mean = 24.2), using the CorThZon MATLAB toolbox, derived from a successful application to early Alzheimer's disease (Querles et al., 2009). This toolbox uses a Laplace-based technique to estimate cortical thickness after segmenting the brain into 96 Brodmann areas (BA). Cortical thickness measures were z -transformed to create a z -score map, as illustrated in Figure 4. Crawford's modified t tests (Crawford & Garthwaite, 2002; Crawford & Howell, 1998) were applied to compare KA's cortical thickness values with those of controls. We found abnormally thin cortex within the left BA 34 ($p = .024$) and right BA 24 ($p = .041$), as well as a trend for the left BA 30 ($p = .074$), these areas corresponding to the dorsal entorhinal cortex, anterior cingulate area, and a subdivision of the retrosplenial area, respectively. Furthermore, we found a trend toward significantly thicker cortex within the left BA 38 ($p = .064$), which corresponds to the temporal pole region. Importantly, no abnormal estimates of cortical thickness were found for critical subhippocampal structures within the MTL, not least the perirhinal and ventral entorhinal cortices (z scores for bilateral BAs 35 and 36, as well as bilateral BA 28, within ± 1 SD of controls, with the exception of Right BA 28; z score = 1.05).

To the best of our knowledge, Patient KA is the first reported case of selective and massive damage restricted to the whole extended hippocampal system, providing a unique window onto the role of that system in learning and memory, and most importantly

TABLE 3 Recall memory performances of patient KA. "La Ruche" test was taken from Violon and Wiljns (1984)

Recall tests	Raw scores	Accuracy, %	Percentile
Immediate, verbal			
Words list I, 1st recall (WMS, 3rd Ed.)	5	42	9
Words list I, Total recall (WMS, 3rd Ed.)	23	48	0.4
Logical memory I, total recall (WMS, 4th Ed.)	18	36	16
Verbal paired associates I, total recall (WMS, 4th Ed.)	1	2	0.1
Selective reminding test, mean recall across 10 trials	5	30	0.1
Selective reminding test, consistent recall	18	35	0.1
California verbal learning test, first recall	2	13	0.1
California verbal learning test, Total recall list A	18	23	0.1
California verbal learning test, recall list B	3	19	3
Immediate, visual			
Family pictures I, recall (WMS, 3rd Ed.)	8	13	0.1
Visual reproduction I, recall (WMS, 4th Ed.)	38	88	50
Visual paired associates I, 1st recall (WMS, revised Ed.)	1	17	
Visual paired associates I, Total recall (WMS, revised Ed.)	6	33	0.6
Roy Odenwith complex figures, recall	7	19	0.1
"La Ruche, spatial localization learning test", first recall	2	20	7.5
"La Ruche, spatial localization learning test", Total recall	9	18	0.1
Delayed, verbal			
Words list II, delayed recall (WMS, 3rd Ed.)	0	0	0.1
Logical memory II, delayed recall (WMS, 4th Ed.)	1	2	0.1
Verbal paired associates II, delayed recall (WMS, 4th Ed.)	0	0	0.1
Selective reminding test, delayed recall	0	0	0.1
California verbal learning test, post interference free recall	0	0	0.1
California verbal learning test, post interference cued recall	1	6	0.1
California verbal learning test, delayed free recall	0	0	0.1
California verbal learning test, cued recall	0	0	0.1
Double memory test, delayed cued recall	10	23	0.1
Delayed, visual			
Family pictures II, delayed recall (WMS, 3rd Ed.)	9	14	0.4
Visual reproduction II, delayed recall (WMS, 4th Ed.)	0	0	0.1

TABLE 3 (Continued)

Recall tests	Raw scores	Accuracy, %	Percentile
Visual paired associates II, delayed recall (WMS, revised Ed.)	2	33	0.1
Roy Odenwith complex figures, delayed recall	1.5	4	0.1
"La Ruche, spatial localization learning test", delayed recall	1	10	0.1

onto the functions of the preserved cortices in KA. In the following three sections, we therefore address three critical questions: (1) could Patient KA retrieve context-free (i.e., semantic) memories?; (2) could he access these memories in the same way as controls do?; and (3) was he able to acquire new context-free knowledge like controls?

5 | SEMANTIC MEMORY RETRIEVAL

Patient KA performed a series of tasks involving the retrieval of semantic knowledge about objects, buildings, events or people listed in Table 6. All raw scores were converted to percentile ranks for the sake of clarity.

5.1 | Standard tests

A series of individual tests or batteries of tests tapping semantic (i.e., context-free) memory was used to extensively assess Patient KA's abilities. The BECS-CRECO battery (Merck et al., 2011) is a French battery of five tests assessing semantic knowledge about objects, either living entities ($n = 20$) or manufactured objects ($n = 20$), matched on various dimensions and presented in both verbal (words) and visual (line drawings) modalities. The Mill Hill Vocabulary test (Raven, Court, & Raven, 1986) is a well-known graded-difficulty test requiring participants to select the correct synonym for each of 44 words (only Part B was administered) from a list of six alternatives. The EVE-30 and TOP-30 batteries (all details about these batteries available in Thomas-Antérion & Puel, 2012) include a series of tests of semantic knowledge about 30 famous public events and 30 famous people (color photographs), respectively. The EVE-30 battery involves 30 public events spanning the early 1920s to the late 2000s, 3 events pertaining to each decade (1920–1929, 1930–1939, etc.) and 9 for the last decade (2000). Each event was presented visually through a short sentence (e.g., "death of Lady Di"). Three subtests were administered in a fixed order for each event, presented in a predetermined random order: the evocation subtest required subjects to provide as many information as he/she could about the event; the multiple-choice recognition subtest consisted in the written presentation of three definitions of the event, the target definition together with two lure definitions, the subject being asked to select the right one (e.g., "Was the death of Lady Di [1] the assignation of a princess by a terrorist; [2] the death of a princess due to a car accident; [3] the suicide of a princess?"); in the last subtest, subjects had to answer a question of detail about the event (e.g., "What was the car's brand?"); subjects also had to point to the correct date of the event on a visual

TABLE 4 Recognition memory performances of patient KA

Recognition tests	Stimuli	Nb. Targets	Test format	Delay (min)	Accuracy KA (%)	Accuracy HC mean (SD)	Percentile	<i>p</i> value
DMS 48, set 1	Concrete and Abstract designs	48	2 AFC	3	100	98 (2)	83	.171
DMS 48, set 2	Concrete and Abstract designs	48	2 AFC	60	96	99 (1)	0.5	.009
DMS 48 words, set 1	Words and pseudo-words	48	2 AFC	3	92	89 (8)	64	.719
DMS 48 words, set 2	Words and pseudo-words	48	2 AFC	60	92	89 (1)	72	.556
Doors test (A + B)	Doors pictures	24	4 AFC	0	75	—	10–25	—
"Reconnaissance de dessins" (see text)	Abstract drawings	24	4 AFC	15	83	—	69	—
Faces I (WMS, 3rd Ed.)	Faces	24	Y/N	0	75	—	25	—
Faces II (WMS, 3rd Ed.)	Faces	24	Y/N	35	83	—	50	—

timeline. A similar logic of assessment (except for the date subset) is used in the TDP-30 battery, but with famous faces as stimuli.

KA's performances are set out in Table 6. For the 13 scores derived from the standardized tasks, Patient KA's performances were in the high range, and it is worth noting that KA even outperformed controls on the Eye-30 and Top-30 batteries, with percentile scores above 95, reaching 99 in one subset.

5.2 | Experimental tasks

We further designed or adapted three series of tasks to assess Patient KA's context-free retrieval abilities for famous buildings, famous people and recent concepts. The famous buildings task featured 16 color photographs of famous buildings taken from the web and (chosen during pilot testing). Participants were asked to (1) make a familiarity judgment, (2) recall the corresponding country, (3) provide as many details as they could about that building, and (4) name the item. Their responses were recorded and independently scored by two raters.

The famous people battery (SemPer battery; Lainey, Eustache, & Desgranges, 2009) featured 16 black-and-white photographs of famous people from different domains and 16 matched unknown faces. The latter closely matched the former on several dimensions. Participants had to (1) make a familiarity judgment for each of the 32 faces, and (2) perform a semantic matching task including an easy part (the foil celebrity had a completely different occupation from the target item) and a difficult part (all the celebrities shared the same occupation, but one foil was closer to the target, for example, three famous politicians displayed, two belonging to the same party). The matching task was administered first with faces as stimuli, then with written names. Finally, each target face was presented again for an oral naming task.

The recent concepts questionnaire was adapted from the New Words Questionnaire developed by Thomas-Antirion *et al.* (2009). A total of 22 newly coined French words were selected from the Larousse dictionary. Of these, 11 entered the dictionary in 1996 or 1997, and the remaining 11 in 2006 or 2007. Since we administered the questionnaire in 2009, the use of two sets of words coined 10 years apart allowed us to look for differences when KA was asked

to retrieve knowledge about the corresponding concepts. In amnesia, we would expect repeated exposure to new concepts for more than 10 years to lead to better performances than more recent exposure.

The 22 words were presented orally, one at a time, and participants were asked to give their best definition of each one (free recall). They then answered a multiple-choice questionnaire in which they had to choose one of three possible short definitions of each word. Finally, they were asked to decide which of two short sentences made the correct usage of each word.

Five healthy male controls matched with Patient KA for age (KA was 28-years old at the time of testing, and the healthy controls' mean age was 29 years, range: 27–30), but slightly more educated (mean years of education: 12, range: 10–14), underwent these tasks, in addition to Patient KA.

The same modified *t*-test procedures as those mentioned above were used, and corresponding percentile ranks were estimated (see Table 6). For a total of 15 scores, KA's mean percentile rank was 69, with a range of 22–88, thus falling within the high range of controls' scores.

These results for Patient KA confirmed prior studies (Kosinger *et al.*, 2001; O'Keefe *et al.*, 2004; Schmolck, Kosinger, Corkin, &

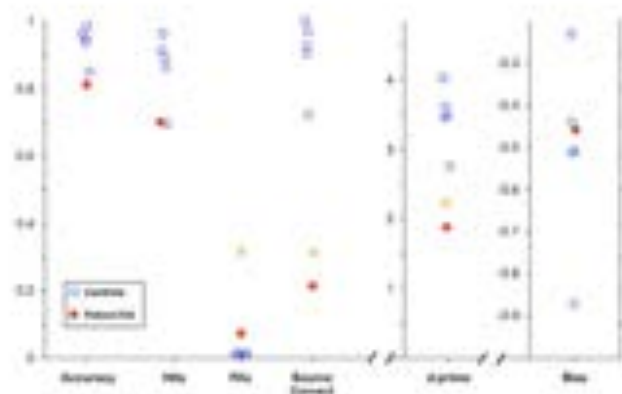


FIGURE 1 Source quadrant location memory task. Yellow asterisks indicate impaired performances ($p < .05$) [Color figure can be viewed at wileyonlinelibrary.com]

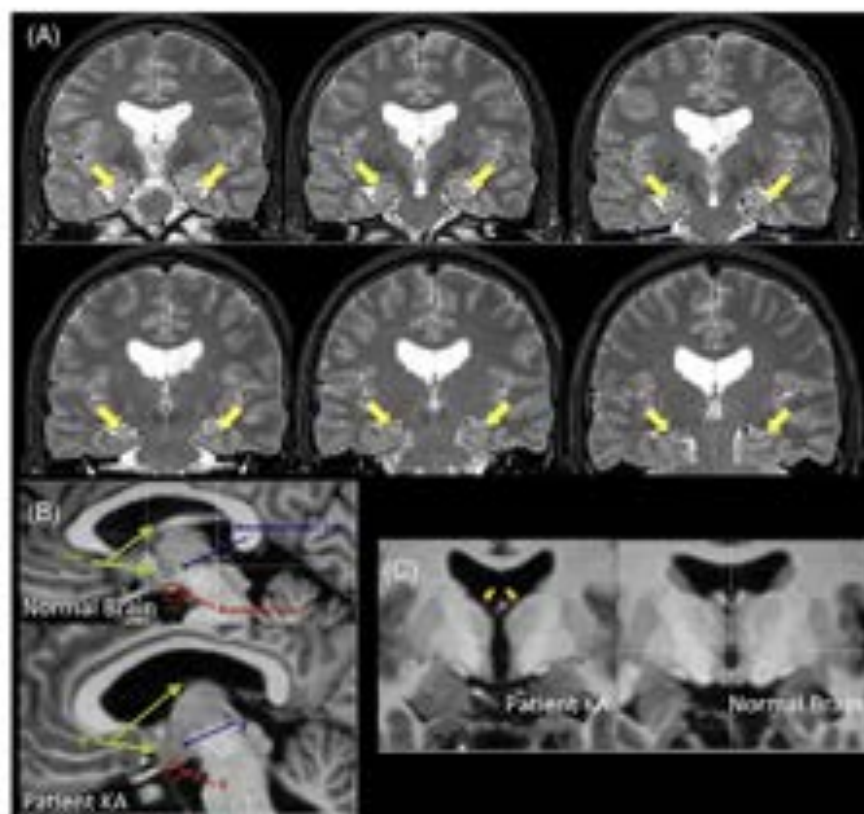


FIGURE 2 (a) Patient KA's T2-weighted MRI scans. Yellow arrows indicate bilateral hippocampal atrophy; (b) fornix, mammillary bodies and mammillo-thalamic tract abnormalities in patient KA (bottom) vs a healthy control (top); (c) anterior thalamic nuclei atrophy in patient KA (left image, yellow arrows) vs a healthy control (right image) [Color figure can be viewed at wileyonlinelibrary.com]

Squire, 2002). However, our tasks did not allow us to speculate about how KA actually accessed these context-free memories. It may be that, as previously suggested for Patient Jon (Blind, Vargha-Khadem, & Burgess, 2008), KA made use of idiosyncratic strategies to access semantic memories, and/or this access, though quantitatively normal, was far slower than that of controls. In the following series of experiments, we therefore sought to strongly constrain the way KA could retrieve semantic memories, to investigate whether he would still perform normally.

6 | SPEEDED SEMANTIC MEMORY RETRIEVAL

The following series of three experiments were adapted from Besson et al. (2017). Participants for these three experiments were 13 right-handed men (mean age = 25 years, range = 22–27; mean education level = 15 years, range = 12–21). Patient KA was 32-years old at the time of these experiments, and thus slightly older and less educated than the controls.

6.1 | Experimental setting

For all experiments, stimuli were presented on a CRT computer screen, using E-Prime 2.0 software (<http://www.psychnet.com/eprime.htm>, E-Prime, RRID: SCR_009567). Participants responded by raising

TABLE 5 Results of automated MRI brain volumetry in patient KA (VolBrain system, Manjon & Coupé, 2016)

	Patient KA raw volumes (cm ³)	Patient KA normalized volumes (%)	Healthy controls normalized volumes (95% IC)
Segmented structures			
Tissue segmentation			
White matter	478.62*	32.26	[32.95–45.17]
Gray matter	762.89	52.76	[44.17–55.44]
Cerebro spinal fluid	222.26	14.98	[5.83–16.44]
Subcortical structures			
Lateral ventricles	48.24*	3.25	[0.00–1.97]
Caudate	4.72*	0.32	[0.41–0.60]
Putamen	7.72	0.52	[0.50–0.71]
Thalamus	9.77*	0.66	[0.73–0.93]
Globus pallidus	2.02	0.14	[0.14–0.21]
Hippocampus	3.30*	0.22	[0.46–0.64]
Amygdala	1.63	0.11	[0.09–0.15]
Accumbens	0.48*	0.03	[0.03–0.07]

*p < .05.

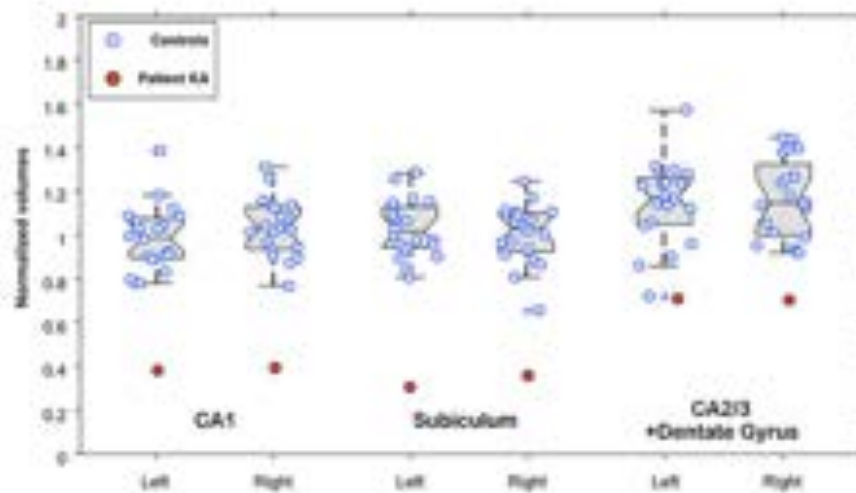


FIGURE 3 Hippocampal subfields volumetry in patient KA vs 20 healthy controls. (Crawford's modified *t*-tests, all *p* values $> .05$) [Color figure can be viewed at wileyonlinelibrary.com]

their fingers from a dedicated infrared response pad, and the need for a speedy response was always emphasized in the instructions.

6.2 | General method: Speed and accuracy boosting procedure

The speed and accuracy boosting (SAB) procedure was introduced by Besson, Ceccaldi, Didic, and Barbeau (2012) to constrain participants to use their fastest strategy, and has been used in several studies (Barragan-Jason, Besson, Ceccaldi, & Barbeau, 2013; Besson et al., 2015, 2017). Based on a classic go/no-go task, the SAB procedure constrains participants to provide a go response for targets within a given response time following stimulus onset. The deadline was set at 600 ms in the present experiments, based on previous studies. A go response before this deadline was followed by audio feedback, which was positive if the item was a target (Hit), and negative if the item was a distractor (FA). Similarly, a no-go response was followed by either positive (correct no-go response for a distractor, i.e., correct rejection) or negative (incorrect no-go response for a target, i.e., omission) audio feedback. Before each item was presented, a fixation cross was displayed with a jittered duration ranging from 300 to 600 ms. Stimuli were flashed for 500 ms, after which participants had up to 500 ms to give their answer. Each of the following experiments comprised two consecutive blocks of 140 items. As the SAB procedure is a very demanding task, two training blocks where 50 target stimuli had to be recognized among 10 distractors preceded each block for each experiment.

The SAB procedure provides a continuous distribution of response times, allowing the minimum reaction time (minRT) for recognition to be estimated (see below). As recognition memory is known to rely upon two processes (recollection and familiarity), and as familiarity is supposed to be a rapid and automatic process, in contrast to the slow, controlled processes that support recollection (Brown & Aggleton, 2001; Yonelinas, 2002), the SAB procedure is assumed to rely mainly on familiarity (Besson et al., 2012; Sauvage Sauvage, Beer, & Eichenbaum, 2008).

6.3 | Experiment 1: Speeded go/no-go human face categorization task

We took 140 photographs of unknown faces and 140 photographs of animal faces from the web. We then selected 70 pictures of each kind to build two lists of 140 stimuli. Upright and inverted presentations were randomly assigned to the lists (half inverted, half upright).

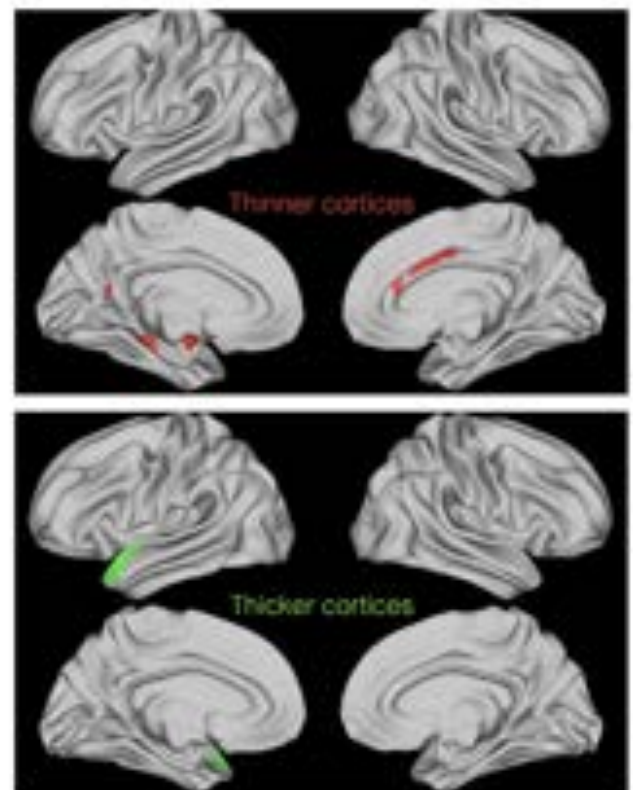


FIGURE 4 Z-score map for whole-brain cortical thickness estimates in patient KA vs 10 healthy controls. Red indicates abnormally thick cortices, blue indicates abnormally thin cortices. Cut-off set at 1.65 SD of the mean. See text for detailed results [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 6 Patient KA's context-free memory retrieval performances

	Stimuli	KA's raw scores	Controls mean (SD)/ cut-off	Percentile	p value
Standardized tasks					
BECS-Greco battery					
Words matching test, max = 40	Words (objects)	40	Cut-off = 39	—	—
Pictures matching test, max = 40	Drawings (objects)	40	Cut-off = 38	—	—
Identity matching test, max = 20	Drawings (objects)	19	Cut-off = 19	—	—
Pictures naming, max = 40	Drawings (objects)	39	Cut-off = 38	—	—
Questionnaire, max = 240	Words (objects)	205	Cut-off = 233	—	—
Mill Hill vocabulary scale					
Part B	Words (concepts)	32		75–90	—
EVE 30 battery					
Evocation, max = 60	Famous events	48		99	—
Multiple-choice recognition, max = 30	Famous events	29		91	—
Details, max = 60	Famous events	39		95	—
Datation, max = 30	Famous events	20		95	—
TOP 30 battery					
Evocation, max = 60	Famous faces	55		96	—
Multiple-choice recognition, max = 30	Famous faces	28		37	—
Details, max = 60	Famous faces	50		93	—
Experimental tasks					
Famous buildings task					
Familiarity decision, max = 16	Famous buildings pictures	16	15.3 (0.5)	48	0.272
Free recall (country), max = 16	Famous buildings pictures	16	15.3 (1.0)	73	0.506
Free recall, details	Famous buildings pictures	54	38.0 (15.8)	78	0.431
Naming, max = 16	Famous buildings pictures	14	11.3 (3.4)	74	0.529
SEMPe battery					
Familiarity decision for names, max = 32	Famous names	32	30.2 (1.3)	86	0.275
Names matching, part A, max = 16	Famous names	16	14.4 (1.1)	87	0.270
Names matching, part B, max = 16	Famous names	14	14.2 (2.2)	47	0.937
Familiarity decision for faces, max = 32	Famous faces	32	30.2 (1.5)	84	0.329
Faces matching, part A, max = 16	Famous faces	16	14.4 (1.5)	80	0.391
Faces matching, part B, max = 16	Famous faces	15	12.0 (3.4)	77	0.465
Naming, max = 32	Famous faces	32	24.8 (4.7)	88	0.231
Recent concepts questionnaire 1996–1997 period					
Free recall (definition), max = 11	Words	10	9.4 (1.5)	63	0.737
Multiple choice questionnaire, max = 11	Words	11	10.6 (0.9)	65	0.703
Real usage forced choice, max = 11	Words	11	11 (0)	—	—
Recent concepts questionnaire 2006–2007 period					
Free recall (definition), max = 11	Words	8	9.6 (1.7)	22	0.431
Multiple choice questionnaire, max = 11	Words	11	10.6 (0.9)	65	0.703
Real usage forced choice, max = 11	Words	11	11 (0)	—	—

Participants were told that the human faces were the targets (go responses), and the animal faces the distractors (no-go responses).

6.4 | Experiment 2: Speeded go/no-go famous face recognition task

We took 140 photographs of unknown faces and 140 photographs of famous faces from the web. Famous faces were selected on the basis of pilot studies showing that they were recognizable to healthy

individuals the same age as KA. Unknown faces were selected because they looked like they could be famous faces (attractiveness and quality of the photographs), and were matched to the famous faces for sex, head orientation and emotional expression. We then selected 70 pictures of each kind to build two lists of 140 stimuli. Again, upright and inverted images were randomly assigned to the lists as in Experiment 1. Participants were told that the famous faces were the targets (go responses), and the unknown faces the distractors (no-go responses).

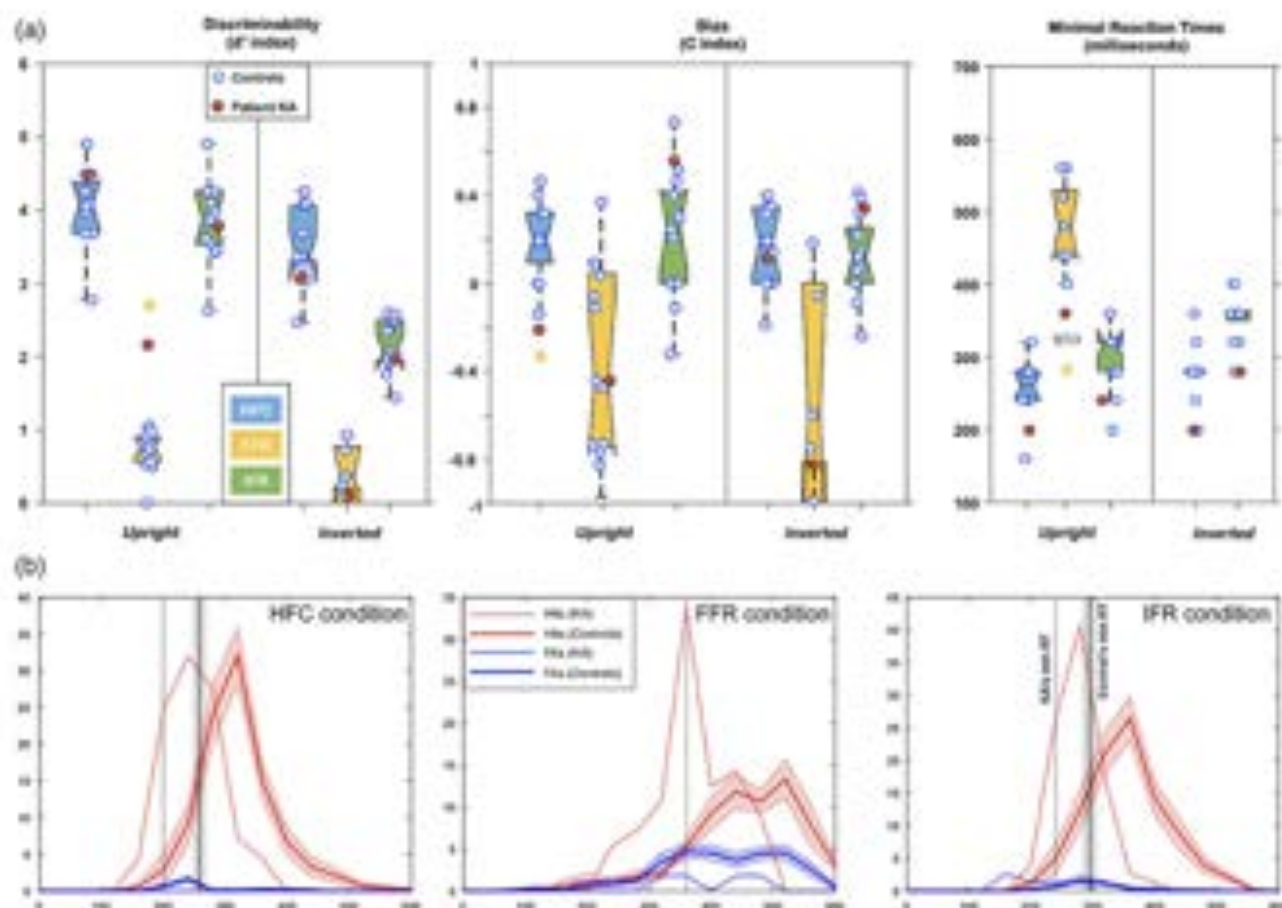


FIGURE 5 (a) Patient KA's performances during experiments 1 (human face categorization [HFC], blue boxplot), 2 (famous faces recognition [FFR], yellow boxplots), and 3 (individual faces recognition [IFR], green boxplots). Yellow asterisks indicate $p < .05$. [HFC = human face categorization, experiment 1; FFR = famous faces recognition, experiment 2; IFR = individual face recognition, experiment 3]; (b) reaction times distributions for each task (upright conditions only), where Y axis shows % responses and X axis time bins. Dashed areas represent SEM [Color figure can be viewed at wileyonlinelibrary.com]

6.5 | Experiment 3: Speeded go/no-go individual face recognition task

We took 140 photographs of two French celebrities from the web: 70 photographs of former French President Nicolas Sarkozy and 70 photographs of the famous and now deceased French singer Johnny Hallyday. Two sets of 70 photographs of unknown faces were then selected from the web so that they matched the famous photographs as closely as possible (i.e., each unknown face looked like it could be famous, had the same orientation, emotion, hair color, apparent age, etc.). This resulted in two lists of 140 photographs. Upright and inverted images were randomly assigned to the lists as before, that is, 70 items upright and 70 inverted within each list. Participants were given the name of a celebrity (i.e., either Nicolas Sarkozy or Johnny Hallyday) and told that the photographs of that celebrity were the targets (go responses), and the unknown faces the distractors (no-go responses).

6.6 | Analyses

Performances were analyzed according to signal detection theory (Snodgrass & Corwin, 1988): correct go responses were regarded as hits, and incorrect go responses as FAs, thus providing measures of

discriminability (d' index) and bias (C index), both indices being corrected according to Snodgrass and Corwin (1988). We applied χ^2 tests ($p < .05$) to hits and FAs for targets and distractors to determine whether participants successfully performed each task. As stated earlier, the SAB procedure provides a continuous distribution of response times, allowing the minimum processing time required for each task to be estimated. The minRT was computed as the latency at which the number of hits started to significantly outnumber the number of FAs. For each participant, we used Fisher's exact test ($p < .05$) with 40-ms time bins to determine whether the hit-to-FA ratios differed significantly. Some participants had low overall performances (i.e., low d' index), when hit and FA distributions tended to overlap, meaning that their minRT could not be computed. Patient KA's performances were compared with those of controls using the modified t -test procedure.

6.7 | Results

Figure 5 illustrates Patient KA's performances on all three experiments. He successfully performed each and every task, despite the strict time constraints (all χ^2 tests yielded p values $> .05$). For upright stimuli, Patient KA exhibited normal discriminability between targets

and distractors in all the tasks, and strikingly even outperformed controls on the famous face recognition experiment, achieving a d' of 2.17 [controls' mean $d' = 0.711$, range = 0–1.053, $t = 5.204$, $p < .01$]. Regarding bias, Patient KA again had normal C indices, with the exception of the human face categorization task, where he proved to be more conservative than controls. Regarding minRTs for upright stimuli, four controls performed too poorly on the famous face recognition task to achieve a minRT. In contrast, Patient KA achieved a normal minRT and even outperformed controls on the famous face recognition experiment, with a minRT of 360 ms (controls' mean = 489, range = 400–560, $t = -2.22$, $p = .05$). Furthermore, Patient KA had a minRT of 280 ms in the inverted stimulus condition of the individual face recognition task, again outperforming controls (controls' mean = 354 ms, range = 280–400, $t = -3.43$, $p < .01$).

When we considered the inverted stimulus results, we found that Patient KA and controls did not differ on either discriminability performances or bias (all p s = .05; see Figure 5). Moreover, the inversion effect on performances was similar in both Patient KA and controls.

The following experiment assessed whether KA could explicitly acquire and retrieve new context-free knowledge as well as controls.

7 | SPEEDED LEARNING OF NEW KNOWLEDGE

Control participants for the following experiment were eight right-handed men matched with Patient KA for age but more educated (mean age = 28 years, range = 22–34; mean education level = 19 years, range = 14–21). Patient KA was 31 years old when he performed this experiment.

7.1 | Experimental setting and stimuli

The experimental setting and analyses were the same as those described above for the SAB procedure. The stimulus set consisted of 200 color photographs of easily nameable objects. The experiment required participants to explicitly learn blocks of 30 pictures of items and to recognize them among distractors after an interval of 3 min. The rationale behind using pictures of objects rather than faces as in the first three experiments was that faces are regarded as having a particular status in amnesia. Research has consistently shown that unfamiliar face recognition can be preserved after hippocampal damage (Aggleton & Shaw, 1998; Aly, Knight, & Yonelinas, 2010; Bird, Shallice, & Cipolletti, 2007; Bird et al., 2008; Bird & Burgess, 2008; Bird, 2017; Carlesimo, Fadda, Turriani, Tomakuolo, & Caltagirone, 2005; Cipolletti et al., 2006; Smith et al., 2014; Taylor, Henson, & Graham, 2007; but see Colehill et al., 2004; Kafkas et al., 2017; for divergent findings). As our aim here was to assess whether Patient KA could acquire new context-free knowledge normally, we wished to rule out any material-specific account of either preserved or impaired new learning.

7.2 | Experimental procedure

Participants were shown 120 pictures of objects, one at a time, across four 30-item blocks of explicit study. Each time, the instructions

emphasized the need to remember each photograph for subsequent recognition. After each study block, participants had to watch a 3-min cartoon randomly chosen from a set of 12 different videos. Following this interference phase, participants were given the instructions for the test blocks. During these blocks, the 30 target pictures were randomly mixed with 30 distractor pictures. Participants had 600 ms to answer, in line with previous studies. Participants were instructed to provide go responses for old items, and no-go responses for new items as quickly as possible.

Given the difficulty of this task, even for healthy young controls, two study blocks of 10 target items and two test blocks with 10 target pictures mixed with 30 distractors were used as practice trials for each participant. None of these 40 pictures were used in any of the subsequent study and test trials. These practice trials generally had to be repeated, to allow participants to become accustomed to the task's speed constraints.

7.3 | Results

Results are displayed in Figure 6. Patient KA correctly discriminated between targets and lures, with a d' index of 1.20, which fell within the low-to-normal range of controls (z score = -1.41, $t = -1.329$, $p = .226$). He exhibited a response bias, in that he tended to be more conservative than controls (Patient KA = -0.54, z score = -2.00, $t = -1.89$, $p = .06$). One interesting possibility is that Patient KA's discriminability may have been underestimated because of his tendency to be more conservative [i.e., he tended to give fewer go responses overall]. We therefore used a regression approach adapted to single-case analyses (Crawford and Garthwaite, 2007b) to roughly estimate the range of d' index values expected for a given response bias. Patient KA's C index (-0.54) predicted a d' index of 2.5 ($SE = 0.66$), which tended to be significantly better than the d' index that was actually found for KA (1.20, $z = -3.8$, $p = .06$). The conservative bias we observed in Patient KA may therefore have led to an underestimation of his actual discriminability abilities.

Regarding response times, Patient KA's median response time was significantly shorter than that of controls (median RT = 398 ms, controls' mean = 469 ms, range = 432–499, $t = -2.91$, $p < .05$), but he did not differ from controls on minRT (KA = 390 ms, controls' mean = 420 ms, range = 390–450, $t = -1.01$, $p = .35$).

8 | DISCUSSION

We report the case of Patient KA, who has early-onset amnesia characterized by extremely rare selective and massive damage to each component of the extended hippocampal system. We found that Patient KA displayed few, if any, residual episodic abilities. However, not only was he able to accurately retrieve semantic memories, but he was also the first patient to show clear evidence of superior or even very superior access to these memories. Even more strikingly, KA performed faster and more accurately than controls on identifying famous faces, despite very strict speed constraints. In addition, we found evidence for preserved abilities of new knowledge acquisition in KA, again in the context of a speed-constraint paradigm limiting the

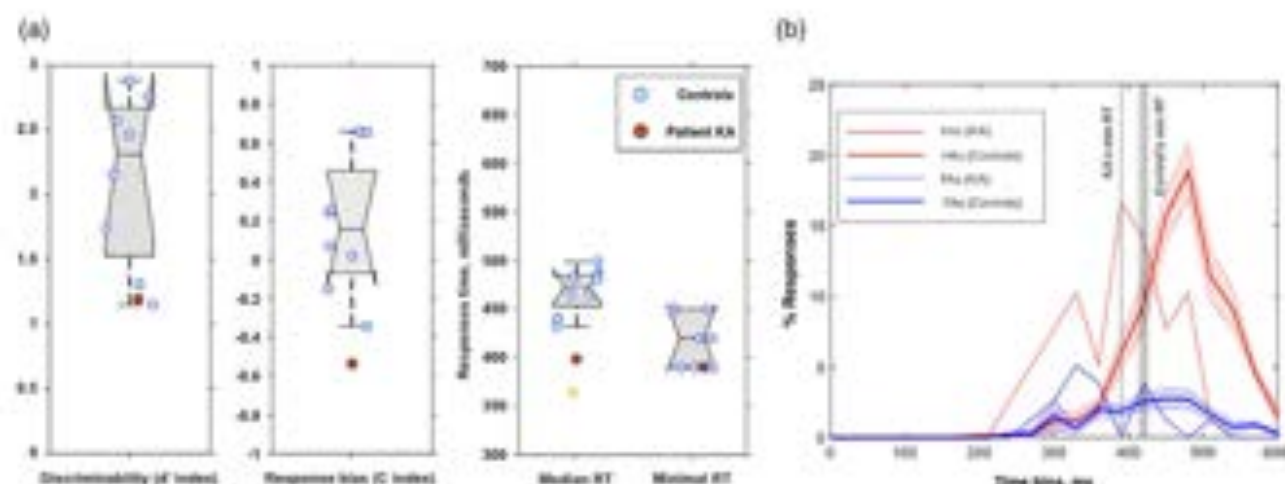


FIGURE 4 Context-free learning experiment. (a) Learning performances of patient KA (red circle) and controls (blue circles) assessed through discriminability (d' index, left plot), response bias (C index, middle plot) and response times (median response time and minimal reaction time, right plot). Yellow asterisk indicate $p < .05$. (b) Reaction times distributions, where Y axis shows % responses and X axis time bins. Dashed areas represent SEM [Color figure can be viewed at wileyonlinelibrary.com]

range of available learning strategies. These findings suggest that under certain circumstances, a very powerful and efficient learning system can allow new knowledge to be acquired independently of any episodic support. Finally, we performed the first ever cortical thickness analysis in DA. This yielded novel findings suggesting profound functional reorganization of the brain in Patient KA. Although we have yet to establish the exact nature of the system preserved in KA and how it developed, the present results are extremely valuable, not least from a clinical perspective.

8.1 | A case of selective and massive damage to the extended hippocampal system

Since 1997, when Vargha-Khadem, Gadian, and Mishkin (2001) first described cases of DA, case studies have mainly focused on hippocampal atrophy, with a typical 30–40% bilateral reduction. Until very recently, little was known about the status of the other brain structures, either within or outside the MTL. As stated in the Introduction, evidence for extrahippocampal damage was rather sparse, but suggested that structures like the putamen, brainstem, thalamus and retrosplenial cortex might be affected (Gadian et al., 2000; Rosenbaum et al., 2011; Vargha-Khadem et al., 2003). Importantly, abnormalities of the mammillary bodies and the fornix were described in Patients VJ and HC (Blindschädel et al., 2011; Olsen et al., 2013; Rosenbaum et al., 2014). Quite recently, a group study found that mammillary body atrophy was present in 66% of participants with DA, and there was a mild reduction in thalamus volumes at the group level (Dzirocz et al., 2017). This research confirmed that in DA, damage probably extends far beyond the hippocampal formations, and may include some other components of the extended hippocampal system, with an apparent variability between patients. Our findings for KA suggest that the entire hippocampal system is compromised, and not just some components.

Hippocampal subfield segmentation indicated severe and homogeneous impairment of hippocampal development across each and

every subfield, extending beyond the CA₁ subfield as one might expect following hypoxia (Kawasaki, Traynelis, & Dingledine, 1990). Hippocampal subfield volumetry has only been reported once in DA (Patient HC; Olsen et al., 2013), and this study also pointed to damage beyond the CA₁ subfield. However, KA's hippocampal atrophy was fully symmetrical compared with that of Patient HC, who was found to have relative preservation of the CA₂₋₃-dentate gyrus subfields in the left hemisphere. Atrophy was very severe in KA: the volumes we measured were below the lowest measures of the 20 controls, and volume reduction exceeded 55%. Patient KA therefore exhibited the most severe hippocampal atrophy of all reported DA cases.

The hippocampus was not the only structure to be severely atrophied in KA. We also report evidence for severe bilateral atrophy of the fornix, as well as an apparent absence of mammillary bodies. Complete agenesis of the mammillary bodies is an extremely rare condition (but see Patient HC; Rosenbaum et al., 2014). Moreover, we failed to visually identify the mammillothalamic tract in KA, suggesting complete agenesis of this tractus, which has not previously been reported, to the best of our knowledge. Thalamus volumetry also showed significant bilateral atrophy. Last, whole-brain cortical thickness analyses in KA revealed thinner left dorsal entorhinal, left retrosplenial and right anterior cingulate cortices. The whole extended hippocampal system was therefore compromised in KA. It is noteworthy that Patient KA and Patient HC were found to have atrophy of the left and right retrosplenial cortices, respectively. Yarn and Abasser (2009) argue that the retrosplenial cortex may be the target of covert lesions after damage to the hippocampal/mammillothalamic system (see also Aggleton, 2008). This region is thought to play a specific role in episodic learning and retrieval, beyond its acknowledged function linking the anterior thalamus nucleus and hippocampus. Evidence of an abnormal retrosplenial cortex in DA therefore reinforces findings of damage extending well beyond the hippocampal formation.

Such extensive injury, together with hippocampal subfield atrophy extending beyond CA₁, raises the question of the potential combined effects of an additional etiology (see Rosenbaum et al., 2014).

and of complex patterns of antero- and retrograde degeneration following early injury (e.g., Caine and Watson, 2000; Loftus, Knight, & Anand, 2003). Nonetheless, hypoxia remains the main probable cause, as recently suggested in Cooper *et al.*'s (2015) case series.

In contrast, in line with previous studies (Britzrolars *et al.*, 2003; Bindschadler *et al.*, 2011; Gadian *et al.*, 2000; Martins *et al.*, 2006; Olsen *et al.*, 2013; Vargha-Khadem *et al.*, 1997, 2003), we found that subhippocampal structures (perirhinal, entorhinal, and parahippocampal cortices) were preserved in KA.

To the best of our knowledge, Patient KA represents the first reported example in humans of such severe damage extending to each and every structure of the hippocampal system. This system is therefore highly unlikely to be functional. If, as Aggleton and Brown (1999) and Aggleton *et al.* (2010) suggest, this system is the core brain network underlying episodic learning, the patterns of both preserved and impaired memories in Patient KA are of considerable interest.

8.2 | A case of knowledge acquisition without episodic learning

As stated in the introduction, prior reports of patients with amnesia consistently showed preserved semantic memory retrieval despite compromised episodic memory, the most striking results coming from patients with DA. However, evidence for preserved semantic knowledge relied upon very limited assessments—mainly tests of academic skills like the Vocabulary and Information subtests of the WAIS, where patients typically perform in the low-to-normal range. This is of great importance, as it has been pointed out that some residual level of episodic learning abilities may allow patients—given sufficient time and repetition—to reach close-to-normal levels of knowledge (see Squire and Zola, 1991). Interestingly, Kan, Alexander, and Verfaellie (2009) suggested that in cases of adult-onset amnesia where key brain structures for the semantic system are preserved (anterior and lateral parts of the temporal lobes), prior knowledge about to-be-learned items enhances some residual episodic learning. Thus, in cases of early-onset amnesia, any residual episodic learning ability may allow, after sufficient repetition, the acquisition of a limited but substantial amount of semantic knowledge, which may, in turn, boost further learning, leading to the putative semantic-episodic distinction reported in prior DA cases. Accordingly, previous investigations of new learning (rather than semantic retrieval) in DA have shown that patients' performances critically rely on the number of repetition trials (Brand, Gardiner, Vargha-Khadem, Baddiley, & Mishkin, 2006; Gardiner *et al.*, 2006; Martins *et al.*, 2006).

Episodic learning in Patient KA was clearly close to zero, with delayed recall scores for a wide variety of stimuli at floor level, and immediate source memory performances also at chance level. In many tasks, we showed that KA did indeed perform more poorly than most previous DA cases. These findings clearly demonstrate that little, if any, residual episodic learning could occur in KA. Even so, his memories about public events, famous people, objects and famous buildings, as well as his lexical knowledge for concepts coined only 2–3 years before testing, were found to be in the normal, superior, or even very superior range. KA indeed outperformed controls on some tasks involving the recall and forced-choice recognition of famous people

and public events. It is hard to see how a slow, inefficient and gradual process of episodic learning can lead to this pattern of semantic memory performances. One limitation that must be mentioned here is the absence of control for media exposure, which may have altered the results (Kapur, Thompson, Kartsounis, & Abbot, 1999). However, across multiple interviews with the patient and his family, and across several meetings at the patient's home, we did not collect any information that may suggest that KA differs from people of his age regarding media exposure. More specifically, the patient reads the newspaper several times a week, and watches TV once a day, which falls in the normal range in France. Another limitation that should be mentioned is that we did not use the "Dead-or-Alive" testing procedure for famous names or faces (Kapur, Young, Busman, & Kennedy, 1999), which has proven particularly sensitive to semantic learning disruption in amnesia (e.g., Manns *et al.*, 2003). However, we have brought extended evidence that patient KA performs normally on tasks requiring not only to accurately make fame judgments about faces or names. We have shown that he could normally name celebrities, provide at least one accurate detail from their lives (see scores at the "TOP 30" tests battery, Table 6), and even correctly perform a rather difficult matching task (see "SEMPer" tests battery, Table 6) that requires far more accurate and detailed knowledge about celebrities than simply giving their name, occupation, or making a Dead/Alive judgment. Our findings for KA are therefore difficult to explain without making the assumption of some functional distinction within declarative memory.

We sought to control for the range of processes involved in semantic memory retrieval, in order to explore whether this apparent preservation of semantic knowledge in KA could be the result of alternative, putatively abnormal, strategies (Gardiner *et al.*, 2006; see also Bird *et al.*, 2008, in Patient Jon). To this end, we carried out a series of recognition experiments featuring time constraints, which greatly limited the range of possible strategies. Experiments 2 and 3 (Section 5) involved the detection and identification of famous faces, respectively. We argue that these tasks could only be successfully performed if a normal representation of each famous face had been built across prior encounters. Moreover, the identification experiment (Experiment 3) further required these representations to include sufficiently detailed visual knowledge for the celebrity to be distinguished from the foils. The fact that KA outperformed controls on both speed and accuracy in Experiment 2, and performed at the controls' level in Experiment 3, strongly supports the idea that not only did he have normal access to context-free knowledge for faces, but also that the representations he had built of these faces were quite similar to those of controls. The normal reductions in accuracy observed in KA when inverted faces were used, further supports this interpretation, suggesting that the holistic processing of faces had similar costs for KA and for controls (Rossion, 2008). However, we acknowledge that both Experiments 2 and 3 can be achieved at a presemantic level, on the basis of "Face Recognition Units" (FRUs) activation solely within a typical face-processing framework (Bruce & Young, 1986). Nonetheless, we argue that these tasks can inform us about the stored context-free, or semantic, knowledge in patient KA, for several reasons. First, the fact that patient KA succeeds in Experiment 3 and outperforms controls in the Experiment 2, despite suffering amnesia from birth, is

in itself a surprising finding. This result might indicate that some learning system independent of the hippocampal system has allowed the building of context-free knowledge about faces at least as efficiently as controls do. The fact that KA outperformed controls in the "TOP-30" task involving famous faces as stimuli strengthens this idea. Second, the most recent revision of the Bruce and Young framework (Burton, Bruce, & Johnson, 1992) adds the "Semantic Information Units" (SIUs) to the above-mentioned FRUs. Within that framework, SIUs activation is expected to result in faster recognition for faces with preexperimental knowledge like the famous faces we used in Experiment 2 (e.g., Herzmann & Sommer, 2020). The fact that Experiment 2 yielded slower RTs than face categorization (Experiment 1) and individual face recognition (Experiment 3) strengthens the idea that late processing stages are involved in the task. Although controls reached min RTs around 490 ms and a median d' around 0.85, patient KA was on average 100 ms faster and far more accurate ($d' > 2.0$) (see Figure 5). We therefore speculate that such an unexpected finding can be at least partly explained by the overreliance of the patient KA on his preserved semantic knowledge (i.e., SIUs) to make familiarity decisions, thus abnormally speeding up his RTs within the Famous Face Recognition task. Future work is however clearly needed to assess more directly the acquisition of semantic knowledge in patients with developmental amnesia (Blumenthal et al., 2017 for a recent report).

Taken together, the results of these experiments speak for normal-to-very-superior abilities in Patient KA for retrieving semantic memories.

Regarding the acquisition of new explicit knowledge, rather than its retrieval, we found that strict speed constraints did not prevent Patient KA from performing just as fast and as accurately as controls (see Section 6). Strikingly, Patient KA even had shorter median reaction times during the test phase, and his minRT was within the controls' shorter range, suggesting that the cognitive processes associated with the judgment of prior occurrence for newly learned material were at least as efficient in KA as they were in controls. This was not achieved after extensive repetition trials, but after a single study trial. It is noteworthy that when he gave go responses to targets, KA proved to be just as fast as controls, strongly supporting the idea that he used fast, automatic, familiarity-based processes.

In summary, despite no evidence for any residual context-rich memories, Patient KA was able to acquire normal or superior levels of context-free memories just as efficiently as controls, independently of the modalities or kinds of concepts we explored in the present study. It is unclear for the time being how he acquired such massive amount of knowledge. Given that he has no episodic memory, he necessarily uses learning strategies that are different from healthy subjects who can use their episodic memory whenever they learn new facts. However, it is very unlikely that his abilities can be explained in terms of residual episodic abilities, and instead it supports the theoretical assumptions that episodic learning is not a prerequisite for semantic knowledge acquisition. Further understanding of how such a powerful learning system could be so efficient in KA is warranted, given the opportunities it might bring for the rehabilitation of amnesic patients. Apart from controversial findings of rapid arbitrary learning in 4 amnesic patients that presumably resulted from the so-called

fast-mapping mechanism (Sharon, Moscovitch, & Gilboa, 2011), we are not aware of any previous findings suggesting normal knowledge acquisition in amnesia without extensive repetition and/or dedicated learning techniques.

8.3 | Cortical thickness in KA: An explanation for his superior semantic memories?

We found that left temporal pole cortices tended to be thicker in Patient KA, while we observed thinner cortices within structures of the extended hippocampal system. Given the critical role of the left anterior temporal lobe in semantic or context-free memories (e.g., Guido, 2017; Jefferies, 2013; Lambon Ralph, 2014), and prior well-known studies relating higher brain volumes to superior abilities or expertise (e.g., Woollett & Maguire, 2011), this requires further discussion.

Cortical thickness is a relevant measure when investigating neurodevelopmental disorders, as it is thought to reflect both synaptogenesis and synaptic pruning, two major maturation processes of the brain (Gogtay et al., 2007; Huttenlocher, 1990; Khundrakpan, Lewis, Zhao, Chouinard-Decorte, & Evans, 2016). Surprisingly, we did not find any prior cortical thickness analyses for DA. Nonetheless, neonatal anoxia-hypoxia has been found to have a specific impact on cortical thinning within medial temporal regions (Bregant et al., 2012; see also Phillips et al., 2011; Zublaume-Eloza et al., 2012, for the specific influence of preterm birth on regional cortical thinning patterns). In Patient KA, we found abnormally thin cortices in regions supposed to follow a cubic developmental trajectory, with an initial rapid increase in thickness followed by an asymptotic decrease (i.e., right cingulate cortex), and thicker cortex within the left temporal pole, a region supposed to follow a quadratic trajectory (i.e., inverted U-shaped curve; Shaw et al., 2008). We can therefore speculate that neonatal hypoxia in KA may have altered the developmental trajectory of cortical thickness, leading to functional reorganization within extrahippocampal structures (for evidence in monkeys and humans, see Braun et al., 2008; Lavenex, Lavenex, & Amaral, 2007). Interestingly, the morphology of the temporal pole has already been associated to extraordinary memory performance in subjects with Highly Superior Autobiographical Memory (HSAM). These subjects are able to recall with very high accuracy a large amount of events of their own past, including days and dates when they occurred (Parker, Cahill, & McGaugh, 2006). LePort et al. (2012) have shown that a sample of HSAM subjects presented with lower estimates of gray matter density in the bilateral temporal poles (i.e., BA 38). Thus, while HSAM is characterized by very superior autobiographical episodic memory but average levels of declarative memory otherwise, including semantic memory, KA presents with dramatically impaired autobiographical episodic memory but superior to very superior semantic knowledge. It is therefore tempting to consider the possibility that the neuronal plasticity within the area of the temporal poles plays a critical role in the differential development of episodic autobiographical and semantic memories.

However, as stated above, borderline or low-average ranges of performances across semantic knowledge tasks are the rule in DA. Evidence for very superior explicit memory in KA was therefore unexpected (but see Kapur, 2011, for an extensive review and discussion of such paradoxical profiles). Whereas bilateral hippocampal

atrophy typically does not exceed 30–40%, it was >50% in KA. A similar counterintuitive finding of better performance despite more severe damage had already been reported (Baxter & Murray, 2001; Murray & Mishkin, 1998; see also Heuer & Bachevalier, 2011; in humans, see Barbeau et al., 2005; but see Zola & Squire, 2001). For example, using DMS procedures, greater impairment in recognition memory following smaller hippocampal lesions has been highlighted in monkeys (Murray & Mishkin, 1998). These authors suggested that in the case of mild hippocampal damage, for example, irrelevant signal processing coming from that partly inefficient subsystem may compete with the relevant physiological signal processing from preserved surrounding subsystems. Earlier studies in monkeys had suggested that the amount of hippocampal damage required to produce a significant deficit in DMS tasks is around 20% (Zola & Squire, 2001), which is close to the suggested 20–30% cut-off reported by Isaac, Watkins, Lucas, Mishkin, and Gadian (2003) for a DA syndrome. Thus, an interesting hypothesis that requires further investigation—possibly in a group study—is that an inverted (convex) quadratic function characterizes the relationship between the degree of context-free memory preservation and the amount of damage to the hippocampal system or the thickness of temporal neocortical areas in DA.

9 | CONCLUSION

We have reported the case of Patient KA, who has developmental amnesia, and was found to have damage beyond the hippocampus itself, encompassing the whole of the extended hippocampal system. As expected, KA was densely amnesic, with no evidence of residual episodic learning abilities. Despite this, he had normal-to-very-superior semantic knowledge, and was able to retrieve that knowledge with the same speed and accuracy as controls. Besides, new explicit learning was found to be possible in for KA, again within the fully normal range regarding accuracy and speed, even under strong strict temporal time constraints. Our findings are consistent with the existence of a functional dissociation, [or division of labor], for declarative memory within the MTLs. Importantly, they add to the growing body of evidence suggesting that rapid learning may occur outside the hippocampus. However, we have yet to fully understand how such rapid, explicit, learning can occur and be promoted in amnesic patients.

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Complementary analysis

While in the process of publication of this case report, we lacked a thorough investigation of the MTL structures volumes independently of the cortical thickness analysis. Still, not only this is critical for further interpretation of KA's profile, but also we need, as much as possible, to seek for replication of our research findings across independent methods if we are to build new empirical knowledge on solid grounds. It further may bring another advantage, namely to highlight the relative limitations of several methods now available for, e.g. automatic MTL structures segmentation. We therefore performed such an analysis to add supplementary data regarding the highly relevant status of the perirhinal and entorhinal cortices in patient KA.

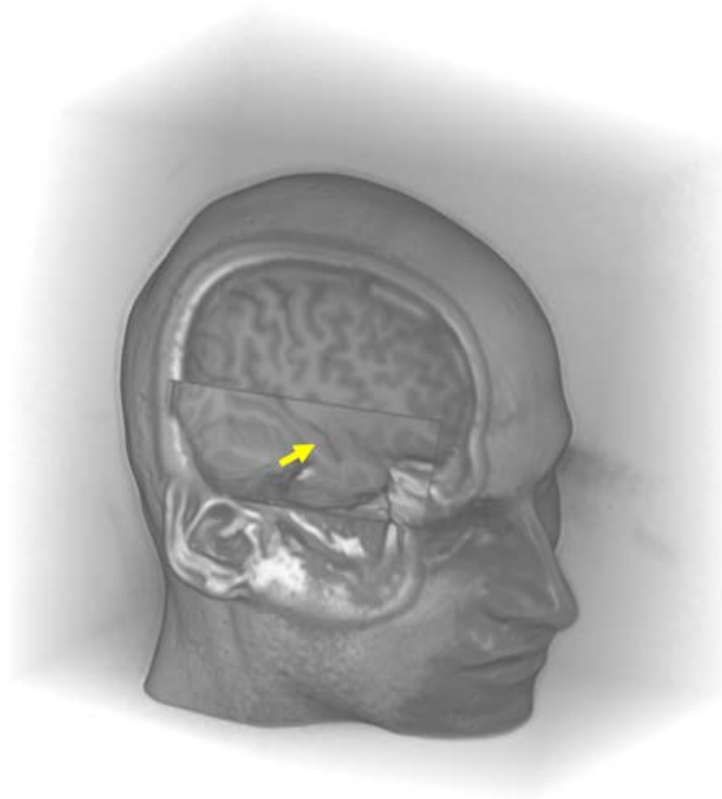


Figure 35. Further MTL structures analysis in patient KA.

Methods

As part of his clinical follow-up, patient KA underwent a new series of MR images acquisitions. Images were acquired with 3-Tesla MR system (Prisma MR B17, Siemens, Erlangen, Germany) using a 64-channel array coil. The parameters of sequences were as

follows. Three-dimensional (3D) sagittal T1-weighted magnetization prepared rapid acquisition with gradient echo (MPRAGE) images: TR/TI/TE=1900/900/2.26ms, 9° flip angle, FOV=256x256x176mm, 1x1x1mm voxel size, yielding 176 contiguous slices. T2-weighted coronal 2D Turbo Spin Echo: TR/TE=8020/80ms, thirty 2mm slices with no gap, 150° flip angle, 0.4x0.4x2mm voxel size.

Image preprocessing and analysis were ran using the Automated Segmentation of Hippocampal Subfields toolbox (ASHS, Yushkevich et al., 2015) that automatically segments regions of the parahippocampal gyrus (perirhinal and parahippocampal cortices) together with the entorhinal cortex and hippocampal subfield. Regarding the hippocampal subfield, an additional analysis was performed using the volBrain HIPS pipeline (Manjón & Coupé, 2016; Romero, Coupé, & Manjón, 2017) that follows a distinct segmentation algorithm. For the sake of comparison regarding the results of the ASHS pipeline, data from 35 healthy controls matched with KA for age was taken from Ota et al., (2017), because the authors used the same segmentation pipeline and image acquisition was performed on a Siemens MRI scanner as was the case for the patient KA. Unfortunately, MTL structures volumes in this study are reported across hemispheres; as a consequence, we also used data from 45 healthy controls also matched with KA for age (Sone et al., 2016), but note that images were acquired on a Philips 3.0-T MR system with a 32-channel coil (Philips Medical Systems, Best, The Netherlands). Bayesian t-tests for single case studies (Crawford & Garthwaite, 2007a) were performed to further assess whether the estimated volumes computed for patient KA differed from the normal range, as sampled in Ota et al. (2017) and Sone et al. (2016). This approach provides a Point Estimates (PE) of percentage of the normal population falling below the patient's volume, together with a 95% confidence interval on the estimation. Given our aim of independent replication of our findings on hippocampal subfields on the one hand, and of further assessment of the perirhinal cortices on the other hand, two-sided tests were performed. Finally, the volBrain pipeline generated comparisons between volume estimates expressed as percentage of the intra-cranial volume and expected volumes at a given age, based on lifespan estimation modelling derived from several MRI databases pooled together (N=2944) (Coupé, Catheline, Lanuza, & Manjón, 2017), which we further report.

Results

Volumes estimates of the hippocampal subfields as computed by the volBrain pipeline based on the dataset of Kulaga-Yoskovitz et al., (2015) (N=25 controls, mean age=31 +/- 7 years old) confirmed the severe atrophy of each subfield in patient KA (see Figure 36).

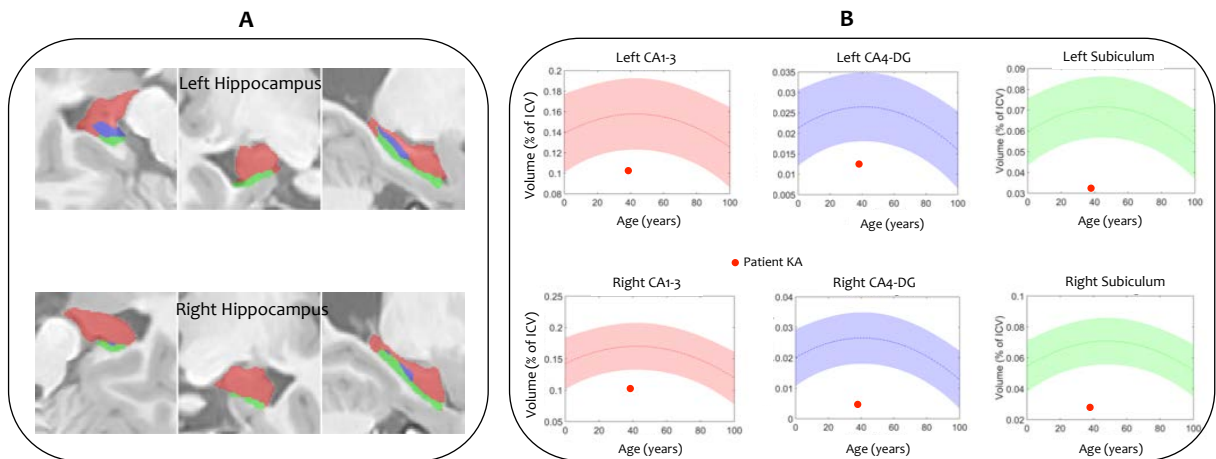


Figure 36. Results from the volBrain pipeline (Coupé et al., 2016; Romero et al., 2017). (A) Hippocampal subfields segmentation in patient KA – dataset from (Kulaga-Yoskovitz et al., 2015); (B) Comparisons between volume estimates in KA and expected values (see Coupé et al., 2017)

The volumes of the bilateral entorhinal and perirhinal cortices (the perirhinal cortex is roughly considered as similar to Brodmann Areas 35 & 36) in KA did not differ from that of controls, and this result was similar with the two independent control samples (Sone et al., 2016; Ota et al., 2017) (see Figure 37). However, hippocampal subfields volumes were dramatically smaller in KA, and again here, the result did not depend on one particular sample.

Considering the Ota et al. (2017) reference sample, for the hippocampal subfields, PEs ranged from 0 to $22e^{-5}$, with a maximum upper credible limit value of $86e^{-3}$. The only exception was for CA3 subfield that failed to reach significance under bilateral testing ($p=0.0682$; $PE=3.41$; $\%95CI=[0.68 - 8.94]$), but still fell within the very low range of controls. Regarding the entorhinal cortex, again we found a significant lower volume in KA ($PE=0.17$; $\%95CI=[0.00 - 0.92]$), while BA 35 & BA 36 volumes were in the normal range (BA 35: $PE=39.46$; $\%95CI=[27.15 - 52.64]$; BA 36: $PE=36.00$; $\%95CI=[24.02 - 49.15]$) (see Figure 38).

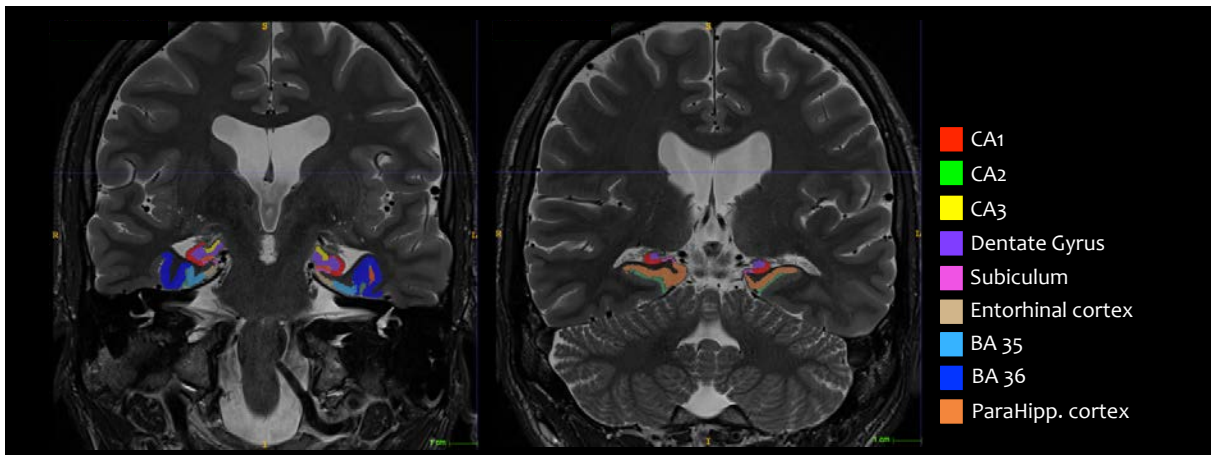


Figure 37. Illustration of the results of the Automatic Segmentation of Hippocampal Subfield toolbox performed with the ITK-SNAP software (www.itksnap.org, Yushkevich et al., 2006; ASHS, Yushkevich et al., 2015), on a T2-weighted, High Resolution, image of KA's brain.

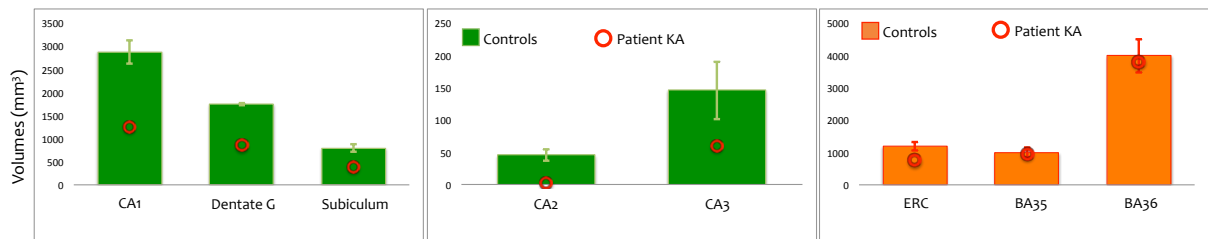


Figure 38. Quantitative results from the ASHS segmentation protocol: data from Ota et al. (2017) serves as a control sample (35 subjects aged 38.9 +/-13.4). Results for the anterior sub hippocampal structures are in orange, while hippocampal subfields are depicted in green. See text for statistical testing.

Use of the Sone et al. (2016) control sample essentially led to the same results, but provided detailed results for left vs. right hemispheres. Thus, we found that the CA3 subfield was slightly more preserved on the left hemisphere (PE=9.47; %95CI=[4.03 – 17.41]) than on the right (PE=3.45; %95CI=[0.89 – 8.20]), albeit both sides showed non-significant differences (left p value=0.189; right p value=0.069) under bilateral testing. Moreover, the findings of entorhinal cortex atrophy actually were replicated only in the right hemisphere (PE=0.02; %95CI=[0.00 – 0.14]), not in the left (PE=16.16; %95CI=[8.61 – 25.92]). In addition, hippocampal subfields (CA1, CA2, Dentate Gyrus and Subiculum) again showed significant levels of atrophy, with PEs ranging from 0.0001 to 0.082, with a maximum upper credible limit value of 0.44. Conversely, BA 35 & BA 36 volumes were again in the normal range bilaterally (left BA 35: PE=61.15; %95CI=[49.54 – 72.07]; right BA 35: PE=64.54; %95CI=[53.00 – 75.19]; left BA 36: PE=89.51; %95CI=[81.22 – 95.34]; right BA

36: PE=76.85; %95CI=[66.04 – 85.90]) (see Figure 39). Note that here, left anterior perirhinal cortex volume in patient KA was found in the very high range of controls, actually close to significance, with a maximum upper credible limit value of 0.95.

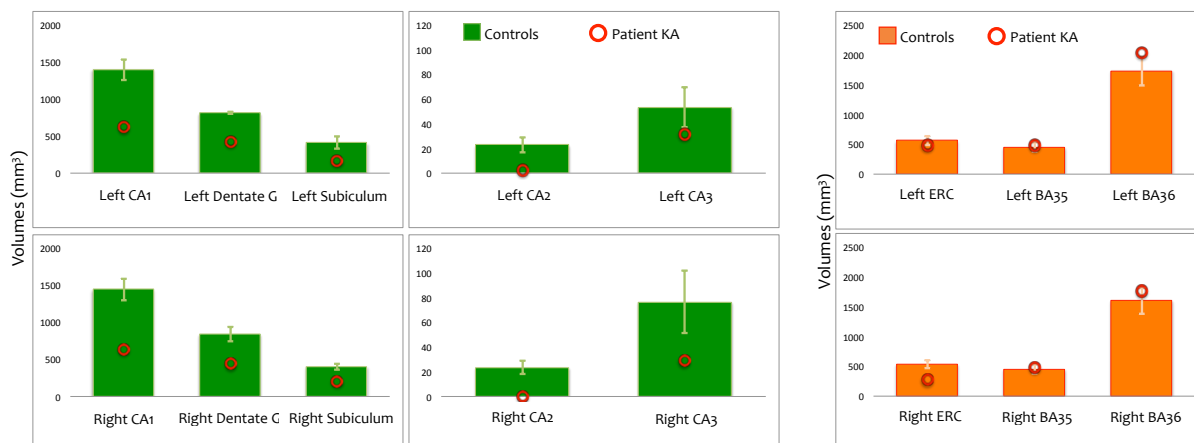


Figure 39. Quantitative results from the ASHS segmentation protocol: data from Sone et al. (2016) served as a control sample (45 subjects aged 42.6 +/-16.4). Results for the anterior sub hippocampal structures are in orange, while hippocampal subfields are depicted in green. See text for statistical testing.

Discussion

These supplementary analyses of the MTL structures in patient KA provide important additional findings beyond those reported in Jonin et al., (2018).

First, we have replicated the findings of severe hippocampal atrophy across each and every subfield, using a different MR-scanner, a different T2-weighted, high-resolution sequence, two distinct segmentation protocols and two independent control samples from the literature. These results make very robust our claim that patient KA presents with the most severe bilateral hippocampal atrophy ever reported in developmental amnesia.

Second, the findings of normal volumes in the perirhinal and entorhinal cortices not only confirm by means of a different approach the results from the cortical thickness analysis, but they add to the limited number of studies in developmental amnesia including full MTL structures segmentation (Bindschaedler et al., 2011; Olsen et al., 2013).

Third, there is a striking consistence between findings of a larger volume of left BA36 in patient KA and our previous finding of a thicker cortex in the vicinity of the left BA38. This

result strengthens in our view the hypothesis of a deep reorganization of the MTL following neonatal damage in patient KA, which in turn may have supported the preserved learning abilities in this patient.

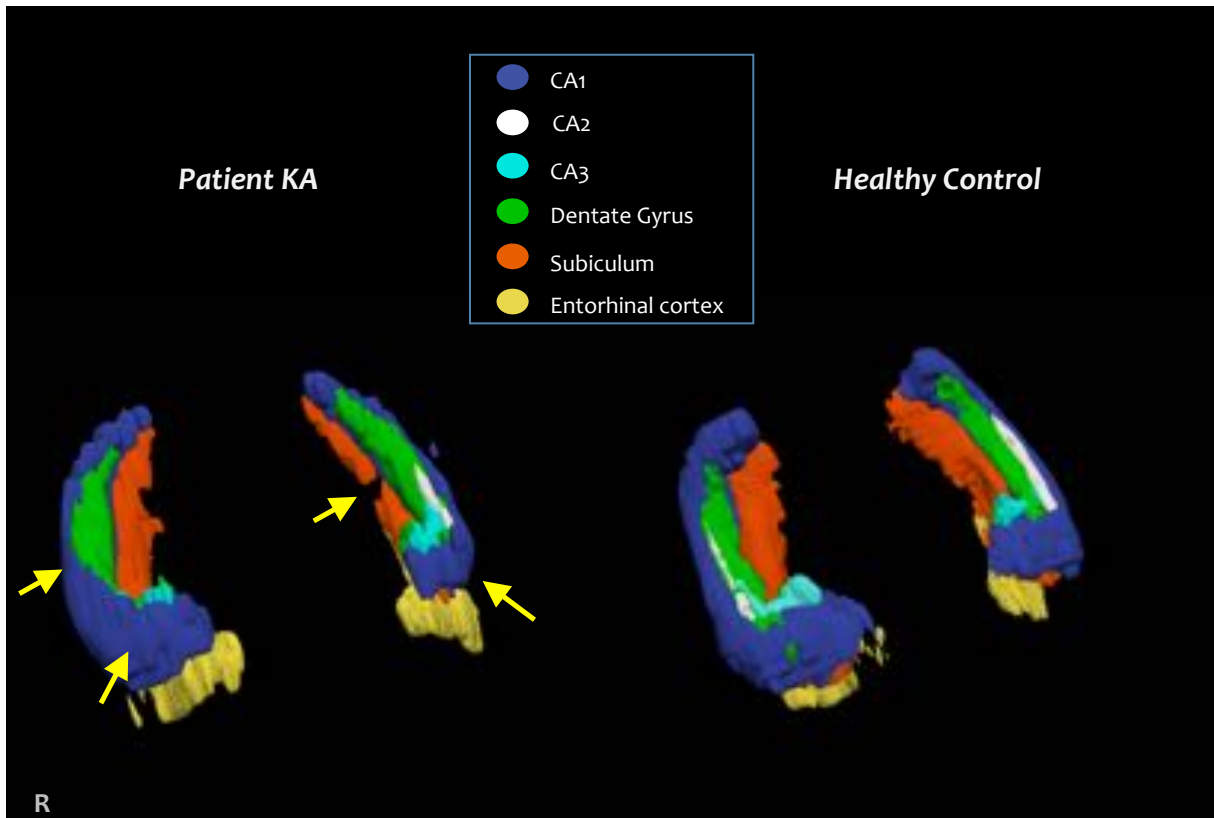


Figure 40. Illustration of the hippocampal complex anatomy in patient KA and a healthy right-handed man matched for age. This is a 3D render derived from a template-based shape analysis recently proposed within the Large Deformation Diffeomorphic Metric Mapping framework (Cury et al., 2018). It therefore represents the shape features of the hippocampal subfields and of the entorhinal cortex, better highlighting critical local abnormalities in KA's hippocampal complex (yellow arrows depicts some of these abnormalities that do not appear in typical 3D renderings).

Experiment 2: Does normal explicit learning in KA generalize to meaningless memoranda?

Highlights from Experiment 2

The demonstration in patient KA that a very effective explicit learning system exists outside the extended hippocampal system (Experiment 1) is shown to be **material-specific** in Experiment 2.

New learning, largely based on familiarity-based retrieval, remains possible in patient KA but only for concrete, meaningful stimuli as it is the case for object pictures. However, **KA is severely impaired for abstract patterns** free of prior conceptual representations.

However, healthy **controls present a clear benefit with meaningful materials, and so does KA**. Controls perform twice as good with objects as with abstract patterns (d' index moving from 1.14 to 2.25 in Controls, from -0.18 to 1.20 in KA), with little impact on response bias overall (in Controls, 0.17 vs. 0.11, and -0.45 vs. -0.54 in KA, respectively).

Findings of Experiment 2 **do not fit with the dual processes models** of recognition memory, and are not in line with prior reports of preserved abstract patterns recognition after bilateral hippocampal damage (patient FRG, Barbeau et al., 2005; Barbeau, Pariente, Felician, & Puel, 2011).

Beyond the possible accounts for this particular pattern of preserved and altered memory in KA, that could be related to a slight right entorhinal cortex atrophy, such a dissociation speaks for either material-specific view of the role of the MTL in recognition memory, or for a (non exclusive) view related **to the benefits of pre-existing knowledge in new learning**.

We will further concentrate on the latter.

Introduction

Patient KA with developmental amnesia associated with extensive and selective damage to the whole extended hippocampal system has acquired superior levels of conceptual knowledge in some domains. Moreover, KA was found able to acquire and retrieve context-free memories at the same speed as controls. This observation was made despite a severe amnesic syndrome, with virtually no residual episodic memory. The case of patient KA therefore strongly speaks for the existence of a very efficient explicit learning system, which does not rely on the extended hippocampal system.

How in the first place KA has acquired such knowledge remains unclear, even though familiarity-based learning is a candidate. In any case, the acquisition of new conceptual knowledge must rely on the successful extraction of regularities in the environment, in order to represent such commonalities within a relevant general category (i.e. new conceptual representation). Extraction of regularities must allow both discrimination and assimilation of events features, so that across episodes, features that are common to a single concept can be assimilated within a conceptual representation, while features that differ across concepts can be discriminated as well (e.g. see Mack, Love, & Preston, 2018). By showing that patient KA is unimpaired at acquiring new context-free memories for object pictures, we thus have brought evidence that new explicit memories for existing concepts can be formed by the patient. However, we did not address directly how new concepts could be acquired. If successive instances of familiarity-based retrieval can lead to the formation of a new concept, it implies that after the inaugural exposure to unknown, or at least very unfamiliar stimuli, further related cues should trigger accurate familiarity-based recognition. To explore this idea, what we need is unknown, meaningless materials, rather than pictures of objects corresponding to pre-existing representations.

In the following experiment, we used abstract coloured patterns as memoranda and asked whether patient KA could acquire new context-free memories for these stimuli. The task was exactly the same as the one reported in Jonin et al. (2018, Expt. 7), apart from the use of different stimuli.

Materials & Methods

Participants

14 right-handers healthy controls aged 22-34 years old and more educated than KA (formal years of education ranged from 14 to 21) participated. All participants provided informed consent for the experiment, and were instructed that this would be a memory test. In addition to the current experiment, they all underwent the same task as the one reported in Jonin et al. (2018, Expt. 7), whereby they had to learn a series of pictures of objects.

Stimuli

280 abstract patterns were chosen from various internet database. They were 200x200 pixels bitmap files picked up to be hard to verbalize and lacking any meaningful pattern (see Besson, Ceccaldi, Didic, & Barbeau, 2012). Among these images, 120 were randomly chosen as targets and 120 as stimuli, the remaining items being used for practice trials.

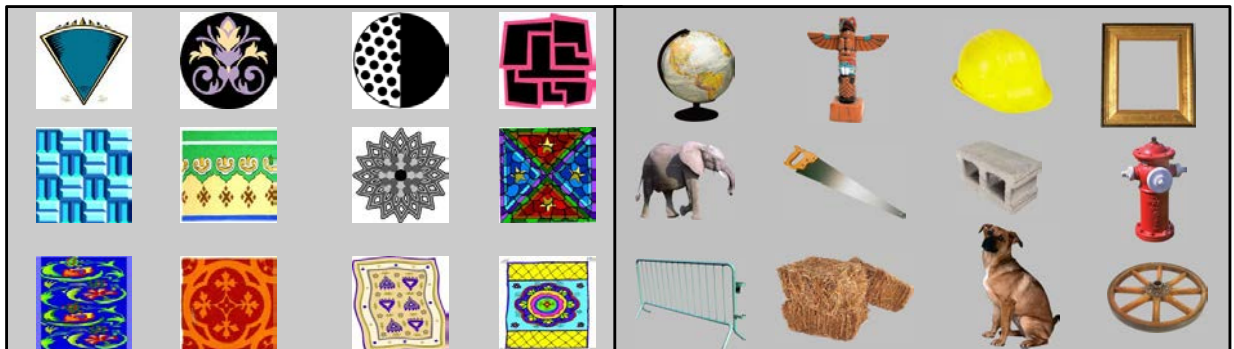


Figure 41. Examples of the stimuli from Experiment 2. Abstract patterns on the left, real objects on the right.

Procedure

The Speed and Accuracy Boosting procedure was used (SAB), as described in Jonin et al. (2018), and adapted from Besson et al. (2012). Briefly, participants were explicitly instructed to encode visual stimuli in a self-paced study phase. Then, after a 3-minutes break filled with a cartoon video, recognition memory was assessed through a Go/NoGo procedure. Subjects had to make Go responses for studied items, and NoGo responses (i.e. doing nothing) for unstudied items. Subjects made their Go responses by using a dedicated infrared response pad combined with a CRT screen, allowing a high fidelity recording of

response times. Each response was followed by a 600 ms audio feedback informing the subject of whether his response was a Hit, a False Alarm (FA), a Correct Rejection (CR) or a Miss (M). What makes the SAB procedure very hard is the use of a constraining response deadline that was set at 600 ms. Thus, at test, the item was flashed on the screen for 100 msec, then the participant had only 500 ms. to make his decision and give his response. A white cross was displayed for a jittered (300-600 ms) duration during Inter-trial intervals. The SAB procedure, as discussed elsewhere, is assumed to provide a direct estimate of familiarity-based recognition with very limited involvement of recollection (Besson et al., 2012; Sauvage, Beer, & Eichenbaum, 2010).

Analyses

Responses at test were analysed in the framework of the signal detection theory, with computations of corrected Hits, FAs, CRs and Ms rates (Snodgrass & Corwin, 1988) together with the d' index used as a measure of discriminability and C index as a measure of response bias. Response times were also analysed, and we were especially interested in the temporal dynamics of Go responses. Our principal analysis was the comparison of patient KA's performance (i.e. d' , Hits, FAs) with that of healthy controls, asking whether preserved recognition memory in KA with the SAB procedure as previously found could generalize to novel, meaningless, visual stimuli. All statistical comparisons were performed using Bayesian t-tests for single case studies (Crawford & Garthwaite, 2007), as described in the previous experiment (p. 170).

Results

The patient obtained a negative d' (-0.184), due to a higher rate of FAs (36%) than Hits (29%). When compared with controls' performance, this suggested a severe impairment in KA since the Point Estimates for the d' index was 0.29, showing that only 0.29% of normal controls would be susceptible to get a lower score. Importantly, the patient was very conservative (patient KA, $C=-0.452$; controls, $C=0.169$; $PE=0.81$, $\%95CI=[0.00 - 5.03]$). This reflected a normal FA rate (patient KA, $FAs=36\%$; controls, $FAs=35\%$; $PE=54.06$, $\%95CI=[33.74 - 73.62]$) but an impaired Hit rate (patient KA, $Hits=29\%$; controls, $Hits=76\%$; $PE=0.02$, $\%95CI=[0.00 - 0.13]$).

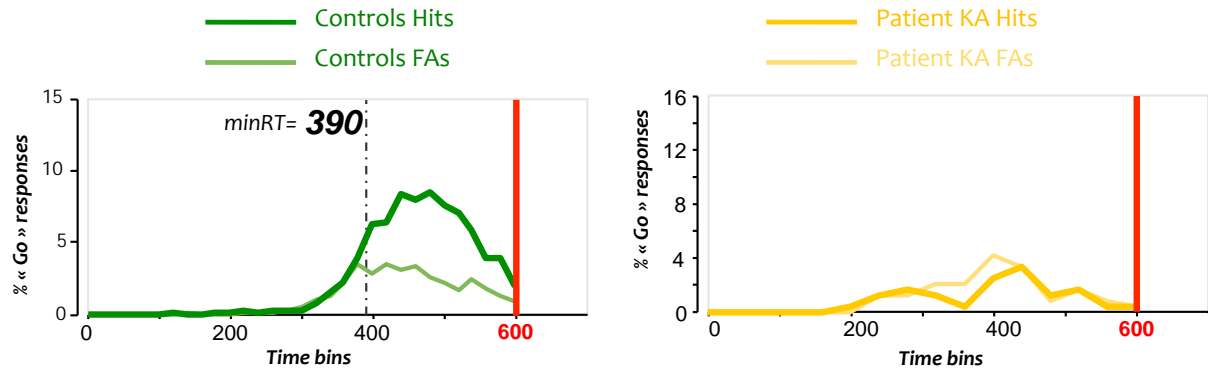


Figure 42. Speed and Accuracy Boosting procedure with abstract visual patterns in patient KA (right) and 14 healthy controls (left).

Response times analysis revealed that controls could achieve accurate recognition below 400 ms (across trials $\text{minRT}=390$ ms), while in patient KA, we could not find successive time bins where Hit rates (i.e. correct Go responses) significantly exceeded FA rates (i.e. incorrect Go responses), thus making impossible to estimate a minimal reaction time (minRT). These results were in sharp contrast with the normal performance of KA at the same task, but with meaningful (i.e. pictures of objects) items (see Jonin et al., 2018).

To further investigate this apparent dissociation, we took advantage of the data collected in the same control sample with the SAB procedure but using object pictures, and performed a regression analysis aimed at providing estimates of d' with Objects given the d' obtained with abstract patterns (Crawford & Garthwaite, 2007b). In short, this method builds a bivariate regression equation from the controls sample summary statistics (mean, standard deviation, t value from a paired-sample t test between conditions), which then can be applied to one single patient. Basically, the method tests whether the discrepancy observed in the patient falls within the normal range, as reflected in a Point Estimate value similar to the one described above.

Considering the discriminability index d' , the predicted score of KA in the Object condition given his score in the Abstract patterns condition was 0.420. This is a large and significant deviation from the actual score of 1.198, yielding a PE of 2,52 (%95CI=[0.00 – 23.20]), meaning that less than 3% of the normal population is expected to present a larger discrepancy.

Finally, we plotted the response times for “Go” responses of the patient KA and controls in both conditions to better apprehend his behaviour at the same task, but with different

stimuli (see Figure 43 & Figure 44). Response times below 200 ms were discarded based on prior work with the SAB procedure.

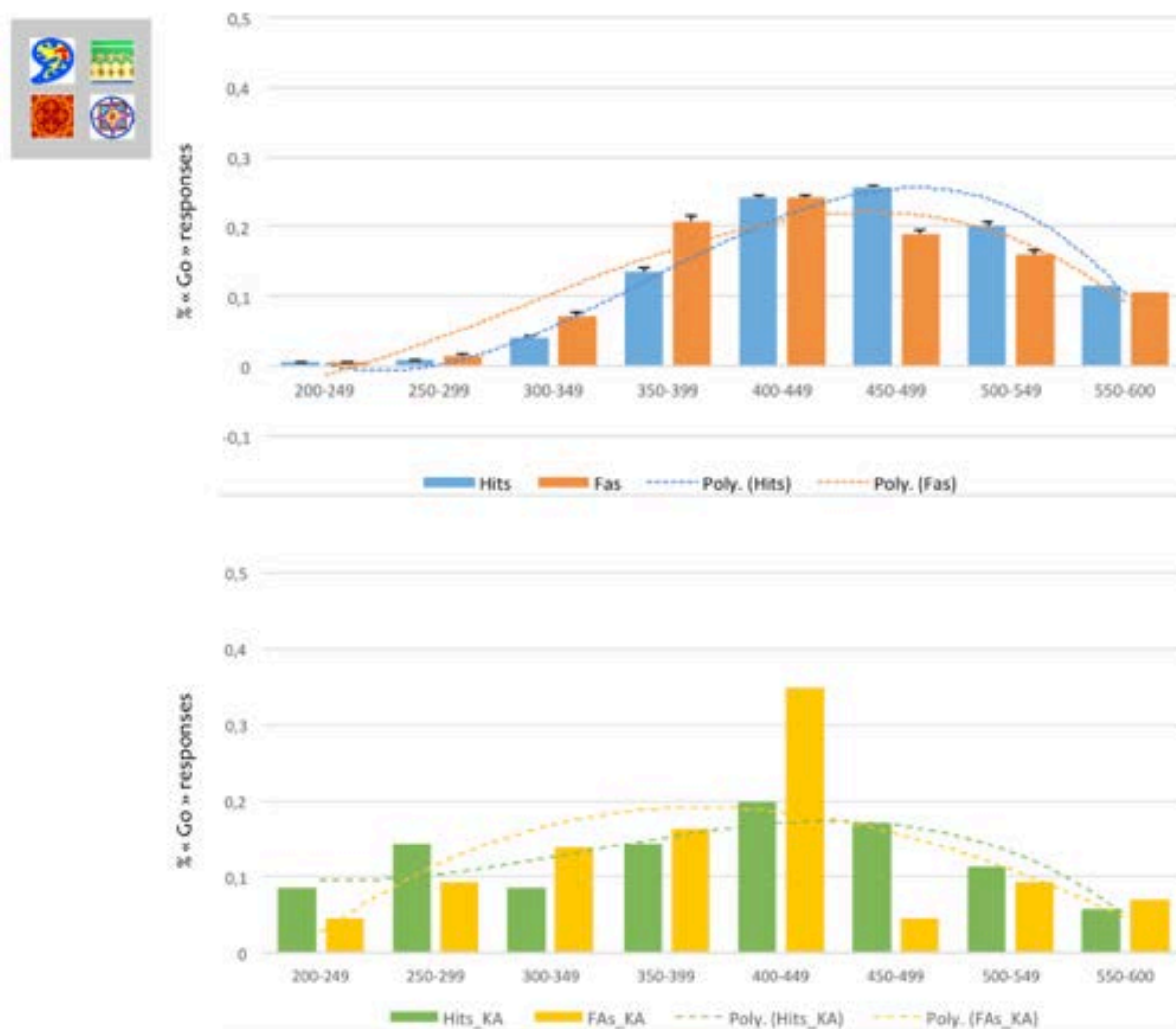


Figure 43. Speed and Accuracy Boosting procedure with abstract patterns. Y-axis shows percentage of “Go” Responses, X-axis represents 50 ms time bins. Top panel depicts average performance across control subjects; bottom panel illustrates performance of patient KA. Dashed lines represent the 3rd order polynomial fitting curves for Hits and FAs.

This analysis shows that controls made more FAs around 350 ms and up to the time bins where Hit rate started to exceed FA rates in the abstract pattern condition, whereas the FA rates remained slightly lower in the object condition. By contrast, patient KA gave many more “Go” (i.e. Hits and FAs) responses as early as 200 ms in the abstract pattern condition, and he could not, even in the later time bins, reliably discriminate targets from lures, yielding rather flat polynomial curves.

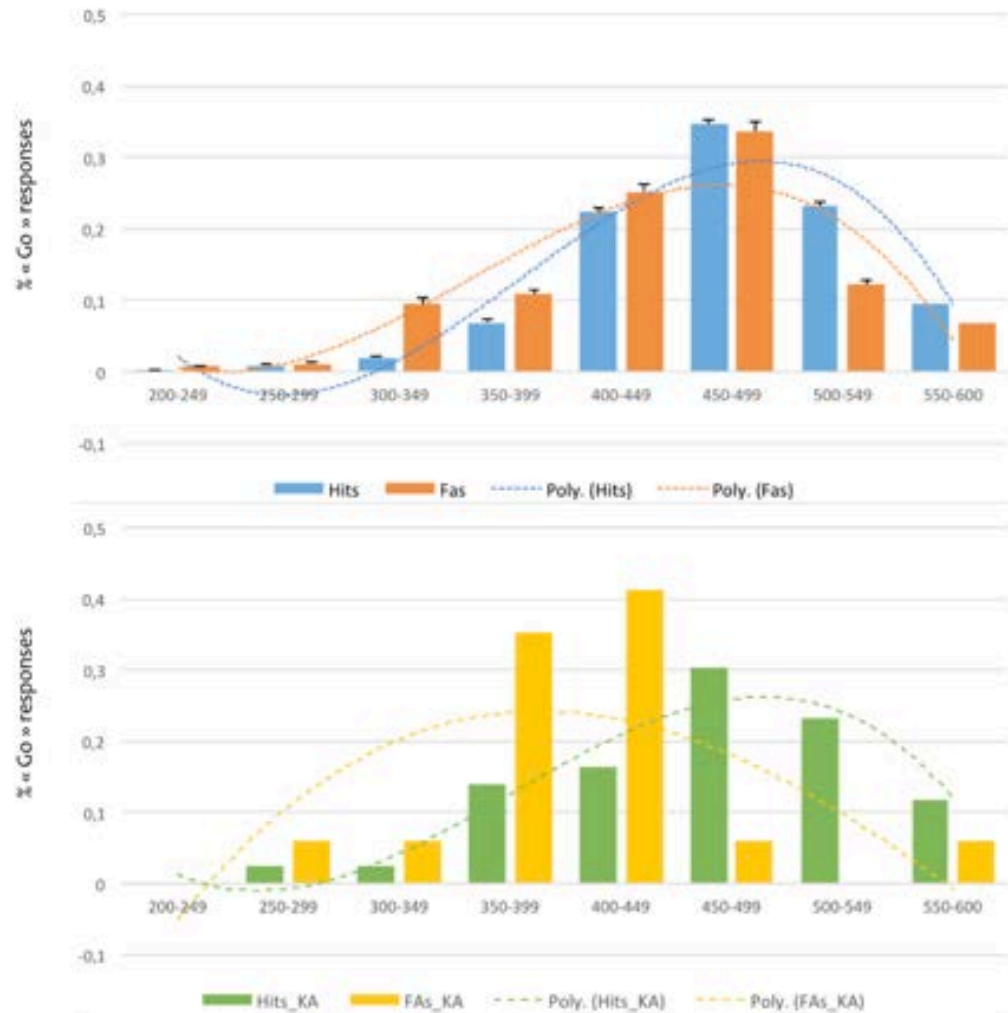


Figure 44. Speed and Accuracy Boosting procedure with meaningful objects. Y-axis shows percentage of “Go” Responses, X-axis represents 50 ms time bins. Top panel depicts average performance across control subjects; bottom panel illustrates performance of patient KA. Dashed lines represent the 3rd order polynomial fitting curves for Hits and FAs.

In summary, patient KA presented a material-specific preservation of familiarity-based recognition memory. While he could acquire new context-free explicit memories of pictures of objects, he completely failed to do so with abstract patterns. Moreover, while the object condition apparently helped control subjects to make less early FAs, it was not the case in KA who globally made more “Go” responses as early as 200 ms post-onset in the abstract pattern condition.

Discussion

The striking dissociation observed in patient KA between preserved learning of object pictures and impaired learning of abstract patterns is not consistent with most process-based theories of recognition memory (e.g. Yonelinas, 1994). These models predict that

recognition of single items can be achieved on the basis of familiarity, or a “feeling of knowing”. Familiarity would in turn depend on the perirhinal cortex but not on the hippocampus. In the case of KA with preserved bilateral perirhinal cortices, the model would have predicted preserved performance irrespectively of the memoranda used. To our knowledge, a very limited number of studies have explored memory for abstract patterns in amnesia.

In a series of amnesic patients with damage thought to be limited to the hippocampus, patients succeeded a visual span task involving abstract designs after an empty delay of 2 seconds, but were impaired after delays of 6 seconds or more (Buffalo, Reber, & Squire, 1998). Similarly, but with a progressive span task requiring detecting novel designs among a gradually increased number of targets, Levy, Hopkins, & Squire, (2003) reported impaired performance in 5 amnesic patients. Interestingly, patients were also impaired in the same task but involving line drawings of objects, but patients like controls performed much better in the line drawings (i.e. meaningful items) condition (Levy et al., 2003, Figure 1). However, long-term recognition memory was not assessed and, as discussed in the Introduction section, for several of these amnesic patients we miss detailed anatomical information regarding extra-hippocampal structures.

More relevant findings come from the case reports of two patients with severely damaged left MTL structures, but a differential profile of damaged and preserved structures in the right MTL (Barbeau et al., 2005; 2011). The patient FRG had extensive damage to the right hippocampus but the anterior right parahippocampal gyrus was preserved. By contrast, JMG (who was not amnesic) had severe lesions of the right parahippocampal gyrus but preserved right hippocampus. As expected, recall and recognition of verbal materials was impaired in both patients. However, JMG presented with impaired recognition of abstract patterns (similar to the ones used in our task) across 4 different tests (mean Z-score=-2.07) while in FRG, performance was in the full normal range (mean Z-score=1.18). Such dissociation provides strong support for the idea that the anterior sub hippocampal structures play a key role in recognition memory for single items. Our results with patient KA are therefore surprising and, again, not predicted by the dual processes models of recognition memory. What could account for these findings?

An obvious possibility is related to the findings of right entorhinal cortex atrophy in KA (see pp. 172-173). Given that abstract patterns processing most likely involve spatial processing (i.e. spatial combinations of separate features), it is possible that the entorhinal cortex is

required to achieve an integrated representation of these stimuli, binding together parahippocampal and perirhinal inputs. Recent support for this hypothesis has come in a study reporting that intra-item configural processing predicts the volume of lateral entorhinal cortex in elderly adults with variable degrees of cognitive decline (Yeung et al., 2017). The prediction was independent of the object novelty, suggesting that the entorhinal cortex does play a perceptual role at encoding, rather than having a memory-specific function. In our task, high discriminative demands are placed on retrieval processes to discriminate between old and new abstract patterns. This can presumably be achieved based on features identity and spatial arrangements, requiring a highly integrated representation of the study items. Such processes may be dependent on structures at the top of the visual stream hierarchy. The entorhinal cortex and hippocampus are thus good candidates, and both were impaired in patient KA, as reflected in an overall impaired performance, and in the high number of Hits and FAs he produced in the earlier time bins. By contrast, healthy controls made more early FAs only in the abstract patterns condition, suggesting a more conservative bias in early responses. This could reflect the need for additional perceptual processing to discriminate targets from lures. An account for why KA failed in the abstract patterns condition could therefore be found in his inability to perform intra-item configural binding required for successful retrieval, due to right entorhinal cortex damage.

Furthermore, an important difference between the abstract patterns and the object pictures used in the experiments is that the former are meaningless, i.e. not associated with any pre-existing semantic knowledge, while it is the case for the latter. In the meantime, while both abstract patterns and objects are composed of individual elements, it is expected that only meaningful objects can be perceptually processed as single entities, because of the pre-existing conceptual representations. This leaves us with at least two additional explanations for the discrepancy between abstract patterns and existing objects memory in KA.

First, existing prior knowledge may increase explicit learning even in the case of amnesia, e.g. through more elaborative encoding and / or higher distinctiveness and / or increased conceptual fluency at retrieval (e.g. Geurten & Willems, 2017; Ozubko & Yonelinas, 2014). In amnesic patients with damage limited to the hippocampus, it has previously been shown that when the memorandum is congruent with existing knowledge, close-to-normal recognition memory performance can be achieved (Kan et al., 2009). Interestingly, the

authors reported that this is not true in patients with damage to the perirhinal cortex. Moreover, and apart from the unresolved debate about whether or not the entorhinal cortex is considered as pertaining to the same system as the perirhinal cortex (see Bastin et al., 2019 for discussion), a recent case study is highly relevant here. The authors reported that a selective damage to the left entorhinal cortex resulted in a selective impairment of familiarity-based recognition for words, but not pseudo-words (patient MR, Brandt, Eysenck, Nielsen, & von Oertzen, 2016). This fits with the idea that pre-existing representations may support recognition memory as long as the rhinal cortex is preserved, irrespectively of the status of the hippocampus, which was no longer possible in MR. Notably, in patient KA, thicker cortex and a slightly larger volume were highlighted in the left rhinal cortices (see Jonin et al., 2018 and pp. 172-173). Thus, one could speculate that the processing of existing objects up to this region (at the object entity level, see (Bastin et al., 2019; Ranganath & Ritchey, 2012) may further serve as a scaffold for subsequent retrieval. This would not be possible in the absence of pre-existing knowledge, thus accounting for the impaired performance with abstract patterns. This hypothesis was previously referred to as the “scaffolding account” (Greenberg & Verfaellie, 2010; Irish et al., 2013; Kan et al., 2009).

Second, it has recently been proposed that extra-hippocampal neocortex in the MTL could support memory for stimuli perceived as a single entity, or stimuli lacking pre-existing representations (Bird, 2017). This hypothesis is broadly in line with the idea (see e.g. BIC model) that whenever unitization could occur at study, allowing separate items to be processed as unit, further familiarity-based recognition could be supported by extra-hippocampal structures. An important prediction from this framework is that recognition memory for stimuli lacking prior representations and that can be processed as a perceptual “whole” does not depend on hippocampal processing. Accordingly, a meta-analysis of unknown faces recognition after hippocampal damage found that it was indeed generally preserved (Bird & Burgess, 2008; Bird, 2017). Conversely, a recent study showed that recognition for famous faces – and recognition for inverted unknown faces as well – was impaired after hippocampal damage (Smith et al., 2014). This could be labelled as the “material-specific framework”.

However, apart from the case reports from Barbeau et al. (2005; 2011), we are not aware of previous studies directly contrasting meaningless vs. meaningful memoranda within recognition memory tasks in hippocampal amnesia. Available data from patient FRG

suggests that recognition memory for abstract patterns made of separate components and free of any pre-existing knowledge is possible after bilateral hippocampal damage, being inconsistent with both the predictions of Bird (2017) and our findings with KA, except if we consider the right entorhinal cortex hypothesis mentioned above. Moreover, as extensively mentioned in the Introduction section, one determinant of unitization may well be the congruence with existing prior knowledge. So if pre-existing representations can indeed serve as a scaffold for subsequent learning independently of hippocampal function, and if unitization processes supported by the rhinal cortices can support such scaffolding, our opinion is that this scaffolding hypothesis provides a more promising account for KA's performance.

Experiment 3a: Does prior knowledge or novelty improve learning? A study in aging

Scientific valorisation

Prize of the best communication, “Journées de Printemps de la Société de Neuropsychologie de Langue Française”, Liège, Belgique, May 2016.

Oral communication, International Conference on Memory (ICOM 6), Budapest, Hungary, July 2016

Article in preparation for the journal Psychology of Aging

Highlights from Experiment 3a

The theoretical accounts putting forward the role of novelty detection in memory formation and enhancement are refuted when novelty is operationalized as stimulus novelty and contrasted with familiar stimuli. **Models like the Novelty encoding hypothesis may refer only to particular class of novelty**, namely novelty resulting from errors of prediction, like in most isolation effect, bizarreness effect (i.e. distinctiveness), or contextual incongruence (i.e. contextual novelty) paradigms.

In a learning task tapping highly common and relevant processes for everyday life, that involves **recognition memory for faces in their visual context**, we report that **faces carrying prior knowledge yields on average a 20% bonus** for subsequent memory.

Moreover, Experiment 3a reveals that **prior knowledge not only benefits item memory, but also that it extends to memory for the context.**

Importantly, **aging does not alter the prior knowledge bonus**, a result that needs replication, since the finding of age-resistant memory tasks is a major concern with respect to the development of cognitive markers of aging-related degenerative conditions.

Finally, Experiment 3a brings evidence that explicit learning improvement due to pre-existing long-term representations could **depend on the kind of prior knowledge**, and that **semantic encoding might not be necessary** to enable enhanced learning.

Introduction

“Learning is often not so much a matter of acquiring new behaviour as it is a matter of organizing previously acquired behaviour into new sequences. The point would be impossible to prove, but it is reasonable that truly new situations and truly new responses seldom occur once people are past childhood.”

Robert Crowder, 2015, p. 408 (first Ed. 1976)

In the field of learning and memory research, the term “learning” typically refers to memory formation for rather new, unfamiliar, materials. In the earliest years of the experimental study of learning and memory, Hermann Ebbinghaus purposely used nonsense syllables as memoranda, because he explicitly aimed at investigating new learning, and so he wished to avoid corruption by prior memories (Ebbinghaus, 1885/1964). It has later been recognized that Novelty detection is a major learning enhancer, and this memory advantage for novel stimuli is now widely accepted in the field of cognitive neurosciences (e.g. Kinsbourne & George, 1974; Tulving & Kroll, 1995; Kumaran & Maguire, 2009). Still, as reflected in the above epigraph, much of our daily learning has more to do with highly familiar items than with unfamiliar, artificial, lab’s stimuli. Given that by definition, routines form a large part of our daily lives, our learning processes may better be tuned to allow us accurate remembering of day-to-day events, so that we can adapt ourselves to our environment. Supporting this view, there is a long tradition in experimental psychology reporting how prior knowledge about the memoranda (and thus, stimulus familiarity) improves subsequent memory formation (e.g. Bartlett, 1932; Bransford & Johnson, 1972; Chase & Simon, 1973a). Besides, the idea that novelty detection is more beneficial than familiarity in new learning seems at odds with the classical and obvious role of repetition in learning (Ebbinghaus, 1885/1964), where more study repetitions yields more memory formation. Two lines of research have therefore yielded contradictory findings regarding the beneficial role of stimulus novelty vs. familiarity on declarative learning.

One classical way of probing learning and memory is recognition memory testing. Recognition memory refers to our ability to detect prior occurrence, i.e. to “know again” (Mandler, 1980), and it is conceived as a simple form of declarative memory (Squire & Schacter, 2002). Dual process models postulate that accurate recognition relies upon two distinct retrieval processes, namely familiarity and recollection. Familiarity leads to successful retrieval of the memoranda alone, while recollection yields retrieval of both the memoranda and its context of acquisition (i.e. retrieval of the learning episode), thus accounting for either context-free or context-rich memories (Atkinson & Juola, 1974; Mandler, 1980; Yonelinas, 1994; Eichenbaum et al., 2007; Wixted & Squire, 2011). Besides, while familiarity is considered an automatic and fast process, recollection is supposedly slower and dependent on controlled processes. Typical experimental methods have used objective or subjective measures to further disentangle the respective contributions of these two processes. Subjective measures include the Remember / Know paradigm (Gardiner), or the use of confidence rating scales at test. In both cases, the basic idea is that recollection is supposedly associated with a sense of reliving the study episode, thus leading to “R” responses (for “Remember”) or to Hits high-confidence “Hits” (true positive). Objective measures generally refer to “source memory” paradigms, where retrieval of the contextual features of the to-be-remembered event is probed at test. Several studies have explored the impact of novelty or familiarity upon recognition memory, yielding mixed findings regarding whether Novelty or Familiarity are beneficial, and regarding which retrieval process is altered.

Numerous reports show a clear advantage of Novelty on recognition accuracy, using either words or pictures as memoranda (Aberg & Nilsson, 2001; Dobbins, Kroll, Yonelinas, & Liu, 1998; Kinsbourne & George, 1974; Kormi-Nouri, Nilsson, & Ohta, 2005; Lekeu et al., 2003; Tulving & Kroll, 1995). More limited effort has been made to address the question of an influence on recollection, familiarity, or both, but available evidence suggests that both recognition processes would benefit novelty (Kishiyama & Yonelinas, 2003; Kishiyama, Yonelinas, & Knight, 2009; Kishiyama, Yonelinas, & Lazzara, 2004). In apparent contradiction with these data, there is considerable evidence for the advantage of stimulus familiarity, not novelty, on recognition memory. For example, Reder et al. (2013) have recently reported that recognition memory for face-scene associations was about twice more accurate when famous vs. unknown faces were displayed at test, even when

considering “Remember” responses only. Similar findings were reported with faces (e.g. Klatzky & Forrest, 1984), proverbs (Poppenk et al., 2010), or other verbal materials (Gardiner & Java, 1990; Perfect & Dasgupta, 1997; see also Belleville, Ménard, & Lepage, 2011), including naturalistic materials (Castel, 2005). Generally, stimulus with pre-existing representations has gathered a differential benefit on familiarity-based vs. recollection-based recognition, with an advantage for the latter (e.g. Long & Pratt, 2002; but see Bird et al., 2011). Such divergent findings come with the apparently contradictory role of the medial temporal lobe (MTL) structures in novelty and familiarity detection. Indeed, the MTL has a well-established role in the detection of prior occurrence, as illustrated in neuropsychological studies of amnesic patients, or in the retrieval success effect reported in fMRI studies (e.g. Kim, 2017). In the meantime, the MTL and especially the hippocampus have long been found to play a key role in novelty detection (e.g. Halgren et al., 1980; Kumaran & Maguire, 2009).

Altogether, these elements leave us with a double paradox. First, stimulus novelty and stimulus familiarity can enhance declarative memory. Second, the core brain system involved in declarative learning (i.e. the MTL) seems responsible for both novelty detection and familiarity detection. Methodological and conceptual differences across studies may account for such puzzling findings.

One important asymmetry between Novelty and Familiarity assessment lies in the experimental manipulations used to induce novelty. A typical feature of experiments reporting a novelty advantage is that they generally induce an isolation effect: while “familiar” items were familiarized through extensive pre-study repetitions, novel items are presented only once at study. Thus, at study, subjects learn novel, isolated items in that they are presented among items that were made experimentally highly familiar. This has led some authors to suggest that novel stimuli have superior distinctiveness at encoding, making them more likely to be remembered (e.g. Dobbins et al., 1998). The benefit of distinctiveness, or isolation effect, has long been demonstrated in psychology (Von Restorff, 1933). Similarly, it has been argued that across the typical novelty experiments, different retrieval demands are placed on novel vs. familiar stimuli during recognition. As Poppenk, Köhler, et al., (2010) pointed out, correct rejection of a familiar

lure involves more discriminative demands than correct rejection of a novel lure. For example, in a classical three-steps procedure using words as memoranda (familiarization phase, study phase and test phase), Aberg et al. (2001) (Expt. 1) replicated the novelty effect and showed that false alarms rates for familiar words (i.e. words presented during familiarization but not at study) linearly increased with the number of presentations during familiarization. The Novelty effect can therefore be accounted for, at least to some extent, differential source discrimination demands placed on familiar vs. novel stimuli during recognition.

Interestingly, the memory advantage for novel items has not been replicated in elderly subjects. Here, an advantage of prior knowledge, and thus stimulus familiarity, has been found. For example, Badham & Maylor (2015) showed that when face-name associations were congruent with prior knowledge, better subsequent memory was observed in young and elderly subjects, the latter being more sensitive to the effect. Similar findings were reported with word pairs (Badham et al., 2015). These results are of utmost importance since aging is considered as disproportionately targeting associative memory, which has been also demonstrated with face-name associations (i.e. Associative Deficit Hypothesis, Naveh-Benjamin, 2000; Naveh-Benjamin, Guez, Kilb, & Reedy, 2004).

Surprisingly, very little data is available regarding how aging alters familiarity- vs. novelty-based learning, whereas prior knowledge has been acknowledged as a powerful candidate to compensate the negative effects of aging on memory (e.g. Umanath & Marsh, 2014; see also Bahrck, Hall & Da Costa, 2008). Given that regions of the MTL have a differential susceptibility to aging, with the hippocampus being much more affected than the parahippocampal gyrus in aging, and especially of the perirhinal cortex (e.g. Insausti et al., 1998; Raz & Rodrigue, 2006), an interesting possibility is that familiarity detection may prove more age-resistant. In fact, some authors consider the perirhinal cortex as pertaining to an explicit learning system that could act independently from the hippocampus, as long as the memoranda is congruent with existing knowledge (Kumaran et al., 2016; but see Fernández & Tendolkar, 2006). Note that similar proposals have been made for regions outside the MTL that are also less affected by aging, like the ventromedial prefrontal cortex (e.g. Van Kesteren et al., 2012). How prior knowledge could boost memory formation remains nonetheless poorly understood. For example, the Levels-Of-Processing account (Craik & Lockhart, 1972; Lockhart & Craik, 1991) would predict that memory for items should increase after deeper (i.e. semantic) processing at

encoding, which would thus account for superior memory in the case of pre-existing conceptual knowledge. However, the extent to which it is conceptual processing *per se* at encoding that is responsible for the effect, or simply the effect of superior prior exposure in the case of pre-existing representations (e.g. Poppenk, McIntosh, Craik, & Moscovitch, 2010b), or how well encoding and retrieval processes match together (i.e. along the Transfer Appropriate Processing framework, Morris et al., 1977), or some combination of these alternatives, remains unclear.

In summary, separated lines of research have established that both stimulus novelty and stimulus familiarity are important learning enhancers. Importantly, novelty is often confounded with distinctiveness or isolation effects, and familiarity generally comes with additional source retrieval demands at retrieval. Little effort has been made to contrast novelty and familiarity in the same learning task, and available reports suggest an advantage for familiarity. Whether familiarity or novelty benefits are preserved in aging, and whether the effects extend to associative memory is currently poorly understood. While some studies point towards a disproportionate benefit of familiarity (i.e. prior knowledge) in elderly, the underlying mechanisms are largely unknown. In addition, since everyday memory formation and most of our social interactions critically rely on recognition memory for people across various contexts, this study used faces and visual scenes as stimuli. Moreover, because human beings have a high degree of expertise for face recognition, the use of faces allowed us to avoid inter-individual variability due to distinct levels of pre-experimental familiarity with other materials such as objects, or words. Given the available evidence suggesting that both familiarity and novelty could enhance recollection-based recognition memory, we particularly focused on this process by using a source memory paradigm.

In the present study, our aims were therefore three-folds. First, we aimed to contrast novel or familiar materials within the same associative learning task to find out which one better improve long-term memory formation. Second, the question we addressed is whether Novelty / Familiarity effects are age-resistant, mainly focusing on associative memory formation. Third, we aimed at testing the hypothesis derived from the LOP framework that memory advantage for familiar stimuli would be accounted for by semantic processing at encoding. To this end, we contrasted two kinds of prior knowledge: experimental prior knowledge resulting from repeated familiarization with

the material and pre-experimental prior knowledge resulting from long-term semantic knowledge about famous faces.

Materials & methods

Participants

66 healthy participants were screened to participate. The inclusion criteria were i) age between 25-75 years old; ii) right-handedness; iii) French native speaking; iv) education level corresponding to at least 8 years of formal schooling; v) able to provide a written informed consent. The exclusion criteria were i) any medical condition susceptible to interfere with cognition; ii) any medical history of neurological or psychiatric condition; iii) any active medication susceptible to interfere with cognition; iv) any sensorial limitation incompatible with the experimental tasks; v) presence of any legal protection; vi) impaired global cognition as assessed with the Mattis Dementia Rating Scale (Mattis, 1973) and the MMSE (Folstein, 1975) by reference with available normative data; vii) impaired episodic memory as assessed by the delayed recall part of the Logical Memory subtest of the Wechsler Memory scale (3rd Ed.); viii) scores above the age- and genre-adjusted available cut-offs at the Beck Depression Inventory (BDI-II, Beck et al., 1996) or at the State-Trait Anxiety Inventory (STAI, A&B, Spielberger et al., 1983). The study was approved by the ethics committee of Rennes University Hospital, and was registered in the Clinical Trial Database (EPMR-MA study 2014-A01123-44). 11 participants had to be excluded due to abnormal subjective levels of anxiety (2) or depression (3); abnormal global cognition (4); or impaired memory (2), thus leaving with 55 participants finally included in the study. Importantly, as detailed below, every participant underwent an extensive neuropsychological assessment lasting 3 hours, thus allowing to ensure that none presented with detectable cognitive deficits. All participants were paid for their time.

Selection of faces stimuli

Given the high inter-individual variability when it comes to knowledge about celebrities, an extensive pilot phase was required. A series of 357 unique pictures of famous faces and 208 pictures of unknown faces was taken from the web. A particular attention was paid to the unknown pictures so that they “looked” like famous faces pictures in terms of resolution, light, and global appearance. Considering that a large variability is expected again for which view of a given celebrity can be most likely to yield identification, we further selected from 2 to 5 different pictures for each famous face. This yielded a total of 1109 photographs of faces. Each pictures was cropped to keep only the face features, then converted to greyscale image and normalized for size (250 pixels width) and luminance with house made MatLab scripts. Then, a Google form was built to gather familiarity judgments for each face in the form of a 4-alternate forced choice questionnaire: 1= “I have never seen that face”; 2= “I think I have seen that face before, but I’m not sure”; 3= “I have already seen that face”; 4= “I have already seen that face, and I know the name, the occupation or both”. 86 subjects answered the form, and none participated in the present experiment. Famous faces yielding ratings of 1, 2 or 3 were discarded, as were Unknown faces with ratings of 2, 3 or 4. We considered a cut-off of 90% for the across-subjects consistency. This resulted in the selection of N=132 famous faces and N=187 unknown faces after matching as closely as possible for sex, estimated age, race, emotional expression, hair colour, and the presence / absence of glasses or earrings. Furthermore, we considered the findings of distinct fame judgments for some famous faces depending on the subjects’ age, yielding a subset of famous faces fulfilling the above criteria in participants aged 50 years old or more, another subset of famous faces correctly identified by participants aged under 50 years old, and a last subset of famous faces that did not depend on age.

From this pool, we randomly drew 6 series of 58 famous and 116 unknown faces to be used as target and distractor items in the experiment. Then, two landscape coloured photographs were gathered from the web (720x484 pixels), one representing the countryside and the other one a beach. They were free of any human character or manufactured or living object. We then used custom scripts to generate all the possible combinations between a face and one of the two landscapes in the form of a visual

stimuli with the face displayed at the centre of the landscape. For each participant of the study, one of the six series was randomly drawn, and 32 famous faces as well as 64 unknown faces were randomly chosen to serve as targets, while 26 famous faces and 52 unknown faces were chosen as distractors.

General study design

Each participant underwent two testing sessions, separated by a maximum 30 days interval. The first session was a screening session involving an extensive neuropsychological assessment. The second session was the experimental session divided in 4 distinct phases.

List of tests from the screening session	Description/Reference
<i>f</i> -NART	French version of the National Adult Reading Test; Mackinnon & Mulligan, 2005
MDRS, max=144	Mattis Dementia Rating Scale
MMSE	Mini Mental State Examination
<i>Logical Memory, I</i>	Wechsler Memory Scale, 3 rd Ed.
<i>Logical Memory, II</i>	Wechsler Memory Scale, 3 rd Ed.
DMS-48, Pictures	2 alternate forced choice recognition memory for colourful meaningless (16) & meaningful (32) clip arts after a 3-minutes delay Barbeau et al., 2004
DMS-48, Words	2 alternate forced choice recognition memory for words (32) and pseudowords (16) after a 3-minutes delay
WMF (50 faces)	2 alternate forced choice Immediate recognition memory for 50 unknown faces
<i>Verbal Fluency, Letter R, 90 sec.</i>	Cardebat et al., 1990
<i>Verbal Fluency, Category Fruits, 90 sec.</i>	"
<i>Graphical Fluency (Nb unique drawings, 3 min.)</i>	-
<i>Stroop Test, Naming (sec.)</i>	Chatelois et al., 1993
<i>Stroop Test, Reading (sec.)</i>	"
<i>Stroop Test, Inhibition (sec.)</i>	"
<i>Stroop Test, Flexibility (sec.)</i>	"
TMT-A (sec.)	Tombaugh et al., 2004
TMT-B (sec.)	"
<i>Oral naming (max = 80)</i>	80 line drawings; Deloche & Hannequin, 19
<i>Limb praxis (max= 23 gestures)</i>	Mahieux et al., 2011
QAM (mean score)	Memory Self Assessment Questionnaire, Van der Linden & Coyette, 1997
STAY-A	Spielberger et al., 1983
STAY-B	"
BDI-II	Beck et al., 1996

Table 1. List of tests used in the screening session. DMS=Delayed-matching-to-sample; WMF=Warrington Memory for Faces; QAM= "Questionnaire d'Autoévaluation de la Mémoire".

The first phase aimed at familiarizing participants with a series of 32 unknown faces, which were repeatedly presented associated with an occupation.

Participants then chose one 8-minutes cartoon (among 3) for immediate viewing. Then they had to complete the “Questionnaire d’Auto-Evaluation de la Mémoire” (Van der Linden, Wyns & Coyette, 1997) lasting 15 minutes.

The second phase then started. It was an explicit encoding phase where participants were asked to learn face-scene associations for 32 famous faces, 32 familiarized unknown faces (seen in the first phase), and 32 unknown faces never presented before. As mentioned above, each face was randomly paired with the “countryside” or the “beach” landscape photograph, with an equal probability for each subset of faces (i.e. 16 beach, 16 countryside pairings).

Participants then chose one 8-minutes cartoon (among 3) for immediate viewing, with the instruction of choosing a different video than the previous one.

The third phase started and involved the recognition memory test detailed below.

After the memory test, participants watched the last 8-minutes cartoon before completing the fourth phase.

The fourth phase was a familiarity judgment task where all the stimuli used in the experiment were shown again to the participants. They had to decide whether each face was famous or not, being instructed to respond “Yes” only when they could give at least the name and the occupation of the person.

Procedure

The tests used in the first session are listed in Table 1. Figure illustrates the general procedure for the second session.

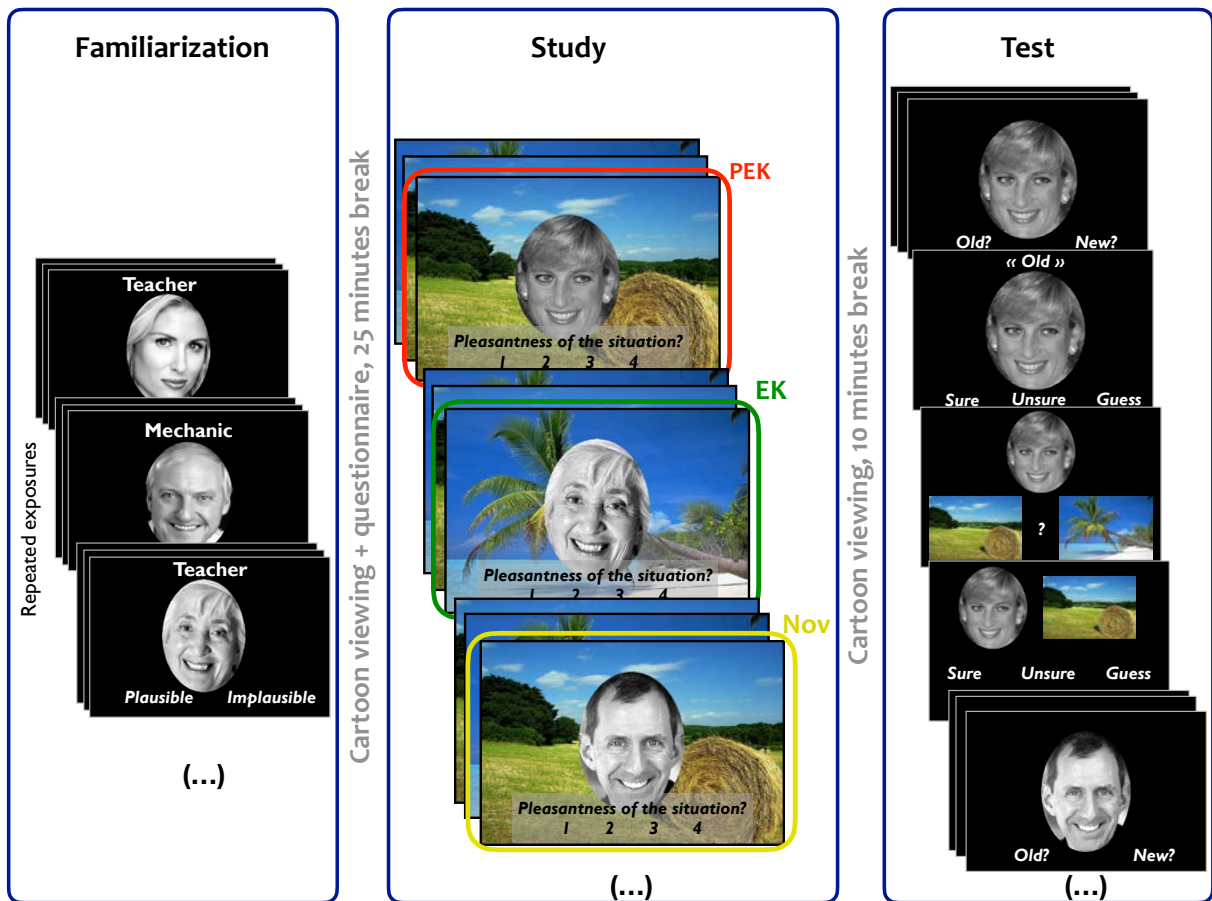


Figure 45. Overview of the memory task design. In the familiarization phase, participants were instructed to judge whether the occupation was plausible for the face displayed, each face-occupation combination was repeated three times; in the Study phase, subjects had to imagine a situation where they would meet the person in the background scene, then judge the pleasantness of the situation; in the Recognition phase, each face was presented first for Old/New judgment followed by a confidence rating, then for each “Old” response, subjects had to make a 2 alternate forced choice source judgment followed by a confidence rating; during the Familiarity judgment phase (not shown) all the faces (i.e. targets and foils) were presented one at a time and the subjects had to make a “famous/unknown” judgment. PEK= Pre-Experimental Knowledge (Princess Diana is depicted on the middle top picture); EK=Experimental Knowledge; Nov=Novelty.

During the experimental session, participants were installed comfortably in a quiet room, approximately 80 cm from a laptop screen, and provided their responses with the keyboard. Stimuli were presented electronically using the E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA).

For the familiarization phase, each unknown face was displayed at the center of the screen on a black background, and the name of an occupation chosen randomly (but face-occupation associations were pre-determined, so that they remained constant across participants) was written on the top of the screen. Participants were instructed to provide a plausibility judgment for the face-occupation combination (i.e. can you easily imagine this person being a Teacher?). Each stimulus was presented three times, with a

minimum lag of 5 items between two repeated trials. A trial started with a white fixation cross for 500 ms, that became red for 250 ms (warning the subject about the presentation of the next stimulus), then the face-occupation pair was presented for 2500 ms. The response options then appeared and remained below the face for 2000 ms, and the subject had to make his response during this interval, pressing one key. A white fixation cross then was displayed during 250 ms before the next trial started. The 96 critical trials, plus 4 buffer trials at the beginning of the session (discarded for further analysis), were therefore administered for a total duration time of about 6 minutes.

For the study phase, participants were instructed that they would see faces upon a landscape depicting a countryside or a beach, and that they would have to imagine the situation where, while walking in the presented scene, they would encounter the person. Subjects were asked to rate the pleasantness of such situation, on a 4-points rating scale from 1= “very pleasant” to 4= “very unpleasant”. Each trial started with a 500 + 250 ms fixation cross as above, then the face-scene association was displayed for 3000 ms, before the rating scale appeared below the face for another 3000 ms, which was the time deadline to give an answer by pressing the corresponding key (i.e. 1, 2, 3 or 4). Then, a 250 ms Inter Stimulus Interval was displayed as above, before the next trial. A total of 96 trials were presented, pertaining to one of three experimental conditions: 1) in the “Novelty” (Nov) condition, 32 unknown, completely novel faces were used; 2) in the “Experimental Knowledge” (EK) condition, the 32 unknown faces previously repeatedly presented in the familiarization phase were used; 3) in the “Pre-Experimental Knowledge” (PEK) condition, 32 famous faces were used. 5 buffer trials were used at the beginning of the session and were not analyzed. This phase of the experiment lasted about 7 minutes.

For the test phase, participants were instructed that they would have to recognize the face-scene associations presented in the study phase in a four-steps testing procedure. First, they were explained that they would see a face that could be either Old or New by reference to the study phase. They were asked to provide first an Old/New judgment on that face. Then, they had to rate their confidence for their Old/New response on a 3-points scale: 1= “I am certain the face was / was not in the study phase”; 2= “I think the face was / was not in the study phase, but I am not sure”; 3= “My response was a guess”. For each “Old” response, subjects were showed the face again together with the two

landscapes used in the study phase. They had to make a source judgment by pressing either “1” if they thought the face was presented in the countryside landscape or “2” for the beach landscape. Finally, they were again asked to provide a confidence judgment on their source memory response. This phase of the experiment lasted from 35 to 50 minutes.

For the last “familiarity judgment” phase, participants were instructed that they would be presented all the faces used in the experiment. For each face, they had to respond whether or not the face was famous. They were explicitly told that much more unknown than famous faces would be presented. They also were asked to respond “Famous” only if they 1) were sure the person was a celebrity; 2) could provide some details like, at least, the name and the occupation of the person. Stimulus presentation and responses were self-paced. The experimenter randomly controlled this after “Famous” responses along the test. Whenever a “famous” response was in fact not associated with accurate details, this was considered as an “unknown” response. Importantly, every item incorrectly sorted was excluded from further analysis, thus leaving only “truly” unknown and “truly” familiar faces. This phase generally lasted 5-10 minutes.

Importantly, only two experimenters administered all tests, and the same experimenter always administered the two test sessions for a given participant.

Analyses

Recognition memory measures

Item recognition memory performance indices (faces only, Hits and False Alarm rates) were computed within the signal detection theory framework. Following Verde, Macmillan, & Rotello, (2006), A_z was computed to estimate sensitivity, namely, how well participants discriminated between targets and distractors. Accordingly, we computed a non-parametric index of bias B'' after Grier, (1971). These indices were preferred to the parametric d' and C indices of sensitivity and bias, respectively, for their superior robustness to the underlying assumptions regarding responses distributions (Stanislaw & Todorov, 1999; Verde et al., 2006), and corresponding formulae were implemented using

a dedicated Excel workbook (Gaetano, J. M. (2017). Signal detection theory calculator 1.2 [Excel workbook downloaded from https://www.researchgate.net/profile/Justin_Gaetano2/]).

Moreover, we will assess the subjective aspects of recognition memory by dissociating between Hit rates associated with High, Middle or Low (guess) confidence levels. The first are typically used as proxies for recollection (Yonelinas, 2002).

Associative learning performance was estimated through source memory accuracy. Source memory refers to the ability to correctly recall the context that was associated to the target item at study. Here, we measured source memory as the conditional probability of a Source Hit (i.e. giving a correct source response) given an Item Hit (i.e. giving a correct “Old” response to a target face), which is a classical behavioural proxy for associative memory accuracy (Cooper, Greve, & Henson, 2017).

Statistical analyses

Repeated-measures ANOVAs were ran to explore whether prior knowledge (EK vs. PEK) or Novelty altered sensitivity (item memory), bias, associative memory (item + context memory), both across and between age groups. Parametric statistical testing was used when the assumptions of normality and variance equality were met. Otherwise, non-parametric methods were used. In addition to null hypothesis significance testing, we ran our inferential statistical analyses with a Bayesian framework. This choice was made on the following grounds. Given our first aim of discriminating whether novelty or familiarity improves learning, the Bayesian approach allowed interpreting the alternative hypothesis. Moreover, the acknowledged limitations in the use and interpretation of p-values (see Jarosz & Wiley, 2014; Krawczyk, 2015; Wagenmakers, 2007) were a concern to us, and we aimed at favouring the methods that are increasingly recommended in psychological sciences and that are less dependent on the underlying assumptions regarding sampling distribution. For each relevant statistical testing, a Bayes Factor (BF) was thus computed. The BF_{10} provides an odds ratio for the alternative vs. null hypotheses, with values < 1 favouring the null hypothesis and values > 1 favouring the alternative hypothesis. To give a concrete example, an estimated BF_{10} of 0.4 would

indicate that data are 2.5 times more likely to occur under the null hypothesis than under the alternate hypothesis, and it is generally agreed that BF_{10} values above 3 favours the alternative hypothesis, while BF_{10} values above 30 are taken as very strong support for the alternative hypothesis (Jeffreys, 1961; Rouder, Speckman, Sun, Morey, & Iverson, 2009). To alleviate the text, the report of Bayesian statistical values was favoured.

All statistical analyses were performed using the JASP software (<https://jasp-stats.org>, JASP Team (2018). JASP (Version 0.9) [Computer software]).

Results

Table 2 presents all the background data for the three groups of participants, showing a close matching across age groups for sex, education, and global cognition. The extensive neuropsychological assessment confirmed the absence of impairment in memory, executive functions, language, limb praxis, and the absence of significant levels of anxiety, depression or memory complaints. As expected, we found that elderly subjects presented impaired verbal memory and speed of processing, by comparison with the youngest subjects. These results suggest that our samples were well matched across several cognitive, mood and meta-memory measures as well as global cognition and background education. Furthermore, these data make it unlikely that our elderly sample include subjects with subtle cognitive decline.

	Young N=21	Middle- Aged N=15	Elderly N=15	BF ₁₀	p value
Demographics					
Age	32.1 (5.0)	47.6 (6.7)	65.5 (3.4)	7.1e¹⁹	<0.001
Education (years)	14.8 (2.5)	13.3 (1.4)	13.4 (3.2)	0.639	0.153
Female:Male	9:12	9:6	8:6	0.272	0.584
Global cognition					
VIQ (f-NART)	108.5 (8.0)	107.5 (5.9)	107.5 (6.6)	0.169	0.871
MDRS, max=144	142.3 (1.6)	142.5 (1.3)	141.9 (1.6)	0.240	0.526
MMSE	29.2 (0.9)	28.7 (1.5)	28.7 (0.9)	0.369	0.307
Memory					
Logical Memory, I	47.1 (8.8)	45.7 (7.0)	39.3 (8.9)	2.472	0.025
Logical Memory, II	30.0 (5.7)	28.0 (4.9)	20.9 (7.6)	101.733	<0.001
DMS-48, Pictures	47.4 (1.0)	47.0 (1.6)	46.3 (1.8)	0.844	0.101
DMS-48, Words	42.8 (3.3)	42.1 (2.9)	40.7 (5.1)	0.406	0.266
WMF (50 faces)	43.7 (4.4)	45.1 (2.8)	42.6 (3.5)	0.525	0.181
Executive Functions					
Verbal Fluency, Letter R, 90 sec.	18.3 (5.9)	18.2 (6.1)	18.3 (6.0)	0.154	0.999
Verbal Fluency, Category Fruits, 90 sec.	22.5 (5.3)	20.7 (4.6)	18.1 (4.5)	1.629	0.040
Graphical Fluency (Nb unique drawings, 3 min.)	24.2 (12.1)	41.3 (26.7)	28.9 (24.2)	1.098	0.071
Stroop Test, Naming (sec.)	59.9 (13.7)	57.7 (10.0)	64.4 (14.8)	0.375	0.292
Stroop Test, Reading (sec.)	41.2 (5.7)	42.3 (12.7)	42.9 (5.4)	0.204	0.688
Stroop Test, Inhibition (sec.)	93.3 (29.1)	97.3 (26.1)	108.6 (28.3)	0.515	0.195
Stroop Test, Flexibility (sec.)	105.3 (21.5)	108.8 (32.6)	127.7 (35.5)	1.509	0.047
TMT-A (sec.)	23.6 (9.4)	26.2 (7.8)	35.8 (17.0)	7.373	0.007
TMT-B (sec.)	48.9 (17.8)	59.4 (18.7)	79.4 (37.1)	23.774	0.002
Language & limb praxis					
Oral naming (max = 80)	79.3 (2.2)	79.8 (0.6)	79.3 (0.8)	0.236	0.548
Limb praxies (max= 23 gestures)	22.6 (0.6)	22.4 (1.1)	22.1 (0.9)	0.491	0.207
Questionnaires					
QAM (mean score)	2.2 (0.4)	2.1 (0.4)	2.3 (0.4)	0.456	0.268
STAY-A	28.1 (7.2)	25.0 (5.0)	28.0 (6.0)	0.370	0.293
STAY-B	37.6 (7.6)	32.4 (7.3)	35.6 (8.6)	0.600	0.158
BDI-II	4.4 (3.2)	3.8 (3.8)	5.1 (4.7)	0.209	0.639

Table 2. Demographics & Neuropsychological background of the 51 participants finally included in the EPMP-MA trial. Acronyms and tests description are detailed in Table 1.

Among the 55 subjects who were successfully screened, 4 were further excluded due to outlier scores (i.e. <-3 s.d.) at the familiarity judgment test, thus leaving a total of 51 participants. The familiarity judgment phase yielded highly accurate scores ranging from 80 to 99% correct, and similarly famous faces were overall well identified as famous (81-100%). Importantly, the number of PEK target stimuli did not differ between age groups ($BF_{10}=0.349$).

Turning to recognition memory, global accuracy (A_z) across prior knowledge conditions was very good, ranging from 0.77 to 0.99, with a large variability of response bias (B''),

ranging from -0.76 to 0.62. However, Source memory assessment yielded performances ranging from 38 to 71% across prior knowledge conditions, suggesting a floor effect (i.e. chance level at 50%).

Novelty vs. familiarity effects on recognition memory

A main effect of prior knowledge was found on A_z ($BF_{10}=2.148e^{25}$) but not on Source memory ($BF_{10}=0.110$). This reflected the floor effect reported above, indeed a binomial test ran for each participant revealed that only 10 subjects (across prior knowledge conditions) performed significantly above chance. We will therefore focus on correct source memory responses associated with a high confidence level. Regarding A_z , post-hoc testing showed that all prior knowledge conditions differed, with Novelty yielding the worst performance and PEK the best (Nov vs. EK, $BF_{10}=9.032e^{10}$; Nov vs. PEK, $BF_{10}=4.033e^{12}$; EK vs PEK, $BF_{10}=37.600$) (see Figure 46). More Hits were observed in the conditions with pre-existing knowledge (one-factor within-subjects ANOVA, $BF_{10}=3.929e^{30}$), with no difference between PEK and EK ($BF_{10}=0.159$), but much less Hits in the Novelty condition (Nov vs. EK, $BF_{10}=6.996e^{17}$; Nov vs. PEK, $BF_{10}=3.272e^{13}$). By contrast, EK and Nov conditions yielded more FAs than PEK (one-factor within-subjects ANOVA, $BF_{10}>356000$), with no difference between Nov and EK ($BF_{10}=0.154$). Finally, response bias also differed across prior knowledge conditions (one-factor within-subjects ANOVA, $BF_{10}=2.711e^7$), mainly due to a more liberal bias in the EK vs. Nov conditions ($BF_{10}=3.602e^8$), with much less strong evidence for difference between EK & PEK ($BF_{10}=13.99$) and Nov & PEK conditions ($BF_{10}=15.91$).

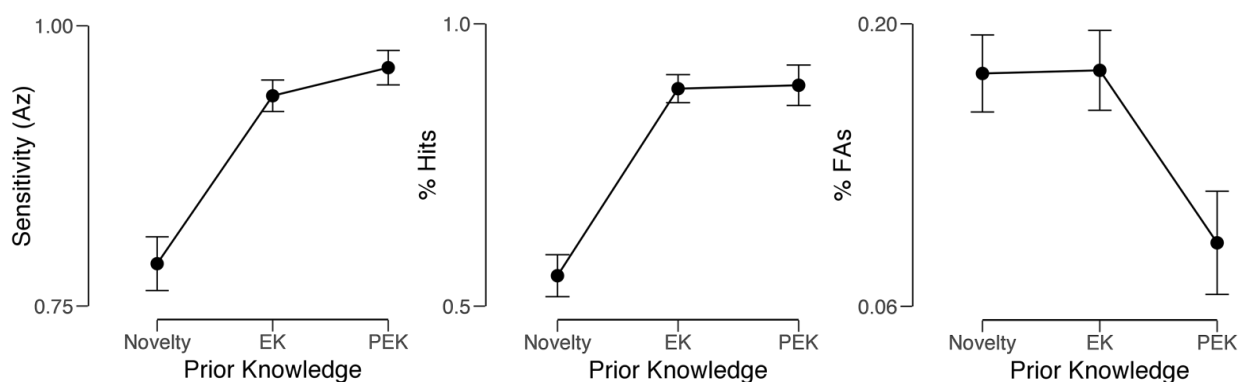


Figure 46. Prior Knowledge effect on recognition memory, across all participants. %95ICs are displayed.

Turning to source memory, again we found a strong effect of prior knowledge conditions across participants ($BF_{10}=1.701e^8$). Here, PEK yielded the best performance but EK and Nov did not differ following post-hoc testing (Nov vs. EK, $BF_{10}=0.471$; Nov vs. PEK, $BF_{10}=4.925e^6$; EK vs PEK, $BF_{10}>14300$) (see *Figure 47*). Importantly, this effect was not supported when considering Middle-confidence ratings associated with accurate source memory responses ($BF_{10}=1.979$).

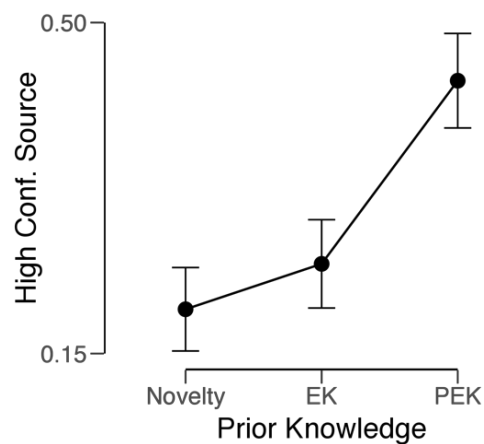


Figure 47. Prior Knowledge effect on source memory, across all participants. Y-axis shows high-confidence correct source responses. %95ICs are displayed.

Finally, we considered whether prior knowledge conditions also altered the confidence associated with Hit responses (see *Figure 48* & *Figure 49*). High confidence Hits were strongly impacted by the prior knowledge conditions ($BF_{10}=3.798e^{21}$), and all post-hoc tests favoured the alternative hypothesis (Nov<EK<PEK; Nov vs. EK, $BF_{10}=2.198e^8$; Nov vs. PEK, $BF_{10}=3.489e^{15}$; EK vs PEK, $BF_{10}=3745$). Accordingly, a coherent pattern was found for Middle-confidence Hits, which were more frequent in the Novelty condition ($BF_{10}=2.388e^{19}$; Nov>EK>PEK; Nov vs. EK, $BF_{10}=1.187e^6$; Nov vs. PEK, $BF_{10}=6.697e^{15}$; EK vs PEK, $BF_{10}=3025$). Finally, Low-confidence Hits similarly were more frequent for Novel than PEK items, with much milder evidence for the alternative hypothesis for the Novel vs. EK comparison, and evidence for the null hypothesis regarding the EK vs. PEK contrast ($BF_{10}=1090.311$; Nov>EK=PEK; Nov vs. EK, $BF_{10}=23.655$; Nov vs. PEK, $BF_{10}=30.852$; EK vs PEK, $BF_{10}=0.366$).

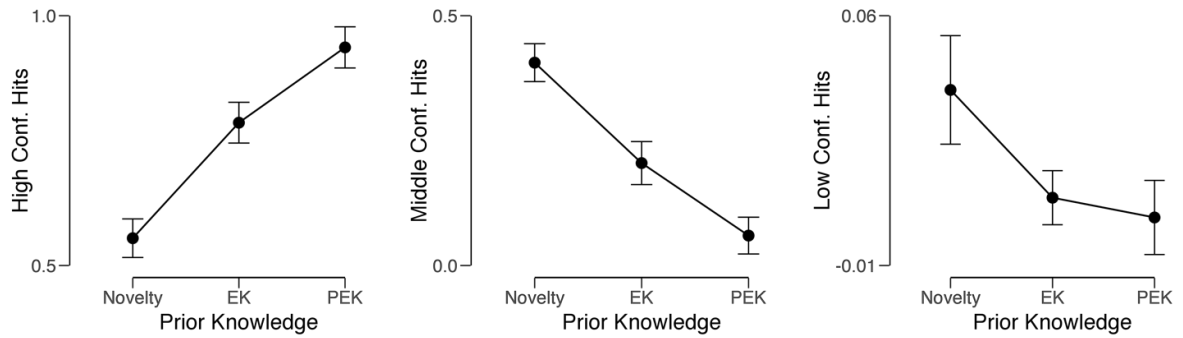


Figure 48. Prior Knowledge effect on the subjective aspects of recognition memory (confidence ratings), across all participants. %95ICs are displayed.

This resulted in strong evidence for the hypothesis of an interaction between prior knowledge effect and confidence ratings ($BF_{10}=3.504e^{174}$): while the frequency of low-confidence ratings did not differ across prior knowledge conditions, middle-confidence and high-confidence ratings were differentially affected by prior knowledge. Items in the Novelty condition yielded slightly more high- than middle-confidence Hits ($BF_{10}=3.048$), while strong evidence was found for more high- than middle-confidence Hits in the PEK ($BF_{10}=4.521e^{37}$) and EK ($BF_{10}=5.167e^{10}$) conditions. Moreover, EK yielded more middle-confidence ratings than PEK ($BF_{10}>3000$) and conversely, PEK yield more high-confidence ratings than EK ($BF_{10}>3700$).

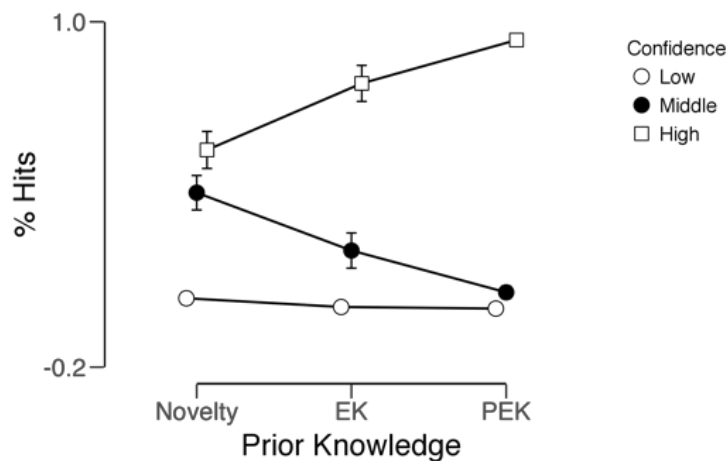


Figure 49. Interaction between prior knowledge and confidence ratings for Hit rates. %95IC are displayed.

In summary, our data can be accounted for by a strong effect of prior knowledge on all the aspects of recognition memory. Existence of prior representations massively

improved item memory, confidence, and memory for the context as long as high-confidence responses were considered for the latter. However, the raw measure of conditional source memory showed a floor effect preventing from further interpretation. Finally, prior knowledge conditions mattered for item memory, but not for source memory. Indeed, PEK yielded better sensitivity than EK due to lower FAs rates, and Hits were associated with far more high-confidence ratings and far less middle- or low-confidence ratings in the PEK than in the EK condition.

Age effects

In the next results section, we will report on aging effects upon the prior knowledge impacts described above. Regarding sensitivity (A_z), a model including the main effect of prior knowledge ($BF_{10}=2.142e^{25}$) accounted for the data the best, since models using Age, Age and Prior knowledge or an interaction did not yield higher BF_{10} (a model with Age and Prior knowledge yielded a BF_{10} of $5.943e^{24}$) (see Figure 50). Importantly, Age on its own was unlikely to have any influence ($BF_{10}=0.138$). The pattern of results reported in the previous section for the Hit & FAs rates was not influenced by age either ($BF_{10}=0.106$ and $BF_{10}=0.338$, respectively), while the main effect of prior knowledge was confirmed ($BF_{10}=3.507e^{30}$ and $BF_{10}>358000$, respectively). Finally, as before, response bias was influenced by prior knowledge ($BF_{10}=2.855e^7$) but age did not alter this result ($BF_{10}=0.100$).

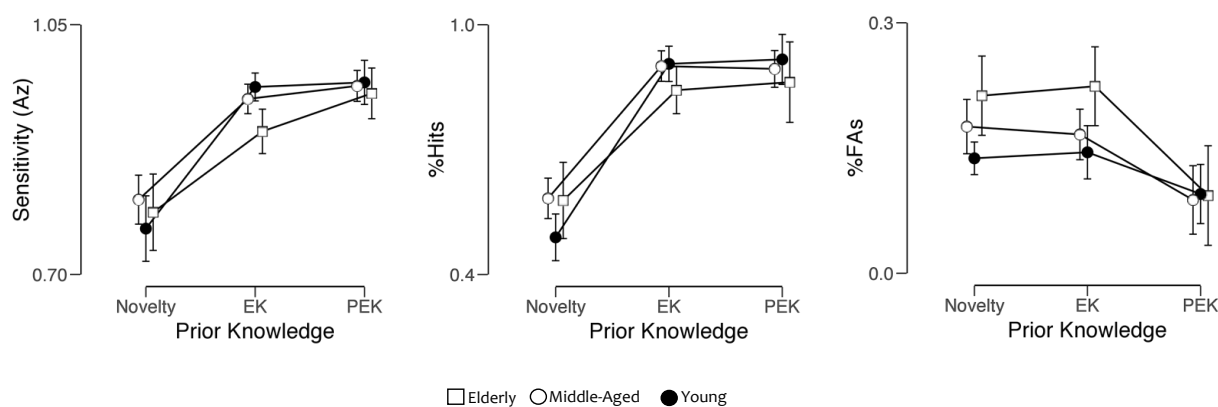


Figure 50. Prior Knowledge effect on recognition memory within each age group. %95ICs are displayed.

Turning to correct source memory responses associated with a high confidence, we also confirmed the main effect of prior knowledge ($BF_{10}=1.715e^8$) without effect of age ($BF_{10}=0.631$). The pattern was again similar to the one described in the previous section, after post-hoc testing (see *Figure 51*).

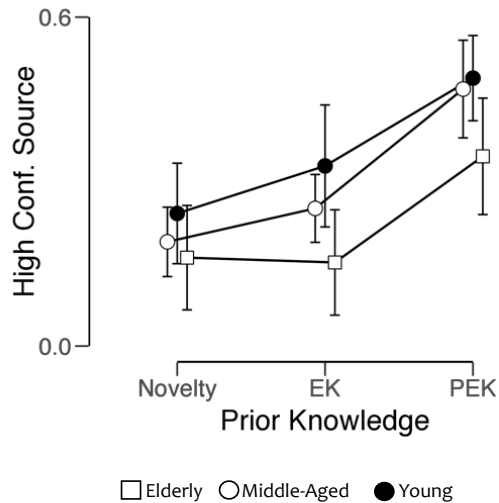


Figure 51. Prior Knowledge effect on source memory, within each age group. Y-axis shows high-confidence correct source responses. %95ICs are displayed.

Considering whether age affected the pattern of prior knowledge effects on the confidence associated with Hit responses, we again found strong support for the null model, be it for High-, Middle- or Low-confidence Hits ($BF_{10}=0.117$; $BF_{10}=0.108$ and $BF_{10}=0.172$, respectively) (see *Figure 52*).

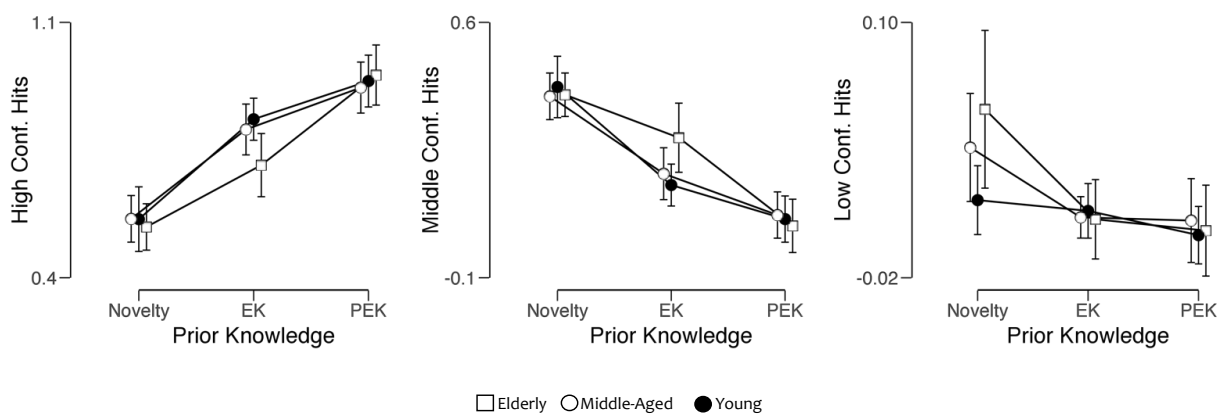


Figure 52. Prior Knowledge effect on the subjective aspects of recognition memory (confidence ratings), within each age group. %95ICs are displayed.

In summary, we found consistent evidence for an age-resistant effect of prior knowledge on all aspects of recognition memory. Due to a floor effect for source memory however, we cannot interpret raw performance in associative memory (i.e. correct source memory responses), but it is worth noting that such responses, when associated with high levels of confidence, were distributed similarly across Age groups and Conditions of prior knowledge. Furthermore, regarding memory for items (i.e., faces), we found that high-, middle- and low-confidence hits also were distributed similarly across Age groups and prior knowledge conditions. Finally, we could not find evidence for an interaction between Age and Prior knowledge conditions on recognition.

Correlation analyses

Finally, we were interested in how recognition memory performance for each prior knowledge condition was related to more standard recognition memory measurements (e.g. Warrington Memory for Faces, “WMF”, and delayed logical memory subtest, see *Figure 53**Figure 54*). This was because, as stated in the Introduction section, we believe that when the amount of prior knowledge is not taken into account in typical memory assessments, we might miss an important aspect of patients’ complaints within clinical settings.

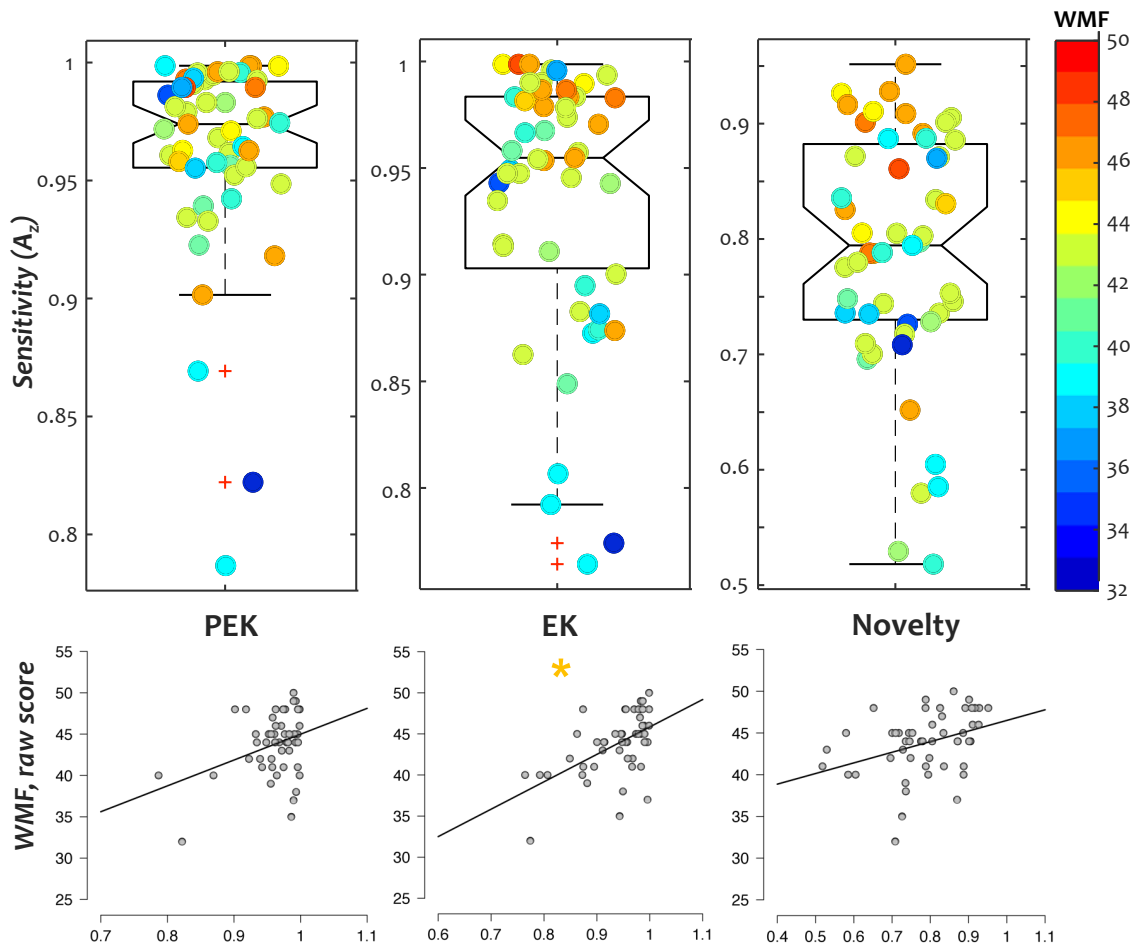


Figure 53. Correlation analysis. Upper panel depicts the distribution (notches represent 95CI for the median) of sensitivity (A_z) scores for each prior knowledge condition, plotted against performance at the Warrington Memory for Faces test as shown in the colormap. Lower panel shows the corresponding regression function, yellow asterisk indicate strong evidence for a positive correlation. “WMF”=Warrington Memory test for Faces.

We therefore computed Bayes factors associated to Pearson’s correlation coefficients under an alternative hypothesis of a positive relationship. We found strong evidence in favour of the alternative hypothesis linking WMF to A_z scores in the EK ($r=0.547$ $BF_{10}>1200$) condition, but evidence remained much weaker regarding Novelty and PEK conditions ($r=0.362$; $BF_{10}=8.965$ and $r=0.355$; $BF_{10}=7.821$; respectively). By contrast, the delayed score at the logical memory subtest was related to EK ($r=0.524$; $BF_{10}=581.59$) and PEK ($r=0.426$; $BF_{10}=35.485$) conditions, while the null hypothesis was supported in the Novelty condition ($r=0.075$; $BF_{10}=0.280$).

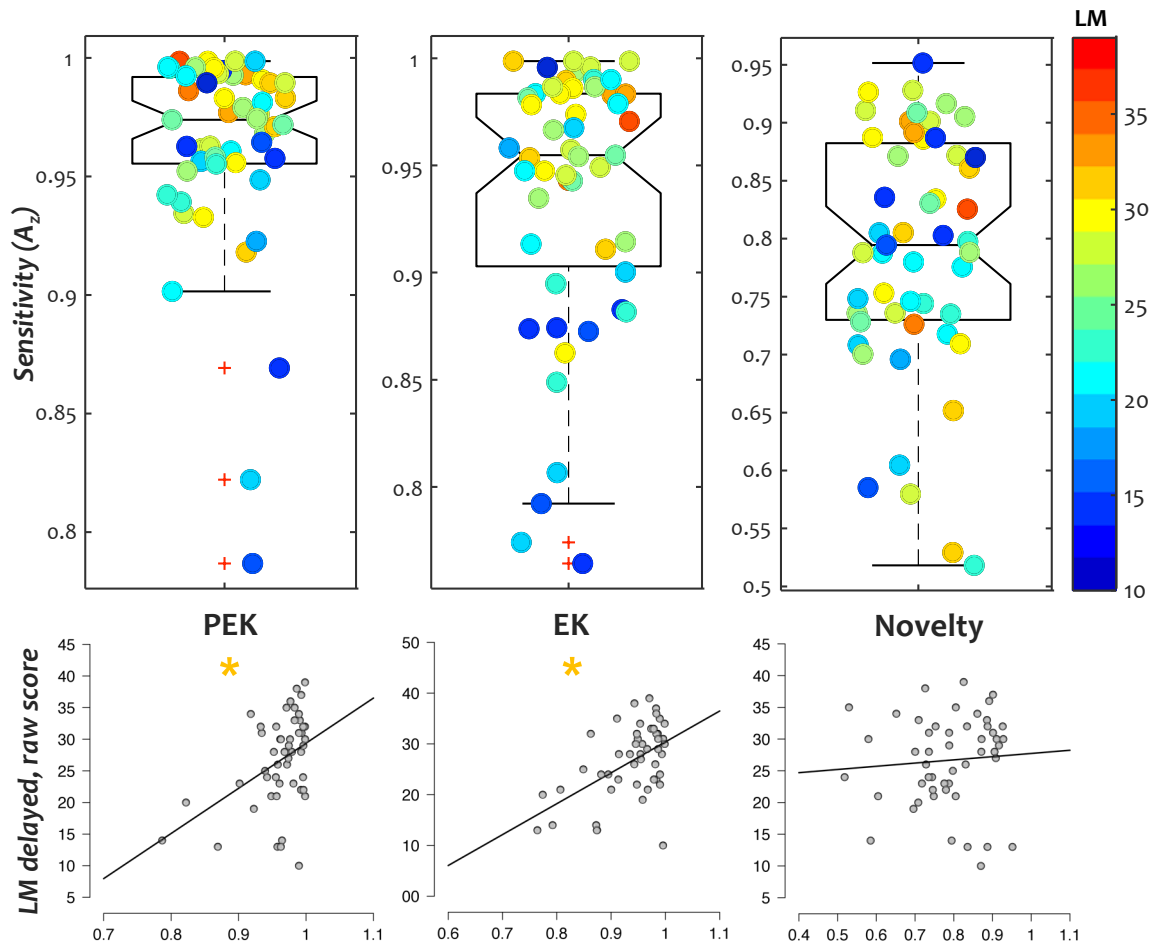


Figure 54. Correlation analysis. Upper panel depicts the distribution (notches represent %95CI for the median) of sensitivity (A_z) scores for each prior knowledge condition, plotted against performance at the Logical Memory (Delayed) subtest of the Wechsler Memory Scale as shown in the colormap. Lower panel shows the corresponding regression function, yellow asterisk indicate strong evidence for a positive correlation. “LM”= Logical Memory.

Discussion

In the present study, we investigated the explicit learning of faces in visual contexts in a lifespan perspective. Our aims were three-folds. First, we aimed at finding whether novelty or prior knowledge would improve recognition memory for items (faces) and items in context (face-scene combinations). Our second goal was to test how aging would affect the findings. Finally, a third goal was to test a core prediction from the LOP framework, namely that prior knowledge improves learning because of conceptual (semantic) processing at encoding. Our main findings can be summarized as follows: 1) recognition memory is improved for items carrying pre-existing representations by comparison with novel stimuli; 2) this pattern of memory improvement is age-resistant; 3) the nature of pre-existing representations matters, since faces carrying conceptual

representations yielded better memory for items than faces lacking conceptual representations but associated to experimental familiarity due to recent exposure. We will first discuss our findings across participants, before the impact of aging.

Familiarity, not novelty, increases recognition memory for faces and face-scene associations

Our findings that familiarity for faces increases recognition memory are in line with prior studies (e.g. Klatzky & Forrest, 1984; Bird et al., 2011; Reder et al., 2013). In the present experiment, accuracy was improved by around 20% on average when contrasting stimuli with or without prior knowledge. These results confirm that stimulus novelty *per se* cannot be viewed as a learning enhancer, rather, in theories highlighting the role of novelty detection, the key factor may be contextual novelty, incongruence or isolation / distinctiveness effects. In the case under scrutiny here where subjects had to learn new face-scene associations, the “Novelty encoding hypothesis” would have predicted an advantage for novel stimuli, thought to trigger encoding processes in long-term memory. While this can be the case when stimulus novelty is defined as an item which occurrence breaks prior expectations, it seems to be no longer verified for absolute, rather than relative, stimulus novelty. These results are of great matter since our task design could have predicted lower performance due to more FAs in the PEK condition. Indeed, a high degree of familiarity with famous faces together with the use of famous faces as distractors could have led to more false alarms in the PEK condition than in the novelty or EK conditions. At test, famous faces used as targets and foils all have been experienced before, by definition, thus requiring at least some source monitoring processing (i.e. did I see that face in the study phase? vs. did I ever see that face?). By contrast, the unknown faces used as foils in the EK and Novelty conditions have never been presented before. This could have led subjects to increase their FAs rates for PEK items. Actually, we observed the opposite: participants made much less FAs for famous than unknown faces, which accounted for their higher sensitivity in that condition. One possibility to explain this result lies in the idea of “elaborative encoding” (see Baddeley, 2009) and “depth of processing”, as suggested in the LOP framework (Craik & Lockhart, 1972; Craik & Tulving, 1975; Lockhart & Craik, 1990). At study, famous faces have triggered elaborative encoding, namely encoding of prior associations related to the famous faces, like previous backgrounds (scenes or other), which strengthens the memory trace by making it richer. Furthermore, famous faces should have been processed deeper than unknown

faces, in that conceptual (rather than perceptual) processing of famous faces at encoding results in the retrieval of multiple facts, attributes, feelings, etc. related to the subjects' knowledge about the famous face. This is thought to increase the distinctiveness of the trace, making it more resistant to interference (e.g. see Wixted, 2004). Thus, better memory for stimuli associated with prior knowledge would be accounted for by the cumulative benefits of elaborative encoding – enriching the trace – and deeper processing – increasing distinctiveness. Our findings of a lower FAs rate in the PEK condition fits well with the idea of higher distinctiveness for famous faces.

However, at variance with most prior studies that did not investigate the nature of prior knowledge (but see Leveroni et al., 2000; Poppenk et al., 2010; Trinkler et al., 2009), here we contrasted entirely new faces to familiar faces resulting from either celebrity or experimental familiarization. Importantly, we found that items memory was also improved for items carrying “experimental knowledge” by comparison with novel stimuli. Moreover, this condition yielded the same degree of improvement regarding the Hits rate than the PEK condition, but also resulted in more FAs than for the famous faces. These findings suggest that conceptual processing during encoding should not to be considered as the sole factor responsible for the familiarity advantage on recognition memory. Indeed, we believe that familiarization to unknown faces is unlikely to have triggered conceptual (semantic) processing at study. The familiarization phase involved incidental repeated encoding of completely unknown faces, with no learning instructions. The subjects had to make subjective judgments regarding whether random occupations were plausible for unknown faces. Of course, the task itself may have involved some conceptual processing, but it was more likely related to the subjects' knowledge about the occupation, than to the unknown faces further serving as memoranda in the study phase. Thus, we would argue that these faces have most likely been perceptually encoded during the familiarization phase, and again mainly perceptually encoded at study, rather than conceptually. Still, they yielded similar Hits rates than famous faces, thus extending prior work with different materials like proverbs (Poppenk et al., 2010) or personally known faces (Trinkler et al., 2009). Obviously, the benefits of repetition on learning are expected here, but what is less expected is that prior exposure results in similar improvement as prior semantic knowledge. This is because prior knowledge for famous faces results from countless exposures all along the lifetime, within countless contexts, while prior knowledge due to experimental familiarization results from three successive presentations in the same context, 25 minutes before study.

The LOP framework would predict that since depth of processing is not equivalent between PEK and EK condition, the former should yield superior performance. In the theory, this is because semantic processing can result in a more distinctive memory trace, as suggested above. However, still according to in the LOP framework, elaborative encoding – which is thought to act independently from depth of processing (Lockhart & Craik, 1990) – can occur when the sensory input is congruent with the study context (in a broad sense). In our study, subjects were asked to make a subjective judgment about how well a background scene “fitted” with a face. Critically, in the familiarization phase, subjects were asked to make a subjective judgment about whether an occupation “fitted” with a face. Thus, and this only holds for the EK condition, elaborative encoding may have occurred because of this high congruency between the orienting task at study and previous knowledge about the familiarized faces. Then, an interpretation could be that both familiarized and famous faces have triggered elaborative encoding, but for different reasons. In the case of PEK, it may have resulted from the congruency between the orienting task and a large amount of previous situations where famous faces are encountered in several different background scenes. In the case of EK, elaborative encoding would have resulted from the congruency between the study and the familiarization phases. By contrast, only famous faces should have been deeply processed, resulting in higher distinctiveness as stated above. In fact, FAs rates were indeed higher for EK than PEK stimuli, and importantly, it did not differ between EK and Novelty condition, strengthening the idea that processing of these items at encoding was rather shallow.

Thus, the LOP framework can account for our findings as long as one assumes that PEK and EK differentially affect depth of processing, which many would acknowledge, but also that these kinds of prior knowledge similarly yields some degrees of elaborative encoding. This last assumption seems harder to sustain since we miss a way to measure the concept of “elaborative encoding”.

One way to move forward would therefore be to consider whether prior knowledge affects not only memory for items, but memory for the context as well. In fact, elaborative encoding is supposed to enrich the memory trace, so that in the case of famous faces that have been experienced within countless prior experiences, the trace should be far more strengthened than for familiarized faces with only one single previous context (e.g. see Zion-Golumbic, Kutas, & Bentin, 2010). If we accept that trace enrichment improves memory by providing additional cues for retrieval, we can suppose

that the study context should have been better integrated to the memory in the case of famous faces. This in turn would predict better source memory, as previously shown (Reder et al., 2013). However, we found mixed evidence for this hypothesis. On the one hand, it was not supported by the findings of equivalent high-confidence source memory accuracy in EK and PEK conditions. While this suggests that the benefits of prior knowledge do extend to memory for the context, not only to item memory, it does not support the idea that more elaborative encoding is expected for famous than familiarized faces. Unfortunately, our task proved too hard and yielded a floor effect for source memory, which is a main limitation of this experiment and prevents from further interpretation of source memory accuracy findings. On the other hand, support for this account in our experiment comes from the analysis of confidence ratings for Hits and correct source memory judgments. Many prior studies have used high-confidence Hits as a proxy for recollection-based recognition (see Yonelinas, 2002). Here, we found that PEK and EK generally yielded more confident Hits, and more specifically we reported an interaction between confidence and prior knowledge whereby PEK yielded more high-confidence Hits than EK, while the reverse was true for middle-confidence Hits. It therefore seems possible that the nature of prior knowledge matters regarding subjective recollection-based retrieval, with a more specific advantage of PEK. How this differential impact of PEK vs. EK on subjective recollection could be accounted for?

An interesting possibility here is related to the idea that binding a face to a context could be easier when pre-existing representations are associated with the face than when the face is entirely novel. This would be due to a differential involvement of working memory resources for unknown vs. familiar stimuli (Reder et al., 2013; Reder, Paynter, Diana, Ngiam, & Dickison, 2007). Stimuli with long-term memory representations would be easier to bind to a new context because such relational binding would need less working memory resources. This hypothesis also echoes prior proposals to explain the memory advantage of primed vs. unprimed words in a recognition memory task (Gagnepain et al., 2008; 2011). Here, the idea was that priming would result in the free up of attentional resources, in turn allowing for a more thorough processing of the context. In that case, like in the Reder et al. (2013) study, prior representations in long-term memory (either due to priming or to explicit prior knowledge) thus yielded a higher probability of recollection-based retrieval. It could therefore be the case that in our task, a large pre-existing associative network of knowledge (i.e. PEK) has allowed more attentional and working memory resources to be allocated to binding operations than a more limited,

mainly perceptually-based, knowledge resulting from experimental familiarization. We will aim at addressing this possibility in the next experiment.

Prior knowledge benefits are age-resistant

One important goal of this study was to test whether aging would alter the subjects' sensitivity to prior knowledge in new learning. Prior studies have generally agreed on the findings of a decline in recognition memory for faces with age, essentially due to higher false alarms rates (e.g. Boutet & Faubert, 2006; Ferris, Crook, Clark, McCarthy, & Rae, 1980; Fulton & Bartlett, 1991; Lamont, Stewart-Williams, & Podd, 2005; Searcy & Bartlett, 1999). Thus our findings that age did not alter recognition memory for faces are surprising. A closer look at prior studies in the field actually reveals that the majority of past studies have used novel, unknown faces, and that young faces were mostly used as stimuli. However, when familiar faces were used as stimuli, the age-related decline was greatly reduced (i.e. Bäckman et al., 1991) and, similarly, when old and young faces were used, again the elderly performed better with own-age faces (e.g. Firestone, Turk-Browne, & Ryan, 2007; Fulton & Bartlett, 1991; Lamont et al., 2005). Thus, available evidence suggests that the age-related decline in recognition memory for faces can actually be alleviated based on either stimuli conceptual or perceptual familiarity, rather than showing a uniform and unavoidable decline. Our results therefore extend this idea by showing that a carefully selected set of unknown, familiarized and famous faces, corrected on an individual basis for the subjects' familiarity with each stimulus, can yield accurate performance from 25 to 75 years old. Of course, the small size of our samples must lead to cautious interpretations and strongly prevents from generalization. Moreover, given that the memory load was relatively high in our experiment (i.e. N=96 target items), participants obtained low performances, especially in the Novelty condition. This might explain why we failed to replicate prior results of lower recognition memory for unknown faces in our elderly sample. Another important point is that prior studies involving elderly subjects not always have the means to exclude subjects with subtle cognitive impairments, or with significant concerns about memory. Similarly, a close matching for education, VIQ, and levels of anxiety and depression is not the rule. In doing so in the present experiment, we found that in the PEK and EK conditions, elderly participants presented with the same patterns of performance than their younger counterparts. Pre-existing representations seemed to increase the Hit rates, but also confidence ratings associated with accurate responses, and high confidence source

memory as well, as reflected in the absence of interaction between age and prior knowledge effects. The results thus require further replication, since these findings could lend support to the hypothesis that the mechanisms underlying prior knowledge-based explicit learning may not depend upon the brain structures particularly sensitive to ageing like the prefrontal cortex and the hippocampus.

Furthermore, given the absence of age effects, we had the opportunity to investigate whether recognition memory for stimuli with or without long-term memory representations is equally related to more standard measures of memory used in clinical settings. This revealed that recognition memory for famous and familiarized stimuli, but not novel stimuli, was strongly positively related to the delayed recall score of the Logical Memory subtest. By contrast, performances at the Warrington memory test for faces (Warrington, 1984) were strongly related to recognition of familiarized faces, while evidence was weaker – but was clearly present - for famous and novel faces. The findings of a positive correlation between our recognition memory test involving faces and a standard recognition memory test for faces were expected, and reinforce the construct validity of our task design. The Logical Memory subtest involves meaningful verbal materials (i.e. short narratives) carrying pre-experimental knowledge, not only about words but also about general schemas (e.g. the robbery part in the first story). The Warrington memory test for faces requires participants to make a two-alternate forced choice at test between a foil and a target face photograph. While the materials consist of unknown faces, stimuli actually depict not only the face features but also a large part of the top of the body with different clothes. Subjects may rely upon this extra-face information as prior research has shown that the task could be successfully performed even after masking the face itself (Duchaine & Weidenfeld, 2003). Thus, both tasks include materials (words, clothes) for which multiple prior exposures have yielded at least perceptual familiarity, and it seems meaningful to us that they correlate positively with recognition of faces carrying experimental (perceptual) knowledge. The fact that only the Logical Memory subtest correlates with recognition memory of famous faces again makes sense, given that conceptual, not only perceptual knowledge is involved at encoding in each task.

These data do suggest that current psychological testing does not capture the role of prior knowledge and novelty in new learning, which may lead to over- or underestimations of memory abilities in the clinical settings. Considering that an improvement of more than 20% was observed on average for items with prior knowledge

in our task, we believe that these results call for a thorough consideration of how current memory tests tap or not on prior knowledge-related mechanisms, and to further include this dimension in the future development of assessment tools.

Conclusion

The present experiment has brought additional evidence for the role of prior knowledge as a powerful enhancer of memory formation, against stimulus novelty. It further adds some new contributions in that prior knowledge benefits extended to memory for the context, and we could demonstrate for the first time that 1) item recognition and high confidence memory for the context may be improved up to very similar levels by conceptual but also perceptual prior knowledge; 2) these positive effects on learning were age-resistant. Thus, while the benefits of prior knowledge have traditionally been accounted for by semantic processing at encoding, in accordance with the levels-of-processing framework, our findings suggest that similar improvements can be reached through experimental exposures only. A promising candidate mechanism to account for the advantage of both kinds of prior knowledge could be that perceptually primed or conceptually familiar faces may release attentional and working memory resources for context processing. This in turn would facilitate binding operations, allowing a more distinctive representation to be built. Due to a limited sample size and to floor effects for our source memory measure, such conclusions however remain speculative and require replication.

Experiment 3b: Can we replicate experiment 3a while increasing the distinctiveness of the study events?

Scientific valorization

Article in preparation for the journal Psychology of Aging

Highlights from Experiment 3b

Faces carrying **prior knowledge strongly benefit subsequent recognition** memory, **not only for the face, but also for the context.**

Such benefits seem to be **immune to aging**, even considering associative memory, thus providing new **perspectives to alleviate age-related memory deficits** and develop **new markers of early cognitive decline** associated with degenerative diseases.

Recollection-based retrieval of faces seems to be particularly sensitive to long-term memory representations resulting from lifelong exposures, but recent exposures also improves memory formation. While most prior studies considered prior knowledge as a homogenous variable (i.e. present or absent), **findings from Experiment 3b plea for a differential impact of experimental vs. pre-experimental prior knowledge.**

The superior memory bonus obtained for pre-experimental knowledge could be accounted for by the **cumulative effects of increased distinctiveness and facilitated long-term memory binding** due to conceptual processing together with the free up of attentional and working memory resources.

A speculation that needs further investigation is that **memory facilitation** (including associative memory) **due to pre-experimental knowledge** could be **independent from brain structures highly sensitive to aging**, like the hippocampus.

Introduction

Stimuli with pre-existing long-term memory representations enable more memory formation than novel stimuli. In the case of face-scene associations, Experiment 3a has shown that this was true for both memory for faces and memory for the association. However, evidence for improved associative memory was very limited due to the floor effect observed across participants who hardly performed better than chance. Still, subjective recollection as assessed through confidence ratings seemed to benefit prior knowledge, with a more subsequent benefit from pre-experimental knowledge (PEK, famous faces) than experimental knowledge (EK, familiarized faces). In the meantime, accurate source memory associated with the highest confidence ratings was similar for stimuli carrying a large amount of pre-experimental conceptual knowledge and for unknown items familiarized across some exposures before to the study phase. This last result was rather surprising, and did not fit with the classical levels-of-processing framework. Strikingly, despite the acknowledged frailty of recollection-based retrieval in aging (Koen & Yonelinas, 2016) and the related influential associative deficit hypothesis (Naveh-Benjamin, 2000), Experiment 3a brought preliminary evidence that the prior knowledge effect could be age-resistant.

These findings require to further address two outstanding issues, namely 1) can we replicate the findings of an age-resistant benefit of prior knowledge on item and associative memory? and 2) what are the underlying mechanisms responsible for the massive increase in memory formation resulting from either immediate prior exposure or lifelong accumulated knowledge about the memoranda? Experiment 3b was aimed at addressing these concerns.

One hypothesis that has been put forward to explain how prior knowledge can improve memory formation is related to working memory and attentional resources allocation. Familiar stimuli would trigger conceptual and/or perceptual fluency (i.e. ease of processing) at study, which in turn would facilitate context processing, and context-item binding (Gagnepain et al., 2008; 2011; Reder et al., 2013). One possibility is that such facilitation may help the building of a more distinctive representation (namely, able to resist interference), which naturally follows deep processing in the levels-of-processing framework.



Figure 55. One possible account for the benefits of prior knowledge on memory for face-scene associations as suggested by Expt. 3a. Faces trigger either no fluency (Novelty), perceptual (EK) or perceptual + conceptual (PEK) fluency at study. As a consequence, more or less attentional and working memory resources are available for face-scene binding. Novelty may thus be more demanding than Pre-Experimental Knowledge, thus leaving more resources for scene processing behind e.g. Princess Diana. As a consequence of decreased attentional and working memory resources for relational binding, increased trace distinctiveness further improve memory formation.

If correct, this account would predict that more intrinsically distinctive stimuli should improve source memory for all conditions. Moreover, any manipulation aimed at increasing context processing similarly should increase source memory. However and importantly, this should have either no impact on item memory, or even impair item memory, due to increased attention to context processing, thus reducing the resources allocated to the face.

In the present experiment, we aimed at testing this hypothesis through a replication study of Experiment 3a, where we introduced only one change. Instead of using two unique photographs of landscape (one representing a beach, the other the countryside), we associated one unique landscape photograph to each target face at study. We reasoned that in Expt 3a, the use of the same two distinct backgrounds for all 96 faces might have shortly shaped the subjects' expectations in the study phase. Subjects were actually shown 96 face-scene associations. However, only the face was unique to each trial, while the scenes were common to half the trials (i.e. 48 "beach" scenes, 48 "countryside" scenes). While this is the standard way of building a source memory

paradigm, we would argue that this choice is not without consequences. In fact, subjects should shortly expect the display of a given background, with little opportunity of prediction error to occur for the scenes. Thus, it is much likely that, in spite of the associative learning instruction, the subject focus much more on the changing face rather than on the constant background. By using a unique face-scene combination for each trial, we aimed at increasing the intrinsic distinctiveness of the stimuli on the one hand, and to enable better contextual processing on the other hand. As stated above, we hypothesized that this manipulation to decrease memory accuracy for faces, but to increase memory for face-scene associations. Moreover, if the attentional – working memory account of prior knowledge effect on learning is correct, these changes in performance might differ depending on whether stimuli carry experimental, pre-experimental, or no prior knowledge. More specifically, increased memory for associations is more likely to occur for items with pre-experimental knowledge, since these are expected to trigger the most distinctive memory representations, following conceptual processing.

Our aims in Experiment 3b were therefore two folds. First, we aimed at replicating the main findings from Experiment 3a, and second, we aimed at verifying the hypothesis that increasing stimuli distinctiveness should improve source memory, but impair or leave unchanged item (face) memory.

Materials & methods

Participants

106 right-handed participants aged 20 to 87 years old provided an informed consent, and the ethics committee of the University of Rennes approved the study. The scientific advisory board of the psychology department further funded this experiment, which was promoted by the University of Rennes (Dr Audrey Noël), and ran in cooperation with the Memory Clinic of Rennes University Hospital (Dr S. Belliard). Screening was meant to check for the absence of any present or past medical condition susceptible to interfere with cognition, and to control for normal memory performance (Logical Memory subtest of the Wechsler Memory scale, 3rd Ed.) and absence of significant subjective cognitive

difficulty (Cognitive Difficulty Scale, McNair & Kahn, 1984). This led to the exclusion of N=23 subjects (active anti-depressant medication in 4; history of neurological or psychiatric diseases in 19). Of the 83 remaining subjects, 9 were further excluded due to impaired scores at the Logical Memory subtest, and 12 were excluded because they obtained outliers scores during the familiarity judgment phase (<-3 s.d.), thus leaving N=62 participants finally included.

Stimuli

The only difference between Experiment 3a and 3b concerned background scenes photographs. For the purpose of the present experiment, 48 coloured photographs of a scene depicting a countryside landscape and 48 depicting a beach landscape were gathered from the web. These pictures were normalized in size (720x484 pixels) and were free of any human character or manufactured or living object. Custom scripts were then used to generate all the possible combinations between a face and one of the 96 landscapes in the form of a visual stimuli with the face displayed at the centre of the landscape. Randomization was similar to the method described in Experiment 3b, except for the addition of random face-scene combinations across prior knowledge conditions and between subjects. This resulted in a completely random set of target stimuli for each subject.



Figure 56. Examples of stimuli used in Experiment 3b. Each face was randomly combined with one unique background. (Top left: former French president Nicolas Sarkozy; Middle left: French singer Charles Aznavour; Top right: Princess Diana)

Procedure

Each participant underwent one single session lasting about 3.5 hours. After completing the screening measures, the experimental procedure were identical to the one described in Experiment 3b. Importantly, during the recognition memory test, the procedure was also identical, and alternate forced choice recognition memory for the context did not use unstudied scene photographs as distractors. The subjects had to decide which one of two scene photographs was paired with the target face, and both scenes had been experienced during the study phase. This replicated the testing format of Experiment 3a, where source memory decision could not be made either on the basis of familiarity judgment.

Analyses

Given the aim of replicating the findings of Experiment 3a in an independent sample, we performed exactly the same analyses, again favouring a Bayesian approach for inferential statistics. Repeated-measures Bayesian ANOVAs were therefore performed on indexes of

item memory (i.e. Sensitivity “Az”, Hits, dans FAs) as well as associative memory (i.e. Conditional source memory index, as in Experiment 3a). Furthermore, similar analyses were ran for confidence ratings associated with item and source memory. Finally, we ran the exact same analyses (i.e. mixed or “Split-Splot” Bayesian ANOVAs) to investigate whether the findings were modulated by age.

To explore the hypothesis that increasing stimuli distinctiveness would improve source memory but worsen item memory, we further contrasted the datasets from Experiments 3a and 3b. That is, the study (3a or 3b) was used as a between-subjects factor to further assess the impact of “constant” vs. “variable” faces’ background on subsequent memory.

Results

General characteristics of the participants are shown in Table 3. The three groups of subjects did not differ on sex ratio, estimated verbal IQ, immediate verbal memory or reported cognitive difficulties. However, a mild difference was observed for education, the youngest subjects having completed more years of formal schooling than the two other groups.

	Young N=33	Middle- Aged N=12	Elderly N=17	BF ₁₀	p value
Demographics					
Age	27.6 (5.9)	53.7 (4.8)	70.2 (6.6)	5.014e ²⁸	<.001
Education (years)	14.2 (2.1)	11.8 (2.3)	11.4 (4.1)	15.347	0.003
Female:Male	18:15	9:3	13:4	0.500	0.215
Global cognition					
VIQ (f-NART)	104.5 (8.7)	105.2 (5.0)	109.1 (6.9)	0.666	0.135
Memory					
Logical Memory, I	43.3 (10.4)	41.3 (7.1)	40.8 (9.4)	0.203	0.644
Logical Memory, II	27.3 (6.5)	25.8 (6.9)	20.8 (9.6)	2.949	0.022
Questionnaires					
Cognitive Difficulty Scale (total score)	46.3 (17.0)	38.8 (11.1)	38.5 (18.8)	0.491	0.215

Table 3. Demographics & Neuropsychological background of the 62 participants included. f-NART=French version of the National Adult Reading Test.

Familiarity judgment for all the faces used in the experiment yielded high accuracy, with an average of 91% (ranging from 76 to 100%), and importantly, accuracy did not differ between age groups ($BF_{10}=0.393$). Recognition memory also yielded accurate scores, with sensitivity (A_z) ranging from 0.71 to 0.99 (mean=0.87). Response bias, like in Experiment 3a, was highly variable, ranging from -0.93 to 0.50. Finally, and critically, the floor effect observed in the previous experiment was reduced for source memory accuracy, but only 32 subjects performed beyond chance level, with a huge inter-individual variability (ranging from 34 to 87%), and as we will see below, important differences between prior knowledge conditions.

Can we replicate findings from Experiment 3a?

We replicated the main effect of prior knowledge on A_z ($BF_{10}=8.337e^{29}$) and extended this finding to Source memory ($BF_{10}>260000$). Post-hoc testing revealed very strong evidence for better sensitivity in PEK and EK conditions by comparison with Novelty ($BF_{10}=6.457e^{17}$; $BF_{10}=1.416e^{15}$, respectively), while less conclusive evidence was reported for the PEK vs. EK comparison ($BF_{10}=7.621$). PEK condition yielded more Hits and fewer FAs than Novelty condition ($BF_{10}=1.288e^{19}$; $BF_{10}=1085.969$, respectively); and only less FAs rates than EK ($BF_{10}=9419.152$), with no difference for Hits rate ($BF_{10}=0.179$). Finally, EK stimuli triggered more Hits ($BF_{10}=1.844e^{23}$) but a similar FAs rate ($BF_{10}=0.139$) than Novelty (see Figure 57).

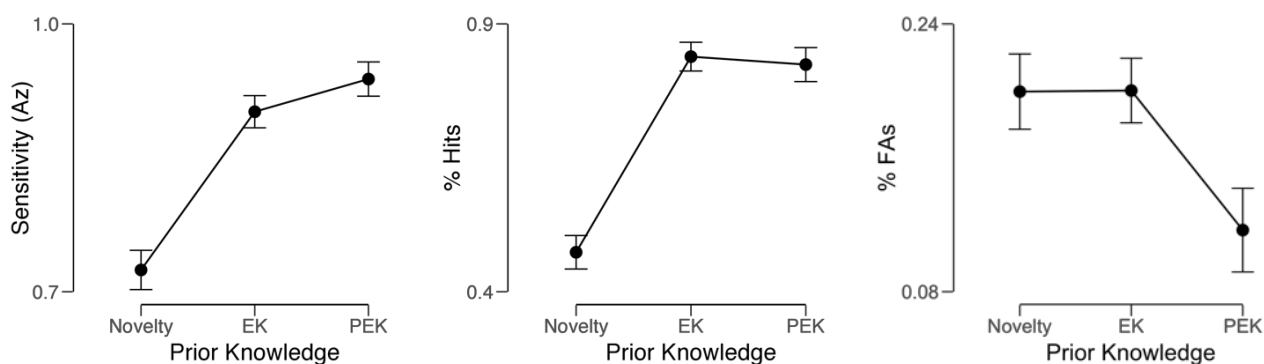


Figure 57. Prior Knowledge effect on recognition memory, across all participants. %95ICs are displayed.

Turning to source memory, we found evidence supporting the null hypothesis for the EK vs. Novelty comparison, and both conditions yielded much less accuracy than PEK ($BF_{10} > 769e^3$; $BF_{10} = 402.211$, respectively). However, as mentioned above, this was like in Experiment 3a associated with a floor effect in the EK and Novelty conditions. By contrast, most of the participants performed above chance in the PEK condition. Note that these results mimic the findings of Experiments 3a for high-confidence accurate source memory responses (see Figure 58). Indeed, the same analysis here yielded similar findings, with a main effect of Prior Knowledge ($BF_{10} = 4.54e^{13}$), where only PEK stimuli yielded higher performance (vs. Novelty, $BF_{10} = 1.529e^{10}$; vs. EK, $BF_{10} = 2.812e^7$).

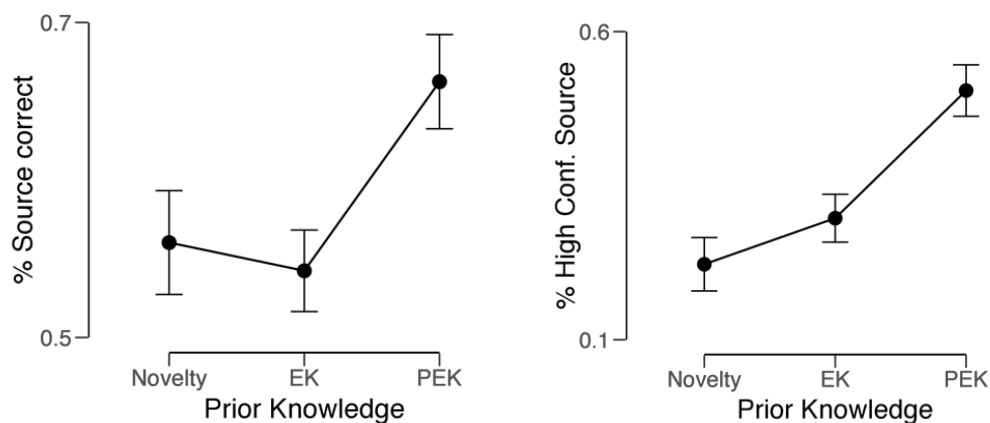


Figure 58. Prior Knowledge effect on source memory, across all participants. The left graph depicts source memory accuracy, and the right shows correct source responses associated with high confidence ratings. %95ICs are displayed.

Finally, we replicated previous findings regarding how prior knowledge also altered the confidence associated with Hit responses. High confidence Hits were strongly impacted by the prior knowledge conditions ($BF_{10} = 2.836e^{22}$), and all post-hoc tests favoured the alternative hypothesis (Nov < EK < PEK; Nov vs. EK, $BF_{10} = 5.922e^6$; Nov vs. PEK, $BF_{10} = 3.124e^{17}$; EK vs PEK, $BF_{10} > 315e^3$). Accordingly, a coherent pattern was found for Middle-confidence Hits, which were more frequent in the Novelty condition ($BF_{10} = 5.899e^{21}$; Nov > EK > PEK; Nov vs. EK, $BF_{10} > 565e^3$; Nov vs. PEK, $BF_{10} = 1.726e^{17}$; EK vs PEK, $BF_{10} = 1.612e^6$). Finally, we extended prior findings for low-confidence Hits: they were more frequent for Novel than PEK and EK conditions, and we confirmed evidence for the null hypothesis regarding the EK vs. PEK contrast (main effect, $BF_{10} = 1.609e^{15}$; Nov > EK = PEK; Nov vs. EK, $BF_{10} = 3.243e^6$; Nov vs. PEK, $BF_{10} = 3.111e^6$; EK vs PEK, $BF_{10} = 0.158$) (see Figure 59).

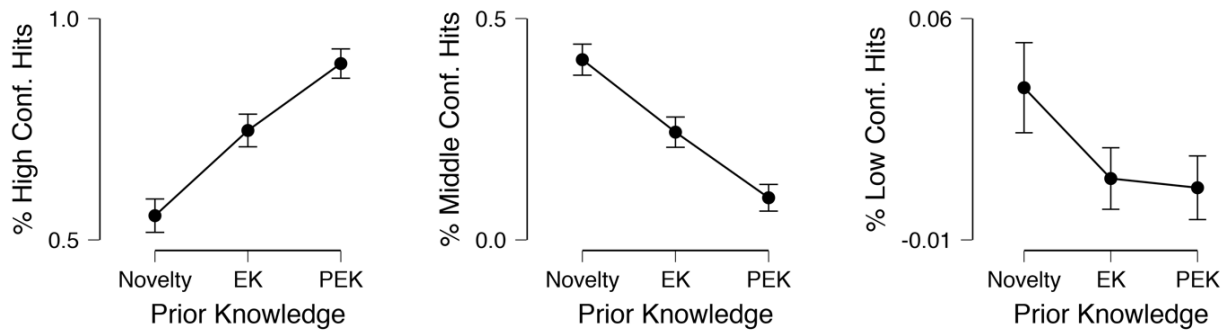


Figure 59. Prior Knowledge effect on the subjective aspects of recognition memory (confidence ratings), across all participants. %95ICs are displayed.

Again, this resulted in strong evidence for the hypothesis of an interaction between prior knowledge effect and confidence ratings ($BF_{10}=6.564e^{196}$): while the frequency of low-confidence ratings did not differ across prior knowledge conditions, middle-confidence and high-confidence ratings were differentially affected by prior knowledge. Items in the Novelty condition yielded slightly more high- than middle-confidence Hits, while strong evidence was found for more high- than middle-confidence Hits in the PEK and EK conditions. Moreover, EK yielded more middle-confidence ratings than PEK and conversely, PEK yield more high-confidence ratings than EK (all $BF_{10}>30$).

In summary, we could replicate on an independent sample the findings of very strong evidence that prior knowledge enhances recognition memory for individual items, but also associative (source) memory for face-scene associations. Moreover, we replicated our prior findings that the nature of prior knowledge seems to matter for item but not source memory. In fact, in the PEK condition, we replicated the finding of fewer FAs than in the EK condition, with no differences regarding the Hits rates. Furthermore, prior results suggesting that item recognition memory based on subjective recollection could be differentially affected by PEK vs. EK was also replicated: PEK led to a higher probability of High-confidence Hits than EK. Finally, this replication experiment has seemingly raised source memory accuracy overall, and we found similar degrees of improvements following PEK and EK by comparison with Novelty.

In the next section, we report on the attempt to replicate the findings of Experiment 3a regarding aging effects.

Regarding sensitivity (A_z), the best model for the data included a Prior Knowledge X Age interaction ($BF_{10}=3.345e^{31}$, the interaction model was 2.8 times more likely to account for the data than a model including the two main effects without interaction). This interaction reflected the fact that elderly participants performed below young and middle-aged subjects in the Novelty condition (Elderly vs. Middle-Aged, $BF_{10}=2.421$; Elderly vs. Young, $BF_{10}=34.584$), while their performance gradually increased in the EK condition (Elderly vs. Middle-Aged, $BF_{10}=1.650$; Elderly vs. Young, $BF_{10}=11.590$) to finally reach that of the other participants in the PEK condition (Elderly vs. Middle-Aged, $BF_{10}=0.558$; Elderly vs. Young, $BF_{10}=0.410$). Note that very strong evidence for the effect of age was only found when comparing elderly with young subjects for novel stimuli, while moderate to strong evidence only was reported for the other contrasts. However, and importantly, in the PEK condition we found clear evidence favouring the null hypothesis that aging does not alter PEK-based recognition memory for faces.

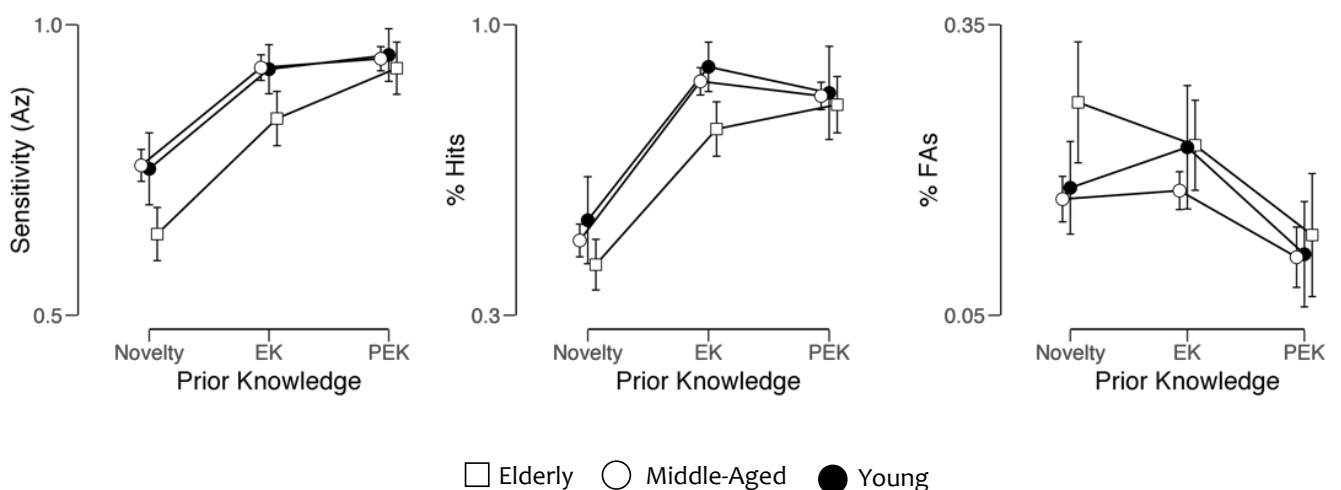


Figure 60. Prior Knowledge effect on recognition memory within each age group. %95ICs are displayed.

Like in the previous experiment, we did not find any evidence favouring the Prior Knowledge X Age interaction for the Hits and FAs rates. In each case, the main effect of prior knowledge was sufficient to account for the data (Hits, $BF_{10}=8.468e^{36}$; FAs, $BF_{10}>122e^3$). Nonetheless, we observed that regarding the Hits rates Age and Prior

Knowledge X Age interaction may contribute the data since the corresponding Bayes factors were very close to the one computed for the best model (Age, $BF_{10}=7.530e^{36}$; Interaction, $BF_{10}=1.584e^{36}$). This suggested a trend for fewer Hits in the Novelty and EK condition in the elderly. Similarly, we observed some evidence for an increased FAs rate in elderly in the Novelty, again with an inconclusive level of evidence ($BF_{10}=1.716$), especially in the context of the absence of interaction (B_{10} for the interaction $>185e^2$ but B_{10} for the main effect of Prior Knowledge $>122e^3$). These subtle effects were in the end responsible for the strong evidence favouring an interaction between Prior Knowledge and Age for item memory (i.e. sensitivity).

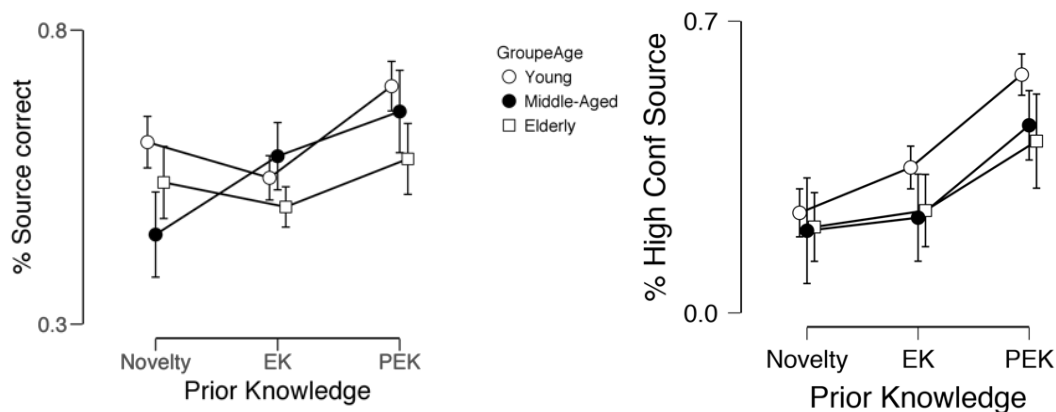


Figure 61. Prior Knowledge effect on source memory, across all participants. The left graph depicts source memory accuracy, and the right shows correct source responses associated with high confidence ratings. %95ICs are displayed.

Turning to Source memory, the repeated-measures ANOVA with Prior Knowledge as within-subject factor and Age as between-subjects factor yielded strong evidence for an interaction ($BF_{10}=7.955e^6$). However, the floor effect observed for all conditions except PEK prevented from further interpreting this result. Focusing on high-confidence source accuracy, we found a main effect of Prior Knowledge ($BF_{10}=2.787e^{22}$) that best accounted for the data. PEK yielded more frequent high-confidence accurate source responses than EK ($BF_{10}>315e^3$), which in turn were more frequent than for Novelty ($BF_{10}=5.922e^{17}$). Age did not account for the data ($BF_{10}=0.310$), thus replicating the findings of Experiment 3a.

Finally, we also confirmed prior results regarding the confidence ratings for Hits, with an effect of Prior Knowledge ($BF_{10}=2.8e^{22}$), but no effect of Age ($BF_{10}=0.316$) or interaction ($BF_{10}=4.818e^{21}$). The same pattern as before was replicated, i.e. PEK $>$ EK $>$ Novelty (PEK vs. EK, $BF_{10}>315e^3$; EK vs. Novelty, $BF_{10}=5.922e^6$).

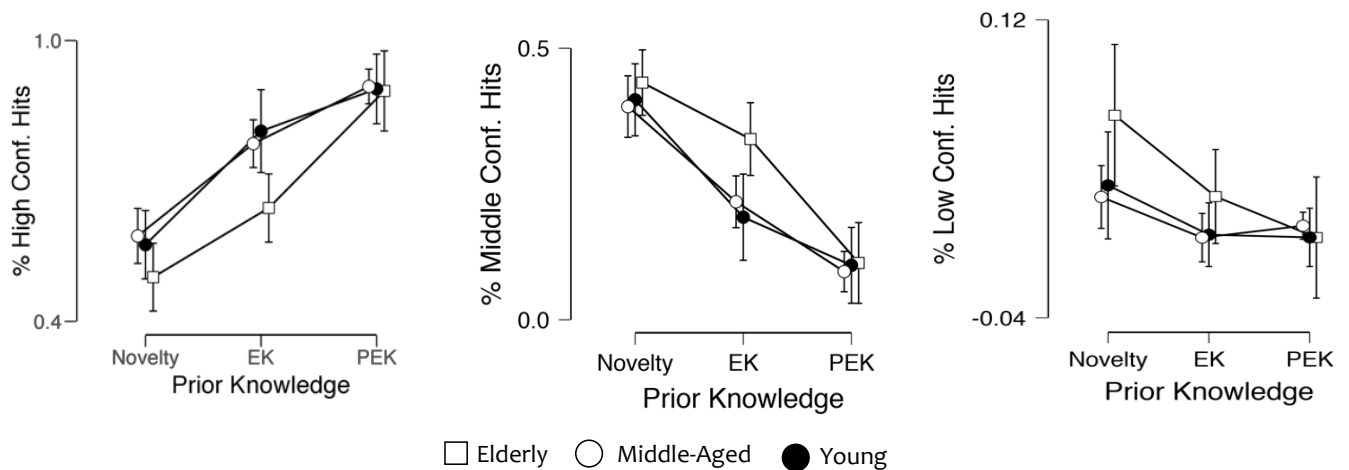


Figure 62. Prior Knowledge effect on the subjective aspects of recognition memory (confidence ratings), within each age group. %95ICs are displayed.

In summary, this replication study confirmed that prior knowledge equally enhances explicit learning of face-scenes associations in young and elderly subjects. However, the interaction observed for recognition memory for faces only suggests that elderly subjects may disproportionately benefit from pre-experimental knowledge.

In the next section, we then address the second aim of this experiment, namely asking whether increased distinctiveness of the stimuli would affect item memory and source memory in different ways.

Constant vs. variable background contexts: the role of distinctiveness

Considering the above findings suggesting that Age plays a marginal role in prior knowledge-dependent learning, subsequent analyses were ran with all participants (Expts 3a & Expt 3b, N=113), but with age as covariate.

Across prior knowledge conditions, we found evidence that variable contexts introduced in Experiment 3b hindered sensitivity (A_z , $BF_{10}= 21.02$) but enhanced Source memory accuracy (% , $BF_{10}=607.63$), which overall supports our hypothesis.

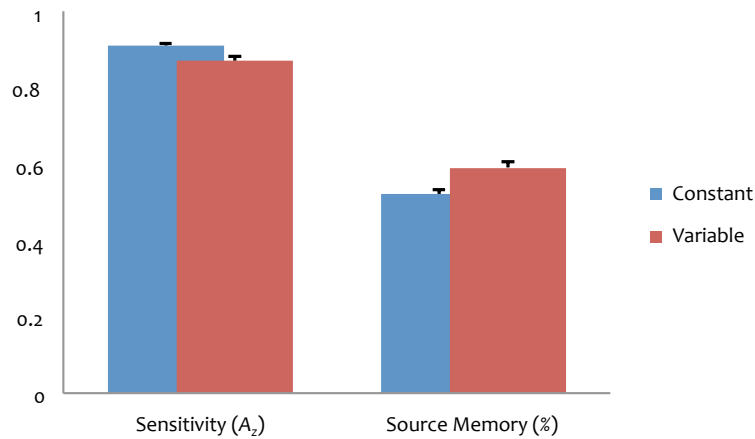


Figure 63. Impact of using variable background scenes (Expt. 3b) rather than constant background scenes (Expt. 3a) on recognition memory for the faces (sensitivity index) and for face-scene associations (Source memory). Error bars display standard error of the mean.

Considering sensitivity index (A_z), repeated-measures ANOVA with Context (Constant, Variable) as between-subjects factor and Prior Knowledge (Novelty, EK, PEK) as within-subjects factors (plus age as a covariate) yielded strongest evidence for a model including Context, Prior Knowledge and Age ($BF_{10}=1.273e^{59}$), with no interaction. The effects of Prior Knowledge and Age have been described before, so what is relevant here is the post-hoc analysis for the Context effect. Evidence favoured the alternative hypothesis that Variable contexts decreased sensitivity overall ($BF_{10}=10.46$), although this remained below the conventional threshold for very strong evidence (Rouder et al., 2009). As a reminder, this value of the Bayes factor suggests that an effect of Context on data is 10.46 times more likely than its absence.

By contrast, Source memory scores were better explained by an interaction model ($BF_{10}=2.763e^6$) resulting from a boost of performance under the Variable contexts condition, only for the PEK condition ($BF_{10}=6853$).

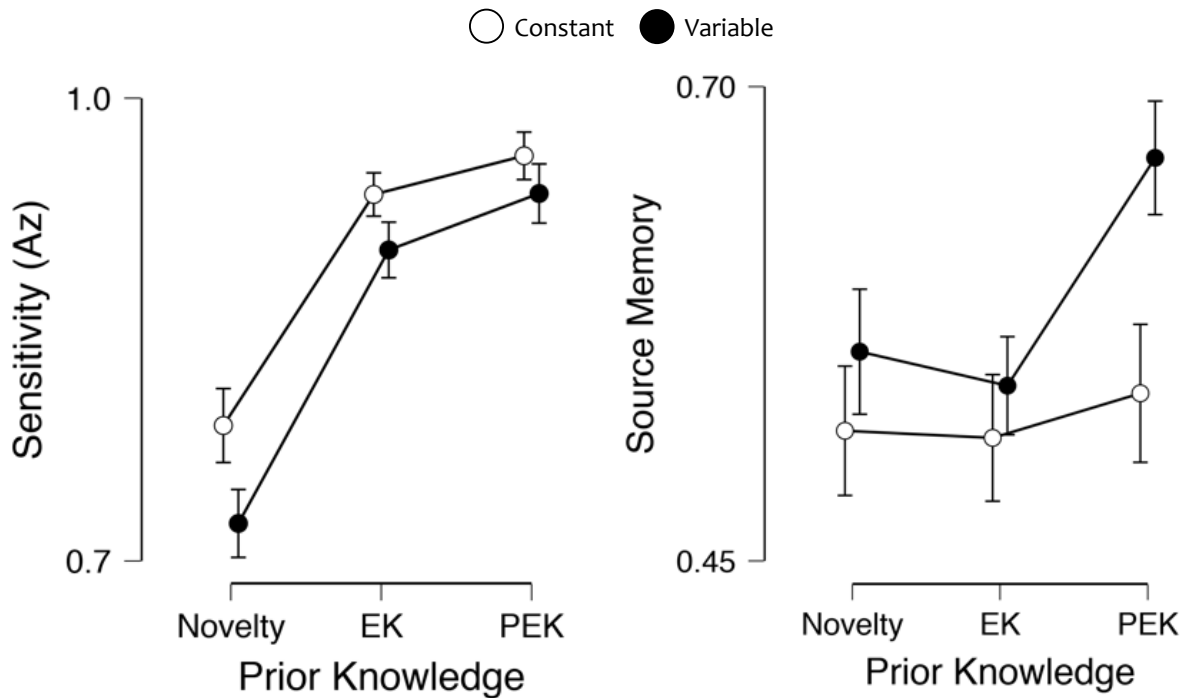


Figure 64. Impact of using variable background scenes (Expt. 3b) rather than constant background scenes (Expt. 3a) on recognition memory for the faces (sensitivity index) and for face-scene associations (Source memory) in each Prior Knowledge condition. Error bars display %95CIs.

Discussion

Experiment 3b allowed us to replicate the main findings from Experiment 3A, thus strengthening the fact that recognition memory performance largely varies depending on the long-term representations associated to the materials prior to study, and that the effects are relatively immune to aging.

First, we replicated the findings, in an independent sample, of better recognition memory for faces with long-term memory representations than novel faces. Second, we extended findings from Experiment 3a in that elderly participants seemed to benefit disproportionately from PEK, not EK condition regarding memory for faces. These results add to the growing evidence that, under certain circumstances, prior knowledge may disproportionately help elderly subjects (Badham et al., 2015; Badham & Maylor, 2015), extending the effect to face-scene associations, which are particularly relevant in everyday life. Moreover, they introduce the idea that the nature of prior knowledge matters. Prior knowledge resulting from lifelong accumulated exposures led to fewer

false alarms than prior knowledge derived from a single recent exposure 25 minutes prior to study. This is in line with the proposal that conceptual and perceptual fluency may have different contribution to recognition memory (Lanska, Olds, & Westerman, 2014). When conceptual together with perceptual fluency is present at encoding (like for famous faces), the memory trace may be strengthened to a greater extent than when the stimulus triggers either no fluency (i.e. novel face) or perceptual fluency only (i.e. EK face). Furthermore, this pattern is also consistent with the concept of “encoding depth” (LOP framework, Craik & Lockhart, 1972), resulting in more distinctive representations of the faces after conceptual processing. One future avenue for research could therefore be to more directly manipulate conceptual fluency to increase item memory in studies of memory aging and in early neurodegenerative conditions like Alzheimer’s disease. If the benefits of pre-experimental knowledge on recognition memory are truly immune to aging, this could represent an interesting opportunity for further cognitive markers of early neurodegenerative diseases. Finally, such findings reinforce the idea that prior-knowledge based learning should rely on neural networks that are more-age resistant, an outstanding issue that we will address in the next experiment.

Beyond recognition memory for the faces, the present study could also replicate the benefits of pre-experimental knowledge on memory for the face-scene associations, which again was immune to aging. Importantly, estimates of subjective recollection (confidence ratings for Hits responses) also were consistent with a benefit of pre-experimental knowledge, but also revealed that experimental knowledge triggered more high-confidence Hits than Novelty, across Age groups. This dissociation between “subjective” and “objective” recollection could reflect the acknowledged fact that source memory paradigms do not capture all possible sources of recollection. For example, one can make an accurate recollection-based judgment based on the retrieval of a particular thought or feeling triggered by the stimulus at study, while failing to recall the correct background. These measures are therefore complementary rather than contradictory. What they suggest here is that when prior knowledge is present at encoding, it facilitates face-scene binding operations independently of the nature of prior knowledge (i.e. mainly perceptual in EK, or conceptual in PEK). However, more retrieval cues might be generated in the case of conceptual processing of famous faces than following perceptual processing of familiarized faces, thus leading to a differential impact on Confidence ratings. Interestingly, this interpretation would offer new perspectives for

the assessment of how elaborative encoding and processing depth could dissociate (Lockhart & Craik, 1990): while EK and PEK stimuli should trigger elaborative encoding, PEK only should yield deep (semantic) processing. One could therefore argue that experimental manipulations yielding distinct e.g. neural or cognitive correlates for EK vs. PEK-based memory encoding would strongly speak for a dissociation between these processes thought as major learning enhancers.

Finally, we aimed at testing the idea that increased stimuli distinctiveness (by using face-scene trials) should improve memory for the association but degrade memory for the items. This hypothesis was largely confirmed by a crossover pattern whereby the introduction of variable background contexts impaired sensitivity across prior knowledge conditions, but enabled better source memory only in the PEK condition. Thus, the present study brought indirect evidence supporting the attentional/working memory account of memory enhancement through pre-experimental knowledge (Gagnepain et al., 2008; 2011; Reder et al., 2013). Our view is that increasing stimuli distinctiveness has reduced the processing demands for the face, thus facilitating face-context long-term memory binding. The specific boost observed for associative memory with famous faces may have resulted from the additional benefits of conceptual processing (i.e. conceptual fluency and semantic encoding at study) and increased distinctiveness, the former lacking for familiarized or novel faces. Further studies are required to confirm that pre-experimental knowledge can alleviate the associative memory deficit associated with aging, and to test the present hypothesis against alternative accounts (see e.g. Delhaye, Tibon, Gronau, Levy, & Bastin, 2018). In any case, it seems that associative memory formation supported by pre-experimental knowledge may depend on brain structures that are relatively more preserved in aging, which would rule out the hippocampal formation. This possibility should be investigated further either through neuropsychological or imaging studies.

Experiment 4: Does prior knowledge play a role in the cognitive and neural substrates for associative memory impairment in early Alzheimer's Disease?

Scientific valorisation

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Article in preparation for the journal Neurobiology of Aging

Highlights from Experiment 4

Before the following study, we ignored whether prior knowledge available at encoding could alter new learning in prodromal AD. We bring evidence that **patients with early AD fail to benefit from pre-experimental prior knowledge** (famous faces) by comparison with experimental knowledge (unknown but familiarized faces) for subsequent source memory (face-scene associations).

fMRI responses at study reveal **distinct networks underlying associative encoding for these two kinds of prior knowledge.**

A subsequent memory effect for **associations with pre-experimental knowledge is reported in subhippocampal structures for Controls, not patients.** Conversely, experimental knowledge yields similar memory effects across groups in the hippocampus.

We might **underestimate the associative learning impairment when using unfamiliar materials to probe memory in early AD.**

Pre-experimental knowledge-based associative encoding may depend on brain **regions specifically targeted by early tau pathology**, like the perirhinal cortex.

Learning what we know: how prior knowledge impairs associative learning in early Alzheimer's Disease

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Emmanuel Barbeau

Abstract

Impaired associative memory is a hallmark of prodromal Alzheimer's Disease (AD). However, prior knowledge associated with the memoranda is hardly considered. We designed an fMRI task to test whether prior knowledge-based associative learning was preserved in early AD, and whether brain substrates could differ depending on the kind of prior knowledge involved. 17 Patients with early AD were scanned while learning face-scene associations. Prior knowledge was manipulated by presenting either famous faces (Pre-Experimental Knowledge, PEK) or unknown faces that were repeatedly familiarized prior to the study phase (Experimental Knowledge, EK). We found that PEK increased subsequent associative memory in Controls (19), but not in patients. Partly non-overlapping brain networks supported PEK vs. EK associative encoding. Moreover, patients lacked the subsequent associative memory effect for PEK in right subhippocampal structures, observed in Controls. These findings call for a thorough consideration of how prior knowledge alters learning. They bring new perspectives both for early detection of AD and neural basis of declarative learning.

Keywords

Associative learning; Alzheimer's Disease; Prior Knowledge; Source Memory; Recognition Memory; Perirhinal Cortex

Introduction

The hallmark of the prodromal stage of Alzheimer's disease (AD) is impaired episodic memory, observable up to 18 years before dementia (Albert et al., 2011; Rajan et al., 2015). The inability to form new associations in long-term memory, namely associative learning, is consistently reported (Chen & Chang, 2016; Fowler, Saling, Conway, Semple, & Louis, 2002; Lowndes & Savage, 2007). Patient concerns typically refer to forgetfulness during their daily routine, thus learning failures occur when highly familiar stimuli are involved within a given life event. These stimuli therefore carry "pre-experimental prior knowledge" (PEK), because a large amount of knowledge is available about the individual event features. Since, memory testing of patients usually involves much less familiar stimuli (i.e. isolated words), presented repeatedly (multiple-trials learning tests). Such stimuli can be considered as associated with "experimental prior knowledge" (EK), namely familiarity resulting from repeated exposures (see Poppenk et al., 2010a). Thus, while subjective symptoms have to do with the inability to form new associative representations about well-known stimuli (PEK, e.g. familiar faces), the proxies we are using tap on processes involved in the gradual formation of new associative representations about much less familiar stimuli (EK, e.g. recent encounter with a new person). It follows that little is known about prior knowledge-dependent associative memory in patients with early AD. Here, we aimed at investigating whether prior knowledge alters associative memory formation in early AD, both at the behavioral and neural levels.

Evidence from behavioral studies has supported the role of PEK in enhancing associative learning in healthy adults (Bird et al., 2011; Carbon, 2008; Castel, 2005; Ellis et al., 1979; Greve, van Rossum, & Donaldson, 2007; Jackson & Raymond, 2008; Klatzky & Forrest, 1984; Long & Prat, 2002; Poppenk, Köhler, et al., 2010; L. M. Reder et al., 2013a; Voss,

2006; Zion-Columbic et al., 2010), including the elderly (Badham et al., 2015; Badham & Maylor, 2015; McGillivray & Castel, 2010). Still, this has received little attention in AD, with available data suggesting a lesser degree of PEK advantage (Bäckman & Herlitz, 1990; Lipinska et al., 1992). Turning to the role of EK, we could not find prior studies in AD, however behavioral evidence in young adults supports the benefits of EK for associative learning. Gagnepain et al., (2008) found that primed (i.e. recently repeated) words were more likely to be further recollected than non-primed words (see also Dennis et al., 2015; Poppenk et al., 2010a, 2010b for similar results with different stimuli). Interestingly, incidental instructions were provided during the familiarization phase, and repeated incidental encoding is acknowledged to advantage amnesic patients (Bayley & Squire, 2002, 2005). It is therefore expected that, when assessing associative memory in patients in early AD with multiple-trials learning tests, EK accumulated across trials may enhance performance.

To the best of our knowledge, the neural correlates underlying the role of prior knowledge in associative learning have not been investigated in AD. On the one hand, task-based fMRI studies in young adults have put forward the role of medial temporal lobe and temporal pole, together with the ventromedial and inferior / middle prefrontal cortex in PEK-based learning when compared with either novel stimuli or recently learned stimuli (Leveroni et al., 2000; Liu et al., 2016; Marlieke T R Van Kesteren et al., 2012). EK-based learning was associated to activity in parietal regions and the posterior hippocampus, as reflecting the role of retrieval processes and attentional enhancement effects (Dennis et al., 2015; Poppenk, Köhler, et al., 2010; Poppenk, McIntosh, et al., 2010; Poppenk & Norman, 2012). On the other hand, neural adaptation fMRI studies have successfully mapped functional encoding networks in AD patients. Neural adaptation refers to the decrease (suppression) or increase (enhancement) of the BOLD signal with

repeated presentations of stimuli (Grill-Spector et al., 2006). Noteworthy, neural adaptation was preserved in elderly controls but impaired in AD patients, notably within medial temporal lobe and regions from the default mode network (Johnson et al., 2004; Pihlajamäki et al., 2011; Vannini et al., 2013; but see Lustig and Buckner, 2004). Yet, here, the role of prior knowledge has never been considered.

In the present study, we asked early AD and controls subjects to encode face-scene associations within an event-related fMRI task design, prior to a recognition memory test. Prior knowledge about the stimuli was manipulated to induce either EK or PEK, and study events were presented twice. We hypothesized that in early AD, associative learning would be less impaired for EK than PEK, and we combined the analyses of fMRI responses to repetition and to prior knowledge in an attempt to identifying the corresponding neural correlates.

Material and methods

Participants

All participants provided a written consent, and the ethics committee of Rennes University Hospital approved the study. The study is registered in the Clinical Trials database (EPMR-MA Study 2014-A01123-44). 22 patients fulfilling the NIA-AA criteria for Mild Cognitive Impairment due to Alzheimer's disease (AD-MCI) (Albert et al., 2011) together with 25 healthy controls were screened to participate. Patients were recruited as part of the "Centre Mémoire de Ressources et de Recherches de Haute-Bretagne" at Rennes University Hospital, a Memory Clinic with over 20 years of clinical expertise in the field, where a senior neurologist (SB) made the diagnosis. Inclusion criteria for AD-MCI patients were: i) evidence of a concern regarding a change in cognition; ii) impaired episodic memory confirmed through neuropsychological assessment by reference to the available normative data; iii) fully preserved independence in functional abilities; iv)

evidence for hippocampal atrophy; v) evidence for amyloidopathy either through cerebrospinal fluid (CSF) measures of lower Ab42 levels or via positron-emission tomography (PET) evidence of Ab deposition. Further inclusion criteria were i) aged 60-75 years; ii) >7 years of education; iii) native french speaking; iv) right-handedness. Exclusion criteria were i) any history of alcoholism, drug abuse, head trauma or psychiatric condition; ii) 7-items modified Hachinski ischemic score >2 (Hachinski, Oveisgharan, Romney, & Shankle, 2012); iii) scores above the age- and genre-adjusted available cut-off at the Beck Depression Inventory (BDI-II, Beck et al., 1996) or at the State-Trait Anxiety Inventory (STAI, A&B, Spielberger et al., 1983); iv) dementia (Mckhann et al., 2011). All subjects underwent two testing sessions. They first underwent an extensive neuropsychological assessment (for details see **Supplementary Materials**) which allowed to (1) rule out any subtle cognitive impairment among control subjects; (2) rule out severe impairments in AD-MCI patients that would be incompatible with the second experimental session; (3) avoid the inclusion of atypical Alzheimer's disease profiles like progressive focal degenerative phenotypes among our experimental group (Alladi et al., 2007). The second visit included the imaging and behavioral experiments. Five AD-MCI were excluded (two presented with severely impaired cognition preventing them to undergo the experiments, one scored above the cut-off at the depression inventory, one gave-up during the second visit, and one proved to suffer claustrophobia in the scanner), as well as six Controls (two due to technical issues at MRI acquisition, one due to cognitive scores below the norms, one due to back pain complaint in the scanner, one due to above-the-cut-off score at the depression inventory, and one due to the discovery of a pituitary adenoma), resulting in the final inclusion of 19 Controls and 17 AD-MCI.

Design & general procedure

Once the first testing session (including an extensive 3-hours neuropsychological assessment) was completed, participants came back to the lab within one month for the second session. The whole procedure of the second session is illustrated in **Figure 1**. It was divided in four phases: 1) familiarization with the MRI environment in a mock-scanner; 2) actual MRI acquisition during study; 3) recognition testing outside the scanner and 4) fame judgment for all the items involved in the study phase. An extensive training was provided both inside and outside the scanner to make sure that participants understood and performed the tasks as expected.

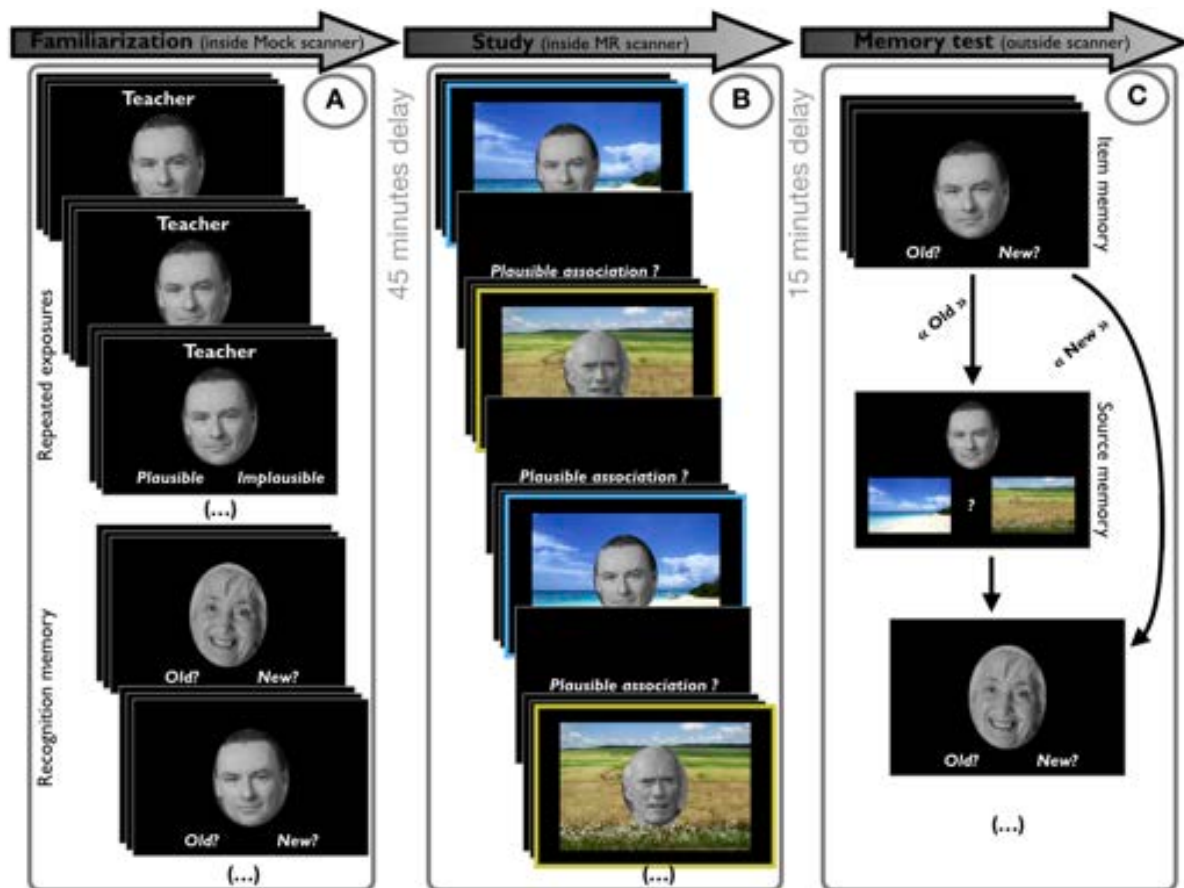


Figure 1. Experimental design. (A) During Familiarization, unknown faces were repeatedly presented inside a Mock scanner. Participants were instructed to make a congruency judgment for the face-occupation association. Then, an immediate Old/New recognition test was administered. (B) Study phase inside the MR scanner involved the explicit encoding of face-scene associations of two types: EK trials (blue outline), involved a face from the familiarization phase; PEK trials (yellow outline) involved a famous face. (C) After a 15 minutes delay, the Test phase took place outside scanner. Participants had to make Old/New judgments for individual faces. For each Hit (i.e. true positive) response, a two-alternate forced choice test asked subjects to recall the correct source (i.e. which scene was associated with the face at study). Finally, after a 5 minutes delay, a Fame judgment test (not depicted) involved the whole set of faces (i.e. targets and distractors).

Cognitive tasks

Stimuli. Unique associations between a scene (landscape picture) and a face were used as stimuli (see **Figure 1**). PEK stimuli were modeled with famous faces whereas EK stimuli were modeled with unknown faces. The faces and the landscapes were gathered from the Internet. Faces images were converted to greyscale pictures, cropped within a 250 px-width oval-shape, and normalized for contrast. Extensive pre-testing of fame judgment in healthy elderly resulted in the selection of two sets of N=132 famous faces and N=184 unknown faces, that were matched as closely as possible for sex ratio, age, ethnicity, hair colors, emotional expression and accessories like glasses or earrings. 98 colored landscape images were selected so that half represented a beach, half a countryside, and none included any human or any artifact, and were normalized to 720x484 px. Two sets of 48 famous and 48 unknown faces were chosen by drawing lots, each being randomly associated with 24 countryside and 24 beach landscapes images, resulting in 96 PEK stimuli (i.e. famous faces - landscape association) and 96 EK stimuli (i.e. unknown face - landscape association), half being used as targets and half as distractors. An additional set of 26 unknown faces was randomly chosen for use as distractors in the recognition test during the familiarization phase (see below & Figure 1). The order of presentation, the set of pictures as well as the face-scene combinations were fully randomized across participants.

Familiarization phase (pre-scan). Participants were installed in a factice MRI-scanner designed to familiarize them with the real MRI scanner environment, including the space, noise, luminosity, handgrip used as response device, and computer screen viewed through a mirror. They were presented a series of faces randomly associated with an occupation, and were instructed to make a congruency judgment about that association. 48 unknown faces were repeatedly presented 3 times across 6 blocks, with face-

occupation combinations remaining constant across repetitions. For each participant, a pseudo-random order of presentation was used so that at least 3 trials separated two identical stimuli. Each stimulus was presented for 2.5 seconds followed by a 1.5 s time response windows. No memory instruction was given. Immediately after that familiarization phase, participants were administered a surprise Old/New recognition memory test involving the 48 targets together with 26 new, unstudied, unknown faces. The purpose of this short testing session was to assert that each participant had correctly incidentally encoded the 48 unknown target faces. Following the recognition test, participants remained in the Mock scanner and received the instructions and some practice trials for the real-fMRI study phase. Importantly, groups did not differ regarding their fame judgment performance, with similar accuracy across all items ($U=132$; $p=0.357$; $d=-0.183$; 95%CI: [-0.514; 0.196]) as well as considering more specifically the PEK faces ($U=122$; $p=0.215$; $d=-0.245$; 95%CI: [-0.560; 0.133]).

Study phase (inside the scanner). 45 minutes after the familiarization phase, participants again underwent a short practice session of the study task. The critical trials required subjects to explicitly learn face-scene associations. Each stimulus was presented for 3.5 seconds, and then the participant had 1.5 second to decide whether the background scene was congruent or not with the face. The congruency task was designed to ensure that enough attention was paid to both the face and the scene at encoding, and participants were explicitly instructed that they would be further tested for their memory of the associations. The arrow task (C. E. L. Stark & Squire, 2001) was adapted and used as an active baseline, and jittered white fixation crosses were displayed between trials. The schedule of events was optimized via Optseq2 (Dale M., 1999). Each run started and ended with a 4 seconds fixation cross, and included 44 events: 16 EK, 16 PEK and 12 Arrow. In total, 48 EK and 48 PEK trials were repeated once so that each study event was

presented twice across 6 runs. Median lag between two identical events was 8 minutes, without repetitions within a run. Lag durations between two occurrences of the same stimulus were similar for PEK and EK events (670 vs. 630 seconds for EK & PEK, respectively, $U=5035$; $p=0.268$; $d=0.093$; 95%CI: [-0.071; 0.251]). The order of the runs was counterbalanced across participants.

Test phase (outside the scanner). 20 minutes after the study phase, participants were administered a recognition memory test in a quiet room close to the scanner. Target faces were randomly mixed with foils, and participants had to make an Old/New decision by reference to the study phase. This provided a measurement of item memory, i.e. memory for faces only. After Hit responses (i.e. “Old” responses to a target face), the face was presented again together with two scenes, one featuring a beach and the other one countryside, both corresponding to scenes used during the study phase. Participants were instructed to choose the correct source, namely the scene associated with the face at study. This provided a behavioral proxy for associative memory accuracy. The order of presentation was fully randomized across participants.

Fame judgment phase (outside the scanner). 5 minutes after the test phase, subjects were shown again all the faces from the test phase and asked to make a “Famous/Unknown” judgment. As a result, any PEK or EK stimulus yielding inaccurate responses at that step was removed from further analysis. This allowed us to contrast truly famous (i.e. items associated with PEK) vs. truly unknown (i.e. items associated with EK due to the familiarization phase only) on an individual basis. The participants were very accurate, ranging from 77 to 100%.

Behavioral data analysis

Item recognition memory performance indices (faces only, Hits and False Alarm rates) were computed within the signal detection theory framework. Following Verde et al., (2006), A_z was computed to estimate sensitivity, namely, how well participants discriminated between targets and distractors. Accordingly, we computed a non-parametric indice of bias B'' after Grier, (1971). These indices were preferred to the parametric d' and C indices of sensitivity and bias, respectively, for their superior robustness to the underlying assumptions regarding responses distributions (Stanislaw & Todorov, 1999; Verde et al., 2006), and corresponding formulae were implemented using a dedicated Excel workbook (Gaetano, J. M. (2017). Signal detection theory calculator 1.2 [Excel workbook downloaded from https://www.researchgate.net/profile/Justin_Gaetano2/]). Associative learning performance was estimated through source memory accuracy. Source memory refers to the ability to correctly recall the context that was associated to the target item at study. Here, we measured source memory as the conditional probability of a Source Hit (i.e. giving a correct source response) given an Item Hit (i.e. giving a correct “Old” response to a target face), which is a classical behavioral proxy for associative memory accuracy (Cooper et al., 2017). Repeated-measures ANOVAs were ran to explore whether the kind of prior knowledge (EK vs. PEK) altered sensitivity (item memory), bias, associative memory (item + context memory), both within and between groups. Parametric statistical testing was used when the assumptions of normality and variance equality were met. Otherwise, non-parametric methods were used. Analyses were performed using the JASP software (<https://jasp-stats.org>, JASP Team (2018). JASP (Version 0.9) [Computer software]).

Structural and functional imaging

Image acquisition

Participants were scanned using a 3-T Siemens Verio MRI system equipped with a 32 channels phased-array whole-head coil. High-resolution (1x1x1 mm³) MPRAGE T1-weighted images were collected for anatomical visualization and normalization. Blood-oxygen level dependent (BOLD) functional images were collected using a T2*-weighted single-shot spin-echo EPI sequence with the following parameters: repetition time = 2,000 ms, echo time = 30 ms, 3x3x3.6 mm³ voxel size, 192x192mm³ field-of-view, 64x64 matrix, slice thickness = 3.6mm, 36 slices, parallel imaging (GRAPPA) factor 2, echo-spacing 0.51ms, bandwidth 2368Hz/Px, spacing between slices = 3.6 mm. A total of 840 volumes divided in 6 sessions (runs) of 140 volumes were acquired for each participant. Each session lasted 4 minutes and 40 seconds. The task was run in EPrime 2.0 on a PC. A mirror device allowed participants to see the stimuli, and they gave their responses using a two-button response handgrip.

fMRI data preprocessing

Image preprocessing was performed using SPM 12 (<https://www.fil.ion.ucl.ac.uk/spm/>). For each participant, a subset of T2-weighted images was randomly selected for visual checking. Functional images were then corrected for slice acquisition temporal delay and spatially realigned to the across-run mean image to correct for subject's motion. Then, they were coregistered to the T1-weighted anatomical image and normalized to the Montreal Neurological Institute (MNI) stereotactic space at a 2x2x2 mm³ resolution before being spatially smoothed using an 8 mm³ full width at half maximum Gaussian kernel.

fMRI data analysis

For each participant, a general linear model (GLM) was estimated voxelwise. The experimental design for the individual statistical analysis was modelled with thirteen regressors: a 3x2x2 factorial design plus a regressor for the active baseline condition. The regressors of interest referred to subsequent memory (Source Hit (SH), Source Miss (SM) and Miss (M)), prior knowledge status (EK, PEK) and the occurrence of a stimulus (first, second). Events of interest (face-scene associations) were modelled with 3.5s boxcar functions and a 3s boxcar function was used to model the active baseline task, but null events (i.e. jittered fixation) were not modelled (Pernet, 2014; C. E. L. Stark & Squire, 2001). The regressors of interest were convolved with the canonical hemodynamic response function. Head motion (6 parameters estimated during the realignment pre-processing step) and magnetic field drift were also modelled and included as confounding factors. At the group level, contrast images from the subject-level analyses were used to perform a one-sample t-test and evaluate the contrasts of interest group-wise. Two sample t-tests were also performed to probe differences between groups. An individual voxel threshold of $p < 0.005$ was used with a cluster extent threshold of 57 contiguous voxels to correct for multiple comparisons (FWE) at $p < 0.05$. This cluster size extent was computed using Monte Carlo simulations (N=10,000 iterations) (Slotnick, 2017; Slotnick, Moo, Segal, & Hart, 2003). For a recent example of a similar thresholding approach, see (Thakral, Wang, & Rugg, 2017).

This factorial design setup allowed to estimate our main contrast of interest, namely the interaction between the effect of prior knowledge and of Repetition (Presentation₁ – Presentation₂): {PEK_{p1} – PEK_{p2} – EK_{p1} + EK_{p2}}, where PEK and EK include SH, SM & M regressors for each prior knowledge type. The other contrasts of interest were the “Encoding” contrast (i.e. all regressors of interest minus active baseline) and the

“Repetition Suppression” contrast across memory and prior knowledge type (i.e. all regressors corresponding to the first presentation set at 1 vs. -1 for the regressors corresponding to the second presentation). Our analysis workflow thereafter involved the following three steps.

First, we investigated whether repetition effects did allow us to identify the brain networks involved in explicit encoding of our stimuli. It is well acknowledged that repetition of stimuli can result in decreased (“Repetition Suppression”) or increased (“Repetition Enhancement”) of the BOLD signal, in brain areas consistent with the ongoing processing, an observation also referred to as “Neural adaptation” (Grill-Spector et al., 2006). Neural adaptation have been successfully used to map functional brain networks, notably memory encoding (Rand-Giovannetti et al., 2006; Reggev, Bein, & Maril, 2016) and especially face encoding (R. N. Henson, 2016; R. N. A. Henson, Shallice, Gorno-Tempini, & Dolan, 2002). We therefore performed a conjunction analysis between the Encoding and Repetition Suppression contrasts, and expected this to highlight common activations within the bilateral visual ventral streams. **Second**, we computed the Prior Knowledge x Repetition interaction contrast to test the hypothesis that prior knowledge may modulate brain activity corresponding to associative encoding. Clusters identified through this contrast were further explored with repeated-measures ANOVAs on the extracted beta weights. **Third**, beta-weights corresponding to the memory regressors were extracted within the above-defined clusters to further look for subsequent associative memory effects. For that purpose, repeated-measures ANOVAs were computed with the following 4 regressors of interest: EK-SH; EK-SM; PEK-SH; PEK-SM. Here, we focused on whether SH and SM differed for EK, PEK, or both. Importantly, only beta weights associated with the first occurrence of the above-mentioned regressors were taken into account for the subsequent memory analysis, thus avoiding

confusion between memory and repetition effects, and keeping the interaction and subsequent memory analyses orthogonal. One can refer to (Reggev et al., 2016) for a recent similar approach coupling repetition and subsequent memory effects.

Results

Behavioral results

Neuropsychological and AD biomarkers findings

See Table 1 for the sociodemographic, global cognition and biomarkers data. AD-MCI patients matched Controls for age, gender, education, and premorbid Verbal IQ, but their mean MMSE scores were significantly lower. Measurements of hippocampal volumes in both groups confirmed the expected atrophy in the patient group.

	Healthy Controls	AD-MCI	p values
N	19	17	-
Age, years, mean (SD) [range]	68.3 (4.4) [61-75]	69.7 (4.1) [63-76]	0.435
Gender, F:M	9 : 10	8 : 9	0.985
Education, years, mean (SD) [range]	12.8 (3.3) [8-19]	11.1 (3.1) [8-18]	0.129
Premorbid VIQ, mean (SD) [range]	110 (7.8) [91-119]	105 (8.7) [91-123]	0.083
MMSE, mean (SD) [range]	28.5 (1.3) [26-30]	25.5 (2.0) [23-29]	<0.001
Hippocampal volumes, normalized % of TIV, mean (SD) [range]			
Right	0.28 (0.03) [0.20-0.33]	0.24 (0.03) [0.17-0.30]	<0.001
Left	0.27 (0.02) [0.23-0.32]	0.23 (0.03) [0.17-0.28]	<0.001
Total	0.55 (0.04) [0.47-0.65]	0.46 (0.06) [0.34-0.58]	<0.001
Biomarkers of Amyloidopathy			
CSF-Abeta42, mean (SD) [range], cut-off = 700	-	569.3 (128.4) [426-735]	-
Florbetapir-AV45	-	All positive	-

Table 1. Demographic, clinical and AD biomarkers characteristics of the participants.

Finally, biomarkers of amyloidopathy were obtained for 14/17 patients (Abeta42 dosage in CSF, or abnormal amyloid retention using 18F-AV-45-PET Scanner). Albeit missing evidence of amyloidopathy for 3 patients, our AD-MCI sample therefore fulfills the research diagnostic criteria for AD as the etiology of their cognitive impairments (Albert et al., 2011). The detailed neuropsychological background of the participants is provided as Supplementary Materials. AD-MCI patients matched Controls for anxiety and depression, however they reported significantly more forgetfulness than controls.

Similarly, as a group, AD-MCI essentially presented impairments in recall and recognition tests.

Familiarization and Study phases

Detailed results are provided in **Supplementary Materials**. Briefly, congruency judgments were similar across groups during the familiarization phase, and importantly accuracy and forgetting rates (i.e. % Misses) did not differentiate between Controls and AD-MCI at immediate recognition. During the scanning phase (i.e. at study), we did not observe any difference between groups for face-scene congruency judgments, and within-groups analyses revealed that PEK and EK stimuli yielded similar congruency ratings. As expected, fastening of responses times with repetition was observed within each group, despite AD-MCI being overall slower than Controls. This repetition priming effect was influenced by the kind of prior knowledge in Controls, being larger for PEK stimuli. In AD-MCI however, priming effects were similar for PEK and EK.

Test and fame judgment phases

Figure 2 illustrates the main results from the test phase. The same pattern of behavioural results was found for sensitivity and source memory: PEK stimuli led to higher sensitivity and source memory than EK stimuli in Controls, but not in AD-MCI patients, resulting in significant Group x PK interactions (Sensitivity: $F(1,34)=5.771$; $p=0.022$; $\eta^2=0.141$; Source memory: $F(1,34)=13.05$; $p<0.001$; $\eta^2=0.189$). However, Prior Knowledge did not alter response bias in either group (Controls: $t(18)=1.703$; $p=0.106$; $d=0.391$; 95%CI:[-0.081 ; 0.853]; AD-MCI: $t(16) =-1.030$; $p=0.318$; $d=0.250$; 95%CI:[-0.237 ; 0.729]).

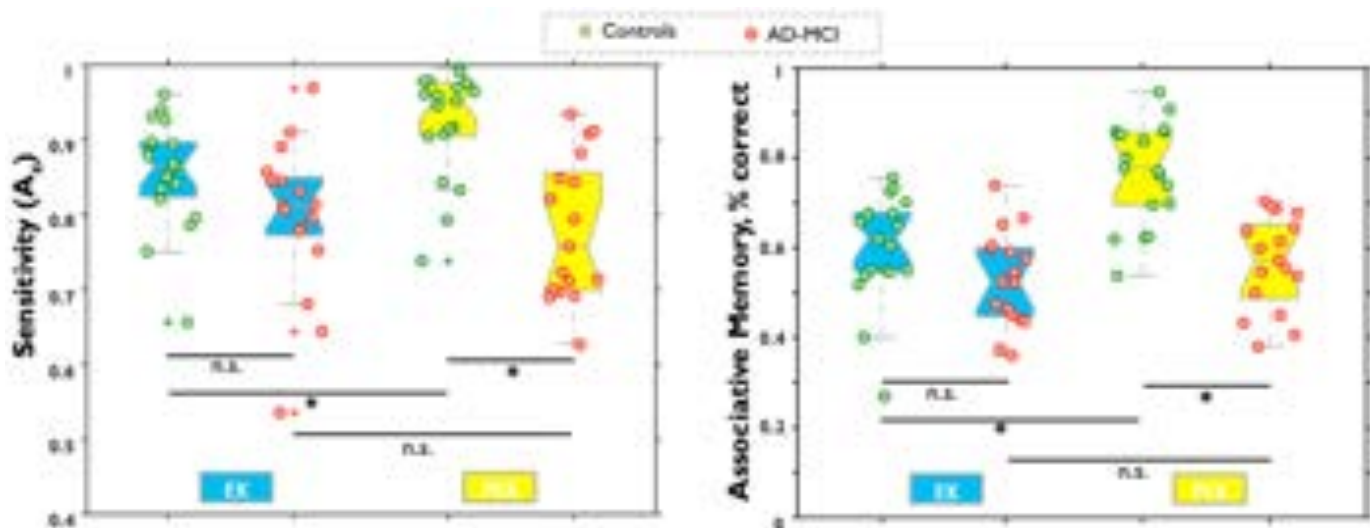


Figure 2. Controls and AD-MCI performance during at test. Memory for faces only (left) and for face-scenes associations (right) was improved for PEK stimuli in Controls, but not in AD-MCI. * = $p < .05$

Imaging results

A conjunction analysis between the Repetition Suppression and the Encoding contrasts yielded activations within occipital and occipito-temporal regions, along the visual ventral pathways (see illustration in **Supplementary Materials**), in both groups. Thus, as expected, neural adaptation (in that case, repetition suppression) allows the identification of functional networks involved in our visual encoding task.

Prior Knowledge X Repetition interaction

Figure 3 summarizes the imaging findings for the Prior Knowledge x Repetition interaction contrast. For the sake of concision, the results for simple contrasts are not displayed here, and the reader is referred to the **Supplementary Materials** for the list of supra-threshold clusters identified for the main effects of Prior Knowledge [i.e. PEK vs EK stimuli encoding] and of Repetition [i.e. Neural adaptation for PEK and EK stimuli repetition].

In Controls, the interaction contrast revealed activations within three sets of regions: bilateral inferior temporal lobes and occipito-temporal cortices, including MTL structures; bilateral medial and lateral parietal structures; left ventromedial and dorsolateral prefrontal cortices. Multiple ANOVAs revealed four distinct patterns of activations resulting in these interactions (see Figure 3). Overall, we found that PEK stimuli led to repetition enhancement while EK stimuli yielded repetition suppression. One notable exception was the finding of a left posterior hippocampal and a right temporal pole clusters, where decreased signal in response to PEK was observed. By contrast, EK stimuli always led to repetition suppression effects. Thus, fMRI response to repeated face-scene associative encoding is clearly altered by the prior knowledge associated with the face. We found that in ventral and dorsal prefrontal cortices, but also bilateral occipito-temporal regions, up to the perirhinal cortex in the right hemisphere, PEK and EK yielded repetition enhancement and repetition suppression, respectively. But we also found regions where neural adaptation was specific to either prior knowledge. So was it for the parietal clusters, showing repetition enhancement for PEK, while bilateral occipital regions showed suppression effects for EK only. In Controls, our results thus support the idea that partly non-overlapping networks underlie PEK- and EK-based associative encoding, but also that distinct prior knowledge generate opposite neural adaptation.

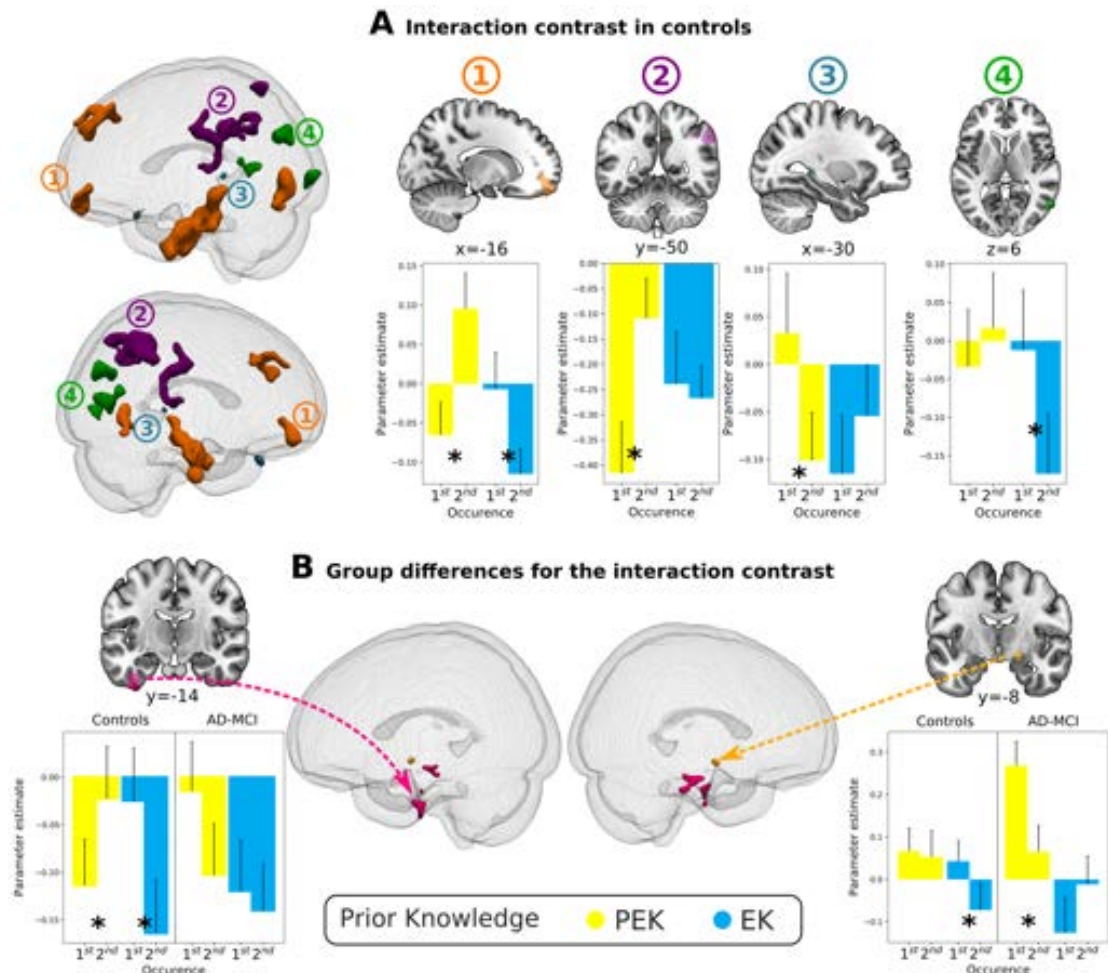


Figure 3. fMRI Prior Knowledge \times Repetition interaction contrast. (A1-4) Distinct patterns of fMRI responses in Controls. For each pattern one plot illustrates the neural adaptation effects found within a given cluster. For example, the first plot shows that within the left vmPFC, opposite neural adaptation effects were found for PEK vs. EK stimuli, resulting in a significant interaction that was similar within all the orange clusters. (B) Significant clusters resulting from two samples t -test with Group as between-subjects variable for the interaction contrast. Plots illustrate the fMRI responses in each group. Asterisks indicate $p < 0.05$.

In AD-MCI participants, the interaction contrast did not yield any significant cluster. However, two samples t -tests yielded differences between the groups for this interaction contrast within two main clusters located in the bilateral inferior temporal lobes (see Figure 3). Two smaller clusters within the right medial temporal lobe did not reach our clustering threshold, but proved significant after small volume correction for medial temporal lobe structures (as defined with the AAL template (Tzourio-Mazoyer 2002 REF), $p < 0.05$; FWE-corrected): right hippocampus ($k = 22$; main peak 18 -8 -12) and right lateral perirhinal cortex ($k = 21$; main peak 34 -16 -36). To further investigate this effect, mixed ANOVAs with Group as between-subjects factor, Prior Knowledge and Repetition as within-subjects factors were conducted on the mean beta weights extracted from the

group differences clusters (see Figure 3). These analyses revealed the absence of repetition effects in the AD-MCI group, with the exception of PEK stimuli, yielding repetition suppression in the right hippocampus. By contrast, in the same cluster, controls also presented a suppression effect, but for EK stimuli. In Controls, the bilateral fusiform gyrus and right lateral perirhinal cortex displayed enhanced signal for PEK and suppressed signal for EK. These findings suggest that early AD impairs neural adaptation effects, more specifically in the regions showing repetition enhancement for PEK stimuli. However, these results only relate to the cognitive processes involved in explicit associative encoding. We further investigated whether these findings also hold for successful associative encoding in the next section.

Subsequent Associative Memory effects

We extracted the beta weights associated with the subsequent memory events at study within the data-driven ROIs highlighted in the previous section (Source Hits, reflecting accurate associative memory, Source Misses, reflecting accurate item, but inaccurate associative memory, and Misses, reflecting forgetfulness of the face, see Methods section). We then looked for subsequent associative memory effects (i.e. significant differences between Source Hits and Source Misses). First, we did so within the clusters derived from Controls; second, we applied the same approach in the clusters derived from the effect of group on the interaction contrast (see previous section). The aim of these analyses was twofold: 1) Do the regions involved during associative encoding of PEK vs. EK stimuli also play a role for successful associative memory formation in Controls? 2) Do the regions exhibiting between-groups differences for the Prior Knowledge x Repetition interaction contrast also display differential subsequent associative memory effects between groups?

In Controls, we found subsequent associative memory effects for both PEK and EK stimuli within the left middle occipital and occipito-temporal areas, as well as within the left vmPFC. However, a series of regions showed selective associative memory effects for PEK, or EK stimuli (see **Supplementary materials** for illustration). Activity in the left DLPFC and in the right medial temporal lobe, including the perirhinal cortex, were higher for PEK Source Hits than PEK Source Misses, but did not discriminate source memory for EK stimuli. Conversely, bilateral precuneus, left fusiform gyrus, left posterior hippocampus, and a right-sided area including the posterior angular gyrus were more activated for EK Source Hits than EK Source Misses.

Between groups comparisons are illustrated in Figure 4, and yielded two main results. Controls and AD-MCI showed similar subsequent associative memory effects for EK stimuli within the right hippocampus (albeit only reaching $p = 0.051$ in the patient group). However, the cluster including the right perirhinal cortex and the fusiform gyrus showed higher fMRI response for PEK Source Hits than Misses, but only in Controls. Moreover, we found that the subsequent associative memory contrast estimates (i.e. beta weights difference between Source Hits and Source Misses) in that region correlated with the behavioural source accuracy measure for PEK stimuli across participants ($r=0.344$; $p=0.02$; 95%IC [0.072 – 1.000]). Interestingly, in Controls, the same area displayed opposite neural adaptation depending on the kind of prior knowledge: repetition enhancement for PEK stimuli, and repetition suppression for EK stimuli (see also **Supplementary Materials** for the list of the main effects behind the Repetition x Prior Knowledge interaction contrast). Thus, we found that in AD-MCI, critical regions within the right medial temporal lobes, as defined through the interaction contrast between repetition and prior knowledge, could either normally contribute to associative memory formation for EK, or fail to show the normal activation involved in associative memory for PEK. As a reminder, this must be

considered in the context of our behavioural findings that AD-MCI patients fail to present PEK-related improvement of associative learning, which we now address in the discussion.

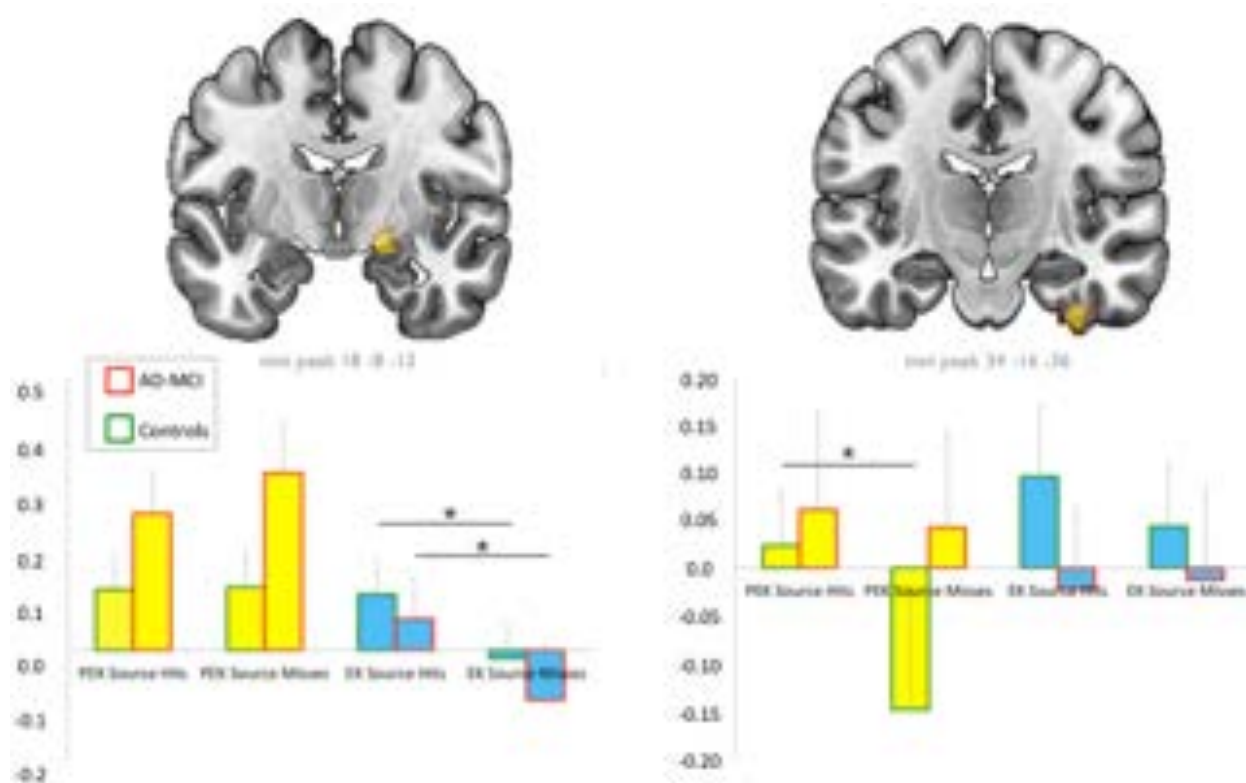


Figure 4. Subsequent associative memory effects within data-driven ROIs resulting from group differences for the Prior Knowledge x Repetition interaction contrast.

Discussion

Here, we aimed at investigating associative learning supported by prior knowledge in early AD, and its neural underpinnings. For that purpose, we asked controls and AD-MCI patients to learn new face-scene associations where the face could be either famous or unknown but repeatedly presented to the participants prior to study. We found that associative learning depending on PEK (i.e., famous face) was impaired in our AD-MCI sample whereas it increased by 28% in controls, by comparison with learning of EK stimuli (i.e. unknown faces). Imaging data revealed that in AD-MCI, neural adaptation across face-scene encoding trials was impaired, and did not interact with prior knowledge, while the pattern of fMRI responses in controls showed a differential recruitment of encoding

networks depending on the kind of prior knowledge. Subsequent memory analyses finally showed that right medial temporal lobe structures were critical for the formation of new associative memories. However, AD-MCI displayed impaired activation within a right subhippocampal region found to correlate with subsequent memory for PEK in Controls. As we further discuss, these findings need further confirmation but they may have important consequences on early AD assessment, and they bring new insights on the nature of the early memory impairment in prodromal AD. More generally, they call for a thorough consideration of the role of prior knowledge in new learning.

Associative learning impairment in early AD is underestimated

The idea that prior knowledge available at encoding enables better learning is not new (see Bartlett, 1932; Tolman, 1948). The advantage of famous over unknown faces in subsequent recognition memory had been put forward before (Ellis et al., 1979; Klatzky and Forrest, 1984; Leveroni et al., 2000; Reder et al., 2013). However, past studies typically contrasted encoding of novel (unknown) stimuli with familiar ones, thus leading to confusion as to whether the benefits of prior knowledge simply arise from a bonus due to multiple prior exposures. Here, we contrasted unknown faces repeatedly presented right before explicit encoding with famous faces, thus ensuring that both PEK and EK items were familiar at study. Moreover, we used a source memory paradigm to estimate associative learning to further focusing on the specific influence of prior knowledge on memory at encoding, greatly minimized its influence at retrieval (see Poppenk et al., 2010a). Our results thus strengthen the idea that in healthy aging, when lifelong accumulated knowledge about a face is available at encoding, it enhances the formation of a new long-term memory, far beyond what could be expected due to multiple recent exposures. Recently, it has been reported that the reliance upon semantic knowledge to enhance episodic learning could alleviate the decline of associative memory with age

(Badham, Estes, & Maylor, 2012; Badham et al., 2015; Bastin et al., 2013; Umanath & March, 2014). Our sample of AD-MCI patients clearly failed to take advantage of such semantic knowledge, which could therefore reflect a critical feature dissociating healthy aging from early AD. This deserves further investigation within a longitudinal study framework. Another important consequence of the present study stems from the early diagnosis perspective. Repeated unfamiliar stimuli are typically used to probe memory in clinical settings. Such tests closely match the EK condition used here (multiple exposures of unfamiliar items), where AD-MCI patients performed fairly well. One must therefore consider that we might well underestimate the actual associative memory impairments in early AD patients.

Prior knowledge, new learning and the level-of-processing framework

Such findings are more generally consistent with the level-of-processing framework (F. I. M. Craik & Lockhart, 1972), predicting that deeper processing at encoding, resulting from semantic knowledge activation for famous faces, will be more likely associated with the formation of a new long-term memory than more shallow encoding resulting from the absence of any prior knowledge. In the present study, the finding that in Controls, response fastening due to repetition priming was higher for PEK than EK stimuli seems consistent with an interpretation in terms of semantic knowledge activation during learning. Such activation of pre-experimental semantic knowledge may not be feasible in early AD, a hypothesis that is consistent with reports of early person knowledge impairment in the course of AD (e.g. Barbeau et al., 2012; Brambati et al., 2012; Joubert et al., 2010, 2008). The findings that in AD-MCI patients, repetition priming was similar for PEK and EK stimuli would fit with this interpretation. Yet, while this could explain the PEK advantage for item memory, it hardly accounts for the finding of 28% increased accuracy for item in context, i.e. associative, memory in controls.

This finding is in line with recent reports of a “familiarity bonus” on source memory (Poppenk et al., 2010a, 2010b; Poppenk and Norman, 2012), albeit more rarely investigated in older adults (Badham et al., 2012; Naveh-Benjamin, Hussain, Guez, & Bar-On, 2003). Two main accounts have been proposed so far. First, it has been proposed that pre-experimental knowledge (corresponding to PEK stimuli here) reduces the attentional resources required at encoding to build up a new association (e.g. see Castel and Craik, 2003; Naveh-benjamin and Craik, 1998), by comparison with novel stimuli. Given that here, both PEK & EK stimuli were familiar to participants at study, this account seems unlikely. Second, an extension of the level-of-processing framework would suggest that famous faces should generate more elaborative processing at encoding, enriching the events representation (Bein et al., 2015). In turn, enriched representations would become more distinctive and therefore less prone to interference at retrieval. This second possibility better fits our data, again suggesting that disrupted semantic knowledge about persons in early AD can impair elaborative encoding. However, preserved repetition priming effect in AD-MCI (LaVoie & Faulkner, 2008; O’Shea, De Wit, Yutsis, Castro, & Smith, 2018), increased by repeated exposure prior to the study phase, may explain their fair performance for EK stimuli. What remains to be elucidated in future studies, is the nature of such “elaborative encoding”. We can speculate on one promising candidate here. It has been suggested that unitization strategies at encoding can alleviate the associative learning deficit in aging (Bastin et al., 2013; Delhaye & Bastin, 2016), but not in early AD (D’Angelo et al., 2016), possibly due to perirhinal cortex atrophy (Delhaye et al., 2019, 2018). The role of the perirhinal cortex in the computational requirements of such unitization have already been highlighted in healthy subjects (Diana et al., 2010; Haskins, Yonelinas, Quamme, & Ranganath, 2008). Following this hypothesis, one would predict that face-scene associations could have benefited unitization strategies more

easily for PEK than EK stimuli, at least in controls, but not in AD-MCI. This PEK advantage, in turn, should critically rely upon the subhippocampal structures involved in visual associative learning. As we discuss below, our imaging data speak for this interpretation.

Recent and remote prior knowledge dissociates encoding brain networks

Our finding that in controls, a series of brain regions displayed a significant interaction between neural adaptation and prior knowledge suggests that encoding networks are sensitive to the nature of pre-existing representations associated with the memoranda. The fact that a common set of regions displayed opposite repetition effects depending on the kind of prior knowledge supports the idea that neural adaptation is not an automatic brain response to stimulus repetition (Henson et al., 2002) and further extends it in elderly subjects. Repetition enhancement has been recently thought to reflect explicit or implicit successful retrieval, while repetition suppression would reflect the reduced involvement of an encoding network (Kim, 2017). Noteworthy, the regions displaying opposite neural adaptation effects for PEK vs. EK stimuli in controls are consistently reported in subsequent memory and / or successful retrieval studies (Ventral and dorsal prefrontal cortices, bilateral occipito-temporal regions, up to the perirhinal cortex; Kim, 2013, 2011; Maillet and Rajah, 2014; Spaniol et al., 2009). Thus, repetition suppression found for EK stimuli along the visual ventral stream may reflect the reduced engagement of a visual encoding network in the absence of pre-existing semantic knowledge. By contrast, repetition enhancement for PEK stimuli in the same regions may reflect successful retrieval of pre-existing knowledge, along with the involvement of congruency detection processes, as reflected by the involvement of the vmPFC. This region indeed plays a critical role in the detection of congruency between incoming perceptual processing and pre-existing knowledge, or “schemas” (Van Kesteren et al., 2012; see also Bein et al., 2014). The observation of repetition enhancement for PEK

stimuli within the right angular gyrus, with no repetition effect on EK stimuli, also lends support to this interpretation, since this area forms a hub for the representation of prior knowledge (Gilboa & Marlatte, 2017; Wagner et al., 2015). Similarly, repetition suppression observed for EK stimuli in bilateral occipital gyri, with no effect for PEK, could reflect the simple detection of prior occurrence, as it is usually reported in subsequent memory studies for visual materials. Finally, our finding of suppressed fMRI response for PEK stimuli in the posterior medial temporal lobe is consistent with its role in associative encoding, especially when pre-existing knowledge is available (de Chastelaine, Mattson, Wang, Donley, & Rugg, 2016). Taken together, our findings therefore underlines the dynamic nature of new associative encoding in elderly, which seems to entail distinct mechanisms along with partly non-overlapping neural networks depending on the kind of prior knowledge involved. More specifically, in the presence of remote, semantic, prior knowledge, enhanced activity is observed in regions involved in memory retrieval, schema detection, and visual encoding. However, when recent, episodic-like, pre-existing representations are available, due to recent multiple exposures, repetition suppression is observed in a visual encoding network, including regions involved in the detection of prior occurrence across the successive learning trials.

This pattern of interactions between prior knowledge and neural adaptation was severely impaired in AD-MCI. The direct comparison between patients and controls revealed that regions pertaining to the anterior ventral stream showed the above-mentioned pattern in controls, i.e. signal suppression for EK and enhancement for PEK, while no neural adaptation was found in AD-MCI. The only exception being a right hippocampal cluster where patients displayed suppressed fMRI response for PEK, while this effect was observed for EK stimuli in controls. Thus, repetition enhancement for PEK stimuli observed in controls was apparently absent, or aberrant in AD-MCI (i.e.

suppression instead of enhancement, see also Supplementary Materials for the detailed within-groups repetition effects). Our results therefore extends prior findings of impaired neural adaptation in early AD (Pihlajamäki, Depeau, Blacker, & Sperling, 2008; Pihlajamäki et al., 2011), and further suggest that stimulus repetition during learning yields aberrant neural adaptation in AD when remote, semantic, prior knowledge is available at encoding. We further discuss whether these results are informative regarding associative memory formation.

Lack of semantic retrieval in early AD critically contributes to the associative encoding impairment

A core finding of the present study may at first sight look counter-intuitive. Namely, subsequent associative memory effects for EK stimuli were found in the right hippocampus in both groups, while the effect was found in the right perirhinal / fusiform area for PEK stimuli only in controls. This might look surprising given the acknowledged role of the hippocampal shrinkage in early memory impairments in AD. However, it has been suggested that some forms of declarative learning could only minimally rely on the hippocampal system, as long as pre-existing representations are available and congruent with the memoranda (e.g. Fernández and Morris, 2018; Van Kesteren et al., 2012). Interestingly, amnesic patients with damage limited to the hippocampal formation can benefit this congruency effect at a close-to-normal level, whereas amnesic patients with damage extended to the subhippocampal structures do not display any congruency benefit in new learning (Kan et al., 2009). Considering that tau pathology in AD primarily targets these subhippocampal structures (entorhinal and perirhinal cortices), rather than the hippocampal formation itself (Braak & Braak, 1995), it has been suggested that at the early stages of the disease, context-free memories and specifically knowledge about unique entities like faces, could be amongst the first memory representations to be

damaged (Didic et al., 2011). The AD-MCI sample in the present study included patients with quite mild cognitive impairments, mostly limited to impaired performances in memory tests. An interesting possibility here is that the absence of subsequent associative memory effect for PEK stimuli within the right anterior subhippocampal structures in our AD-MCI sample could reflect the early disruption of semantic knowledge retrieval about famous faces. Support for this interpretation comes from our findings that in controls, activity within right subhippocampal structures and left middle frontal gyrus predicts successful associative encoding for PEK, not EK stimuli. These frontal and temporal areas have consistently been associated with semantic retrieval (Barbeau et al., 2012; Joubert et al., 2008, 2010; Kapur et al., 1994; Martin, 2007; Pineault et al., 2018). Moreover, we found that activity in this subhippocampal cluster in controls correlated with associative memory for PEK, not EK, stimuli. Consequently, it may well be the case that semantic retrieval at study is critical for the successful formation of new face-scene associations in controls, a process impaired in AD-MCI.

Conclusion

The present findings bring new evidence for a critical difference in the way early AD patients and healthy elderly form new associative memories. Pre-experimental prior knowledge proved beneficial for subsequent memory formation in normal aging, in a way suggesting higher encoding elaboration resulting from accurate semantic memory retrieval. Importantly, prior knowledge associated with remote semantic knowledge or prior knowledge resulting from recent repeated exposures dissociated the neural correlates of associative encoding. In early AD however, tau pathology may specifically target brain networks involved in associative encoding when prior semantic knowledge is involved, which opens new perspectives in the assessment and early detection of the disease.

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Supplementary Materials

1. List of the tests used and neuropsychological background

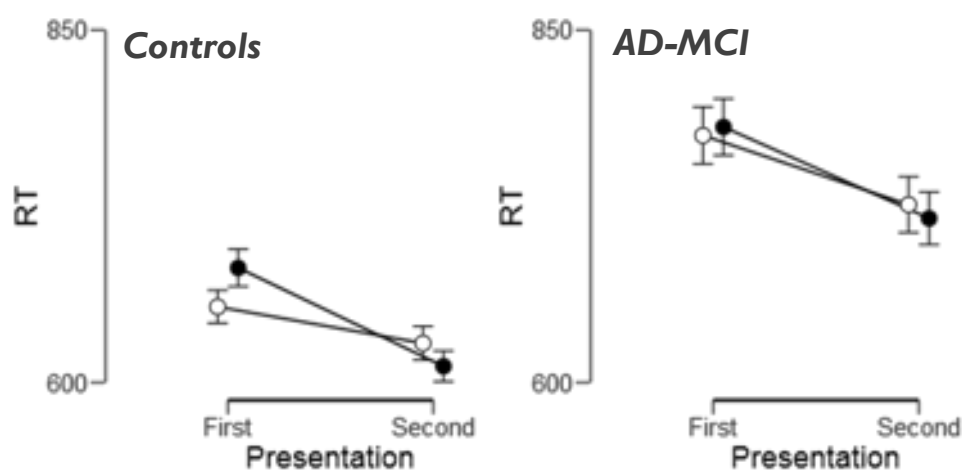
	Healthy Controls	AD-MCI	p values
	mean (sd)	mean (sd)	
Global cognition			
MDRS			
Global score, max=144	141.2 (1.8)	130.8 (6.5)	<0.001
Attention, max=37	36.2 (1.0)	36.1 (0.9)	0.696
Initiation, max=37	36.7 (0.7)	31.5 (4.3)	<0.001
Construction, max=6	6.0 (0.0)	6.0 (0.0)	-
Concepts, max=39	37.7 (1.7)	37.3 (1.6)	0.308
Memory, max=25	24.6 (0.7)	20.7 (3.6)	<0.001
Memory			
Logical Memory, WMS-III, Immediate recall	41.9 (6.8)	18.1 (7.6)	<0.001
Logical Memory, WMS-III, Delayed recall	25.8 (5.0)	3.8 (4.1)	<0.001
DMS-48, pictures, max=48	46.2 (2.2)	41.2 (4.3)	<0.001
DMS-48, words, max=48	40.1 (3.9)	31.9 (4.8)	<0.001
Warrington Memory Test (Faces), max=50	41.2 (4.5)	35.6 (6.5)	0.005
Naming			
D.O. 80, max=80	78.3 (1.5)	76.2 (3.5)	0.046
Limb praxis			
Symbolic gestures, max=5	4.9 (0.2)	4.6 (0.6)	0.056
Tools pantomimes, max=10	9.5 (0.8)	9.1 (1.2)	0.253
Imitation of abstract gestures, max=8	7.6 (0.8)	6.7 (1.0)	0.003
Executive functions			
Trail Making Test Part A (seconds)	33.5 (9.0)	42.5 (10.0)	0.007
Trail Making Test Part B (seconds)	70.2 (21.6)	133.0 (55.9)	<0.001
Trail Making Test Part B (errors)	0.5 (1.0)	0.9 (0.9)	0.043
Stroop test			
Naming (seconds)	61.1 (8.1)	79.6 (16.4)	<0.001
Naming (errors)	0.6 (1.2)	2.3 (2.7)	0.009
Reading (seconds)	43.3 (5.0)	48.4 (7.7)	0.045
Reading (errors)	0.3 (0.7)	0.06 (0.3)	0.339
Interference (seconds)	106.7 (14.0)	165.4 (65.2)	<0.001
Interference (errors)	1.5 (3.3)	4.8 (4.2)	0.003
Flexibility (seconds)	123.1 (20.3)	211.8 (80.8)	<0.001
Flexibility (errors)	5.4 (5.4)	11.2 (6.8)	0.002
Verbal Fluency			
Letter "R", 90 seconds, nb. Correct			0.012
Category "Fruits", 90 seconds, nb. Correct			<0.001
Anxiety & Depression			
Spielberger STAY-B, raw score	35.5 (6.9)	38.9 (8.7)	0.214
Beck Depression Inventory-II, raw score	4.8 (5.7)	7.4 (6.6)	0.296
Subjective forgetting			
Memory Self-Evaluation Questionnaire, mean score	2.2 (0.5)	2.7 (0.5)	0.003

Supplementary Table 1. Neuropsychological background of the participants. MDRS=Mattis Dementia Rating Scale; DMS=Delayed Matching to Sample procedure (Barbeau et al., 2004) consisting in a 3 minutes delayed 2-alternate forced choice recognition memory test; D.O. 80="Test de denomination orale de 80 images", Deloche & Hannequin, 1997; Stroop test was taken from Chatelois et al., 1993; Verbal fluency test: Cardebat et al., 1990.

2. Behavioral results from the familiarization and study phases

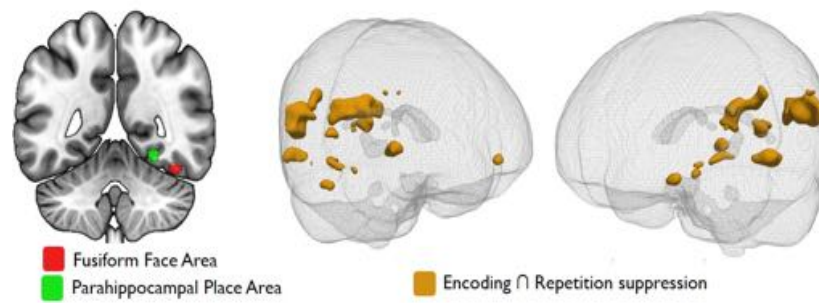
		Controls	AD-MCI
Presentation	Prior Knowledge	Response times Mean (sd)	Response times Mean (sd)
First	EK	653.7 (223.4)	775.2 (294.9)
First	PEK	681.3 (254.9)	781.2 (291.1)
Second	EK	628.0 (219.6)	726.2 (275.3)
Second	PEK	611.6 (200.8)	716.5 (263.9)

Supplementary Table 2. Response times during the study phase.



Supplementary Figure 1. Repetition priming effects on Response Times in Controls (left) and AD-MCI (right). Black circles = PEK; White circles = EK. Error bars show %95 IC around the mean. AD-MCI displayed slower RTs overall, but presented a significant priming effect (i.e. RT fastening for both PEK & EK stimuli). However, the amplitude of priming in Controls was higher for PEK than for EK stimuli (significant PK x Repetition interaction, $F=13.388$; $p<0.001$; $\eta^2=0.014$), while it did not differ with the kind of PK in AD-MCI (non-significant PK x Repetition interaction, $F=0.667$; $p=0.414$; $\eta^2=0.001$).

3. Conjunction analysis: Repetition Suppression and Encoding contrasts



Supplementary Figure 2. Significant overlaps between {Encoding} and {Repetition suppression} contrasts maps in Controls, $p < 0.005$ corrected. The right-sided 3D view illustrates the significant clusters from the conjunction analysis; the left-sided coronal view focuses on two subregions of the conjunction map, located in the vicinity of FFA and PPA. Note that in AD-MCI patients, the same analysis yielded activation in the Left Parahippocampal Place Area only, albeit at an uncorrected $p = 0.005$ threshold ($k = 19$ voxels, peak mni coordinates = -26; -48; -12).

4. [List of supra-threshold clusters for the main effects of Prior Knowledge and Repetition](#)

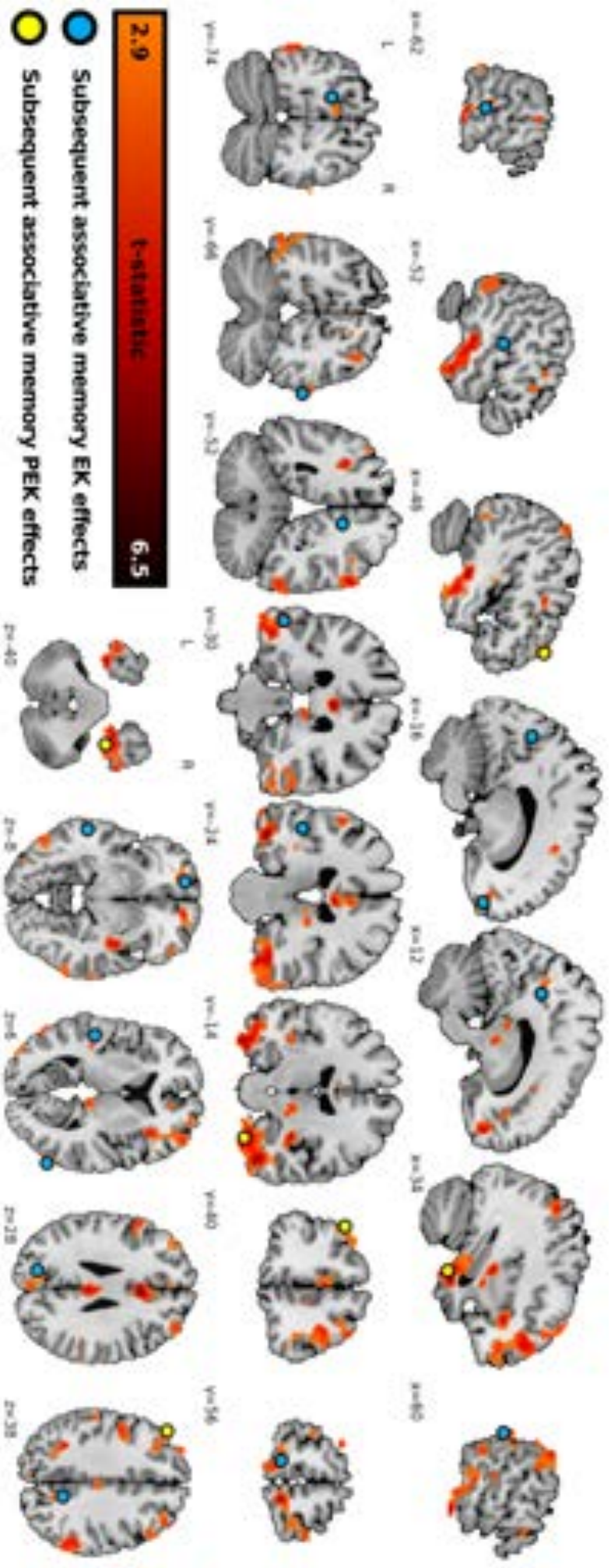
Group	Contrast	x	y	z	k	T	Label
Controls	PEK>EK	-58	-8	-10	5510	10,47	Temporal_Mid_L
		-32	36	-6	12144	8,99	Frontal_Inf_Orb_L
		-6	-52	12	2277	8,78	Precuneus_L
		30	40	-8	1102	7,42	Frontal_Inf_Orb_R
		50	-66	36	825	6,68	Angular_R
		66	-4	-18	663	6,58	Temporal_Mid_R
		66	-10	26	61	6,48	Postcentral_R
		28	-14	-10	1599	6,37	Hippocampus_R
		-14	-4	-6	117	5,51	Pallidum_L
		20	8	22	300	5,45	Caudate_R
		-16	8	10	176	5,05	Caudate_L
		-8	0	46	62	4,66	Cingulum_Mid_L
		-18	-78	8	95	4,56	Calcarine_L
		-24	-14	34	102	4,51	Caudate_L
		20	-96	20	81	4,32	Occipital_Sup_R
		0	-88	4	198	3,88	Calcarine_L
		10	-14	54	89	3,71	Supp_Motor_Area_R
	28	-30	-14	23	4,57	ParaHippocampal_R	
	EK>PEK	58	-34	50	179	5,33	Parietal_Inf_R
	RS EK	12	-6	48	62	6,52	Supp_Motor_Area_R
		42	-16	-36	687	6,44	Fusiform_R
		-42	-16	-42	200	6,29	Temporal_Inf_L
		-12	-90	20	438	5,64	Occipital_Sup_L
		56	-72	18	991	5,56	Temporal_Mid_R
		-28	-50	-6	128	5,51	Lingual_L
		-52	-14	-2	76	4,92	Temporal_Sup_L
		-40	14	-34	158	4,42	Temporal_Pole_Mid_L
		22	-50	-12	126	4,28	Fusiform_R
	50	44	-16	85	4,13	Frontal_Inf_Orb_R	
	RS PEK	-34	-88	30	674	7,29	Occipital_Mid_L
		-12	-58	-4	180	5,44	Lingual_L
		-62	-4	-6	88	5,39	Temporal_Mid_L
		46	-78	2	1256	5,27	Occipital_Mid_R
		-44	16	-32	117	4,81	Temporal_Pole_Mid_L
		38	-42	-22	62	4,69	Fusiform_R
		16	-76	18	75	4,33	Calcarine_R
		48	18	-28	93	4,26	Temporal_Pole_Mid_R
		8	70	16	83	4,22	Frontal_Sup_Medial_R
	-54	-66	34	102	3,79	Angular_L	
	RE PEK	70	-24	-12	426	6,58	Temporal_Mid_R
		62	-50	42	1400	6,54	Parietal_Inf_R
		4	-18	36	371	5,47	Cingulum_Mid_R
		42	50	8	506	5,33	Frontal_Mid_R
		-64	-28	-12	126	5,1	Temporal_Mid_L
		-42	-62	58	276	5,07	Parietal_Sup_L
		34	-14	-38	78	4,72	Fusiform_R
		10	-56	36	350	4,72	Precuneus_R
-38		46	36	201	4,43	Frontal_Mid_L	
-40		58	18	153	4,13	Frontal_Mid_L	
-20	54	-10	99	3,88	Frontal_Sup_Orb_L		

Supplementary Table 3. List of suprathreshold clusters for the main effects of Repetition and Prior Knowledge. PEK=Pre-Experimental Knowledge; EK=Experimental Knowledge; RS=Repetition Suppression; RE=Repetition Enhancement

MCI	PEK > EK	30 -12 -12	343	6,94	Hippocampus_R	
		-58 -8 -16	429	6,13	Temporal_Mid_L	
		-18 18 40	1101	5,95	Frontal_Sup_L	
		26 42 50	197	5,48	Frontal_Sup_R	
		54 -8 -12	288	5	Temporal_Sup_R	
		0 -56 22	698	4,99	Precuneus_L	
		-34 -30 -30	138	4,83	Cerebelum_4_5_L	
		-48 10 -44	94	4,71	Temporal_Inf_L	
		30 -36 4	153	4,3	Hippocampus_R	
		54 26 28	72	4,17	Frontal_Inf_Tri_R	
		-48 -40 -2	68	3,9	Temporal_Mid_L	
		-2 62 38	203	3,9	Frontal_Sup_Medial_L	
		70 -36 0	57	3,78	Temporal_Mid_R	
		62 -64 16	131	3,6	Temporal_Mid_R	
		-14 0 -32	51	4,67	ParaHippocampal_L	
		36 -16 -40	46	3,73	Fusiform_R	
		EK > PEK	20 -68 40	96	3,93	Occipital_Sup_R
		RS PEK	20 -6 -12	82	5,48	Hippocampus_R
28 -36 4	101		4,01	Hippocampus_R		
RE PEK	18 48 -8	75	5,21	Frontal_Sup_Orb_R		
	-38 -72 54	67	4,67	Angular_L		
	-18 16 -10	77	4,11	Putamen_L		
HC>MCI	PKE	-14 -6 -4	57	4,36	Thalamus_L	
		-48 40 26	88	4,26	Frontal_Mid_L	
		-44 6 30	535	4,19	Frontal_Inf_Oper_L	
		4 72 2	103	3,86	Frontal_Sup_Medial_R	
		10 -78 56	65	3,62	Precuneus_R	
	RepPEK	-62 -4 -6	126	6,04	Temporal_Mid_L	
	-46 14 -32	69	4,45	Temporal_Pole_Mid_L		
MCI>HC	RepPEK	32 -14 -40	74	3,88	Fusiform_R	
		-40 46 34	129	3,78	Frontal_Mid_L	
		68 -24 -14	57	3,44	Temporal_Mid_R	
		20 -6 -12	8	3,55	Hippocampus_R	

Supplementary Table 3 (next). List of suprathreshold clusters for the main effects of Repetition and Prior Knowledge. PEK=Pre-Experimental Knowledge; EK=Experimental Knowledge; RS=Repetition Suppression; RE=Repetition Enhancement

5. Subsequent associative memory in Controls



Supplementary Figure 3. Subsequent associative memory effects within data-driven ROIs resulting from the Prior Knowledge x Repetition interaction contrast in Controls. Blue circles depict Subsequent Associative Memory effects for EK stimuli only; Yellow circles signal Subsequent Associative Memory effects for PEK stimuli only. Regions showing associative memory effects for both PEK and EK stimuli are not shown (see text).

Experiment 5: Back to patient KA. Does prior knowledge increase new learning despite severe amnesia?

Highlights from Experiment 5

There is a dearth of studies investigating whether prior knowledge can benefit recognition memory in patients with hippocampal damage. Considering memory for faces, available evidence actually suggests that familiar memoranda would hinder memory, leaving unaffected memory for unfamiliar items processed as a single entity.

In the following Experiment, **patient KA** with extensive and selective damage to the extended hippocampal system shows **preserved recognition memory for unknown, familiarized and famous faces.**

He also **performs at a fair level for face-scene associations in the case of famous faces,** and displays **similar high-confidence Hits as controls.**

These findings suggest that **item conceptual processing at encoding** may enable **successful context-free and context-rich learning, even when the hippocampal system is severely compromised.**

Whether pre-experimental knowledge promotes unitization, thus enhancing familiarity-based recognition of novel associations, or fastens consolidation in a hippocampus-independent manner needs further investigation.

Introduction

One of the greatest challenge for the neuropsychology and cognitive neurosciences of memory is to provide a consensual account for preserved declarative learning abilities in amnesia. While the description of the syndrome of developmental amnesia has provided evidence for this preservation (Vargha-Khadem et al., 1997), in this thesis we have contributed to strengthen this observation with the case report of patient KA (Jonin et al., 2018). Rather than bringing additional evidence for the view of separate episodic and semantic stores (for evidence against normal semantic memory in developmental amnesia, see Blumenthal et al., 2017), the case of patient KA suggests that very efficient declarative learning processes can take place even after severe damage to the whole extended hippocampal system. Here we argue for “very efficient” processes because patient KA, in striking contrast with previous cases, proved to have supra-normal semantic knowledge in some domains.

However, the question remains as to how new declarative memories have been learned, and actually no consensual account has shown up so far. Even worse, recent ambitions regarding the hypothesis that rapid neocortical learning could benefit patients with developmental amnesia under “fast-mapping” learning conditions have just turned into a dashed hope (Cooper, Greve, & Henson, 2018; Elward, Dzieciol, & Vargha-Khadem, 2019).

Still, it has been suggested that regions of the temporal pole as well as rhinal cortices could support new declarative learning, even after damage to the hippocampal system (e.g. Vargha-Khadem et al., 1997). Moreover, some models of cognitive learning suggest that these structures could support rapid learning as long as the sensory input is congruent with prior knowledge (e.g. REMERGE; Kumaran et al., 2012; 2016), or that congruency with existing memory schemas could fasten system consolidation (Van Kesteren et al., 2012). Similarly, the PMAT framework underlines the role of prior experiences (i.e. “situation models” for context representations, and conceptual knowledge for items representations) in the formation of new memories (Ritchey et al., 2015). These theoretical accounts generally put forward the rhinal cortices, and especially the perirhinal cortex as a core structure that could support hippocampal-independent explicit learning.

For example, several studies have shown that unitization strategies at encoding (i.e. encoding instructions emphasizing the integration of separate elements in a single entity) can benefit recognition memory, and that such benefit is related to the activity or volume of the perirhinal cortex (e.g. Delhaye et al., 2019; Diana et al., 2010; Haskins et al., 2008). Interestingly, this line of research has also provided evidence that associative memory could be increased for unitized vs. non-unitized word pairs in amnesic patients, but only with presumably preserved perirhinal cortices (Quamme et al., 2007). A consistent feature in these studies is that the unitization condition involves conceptual processing that allows the attribution of a single meaning to separate elements. In the typical paradigm, a pair of unrelated words, e.g. “Cloud – Lawn” is presented in a unitization or standard condition. In the standard condition, the word pair is presented with the sentence “The _____ could be seen from the _____”, and the subjects have to rate how well each item in the pair fits with the corresponding blank in the sentence. In the unitized condition, the pair is presented together with the definition “A yard used for sky-gazing”, and participants have to rate how well the pair fits with the definition (Quamme et al., 2007; Haskins et al., 2008; Delhaye et al., 2018). Similarly, the unitization condition used in Diana et al. (2010) required participants to imagine a study item (words were used) as if it were coloured with a colour displayed as an external feature (background), then to read a short sentence explaining why the item is that colour, and rate the difficulty of the imagery task. Again here, “unitization” actually involves some conceptual integration between separate features. Our view is that the conceptual processing involved in these paradigms might be an important factor for successful unitization. In support of this view, Staresina & Davachi, (2010) found that when unitization demands are varied by use of perceptual rather than conceptual integration, it is not modulated by perirhinal cortex activity, but rather can be achieved earlier in the ventral stream.

An interesting possibility therefore is that conceptual processing triggered by prior knowledge available at encoding may enable perirhinal-dependent (or, “Anterior Temporal” AT system-dependent) explicit learning. So far, the experiments performed in the present thesis have brought some relevant findings to this issue.

First, in patient KA, we have brought evidence for left MTL reorganization in that the left temporal pole and left perirhinal cortices were either preserved, or thicker than matched controls. Paralleling these findings, patient KA proved faster than controls in some tasks requiring time-constraint familiarity detection, and performed better than controls in a

few semantic tasks. It is therefore tempting to speculate that such MTL reorganization “favouring” grey matter density within the left anterior and subhippocampal structures might be involved in preserved learning abilities.

Second, we have demonstrated that prior knowledge, and especially pre-experimental knowledge resulting from multiple, lifelong exposures, is a very powerful learning enhancer. Strikingly, our results along with emerging studies (Badham et al., 2012, 2015; Badham & Maylor, 2015; see also Umanath & Marsh, 2014) suggest that this effect could be immune to aging. Moreover, elderly could disproportionately benefit from that kind of prior knowledge by comparison with their younger counterparts. Thus, it might be reasonable to argue that brain structures highly sensitive to aging like the hippocampal formation would not be critical to underlie these prior knowledge benefits in learning.

Third, Experiment 4 in the present thesis has confirmed that the elderly benefited from pre-experimental prior knowledge far more than experimental knowledge (namely, pre-study familiarization with the memoranda), and this was true for associative memory as well. In sharp contrast however, patients with early AD could not benefit from pre-experimental knowledge, and we found that the perirhinal cortex was involved here. Indeed, patients with early AD did not show any subsequent associative memory effect for pre-experimental memoranda in that region.

We therefore reasoned that patient KA could rely on prior knowledge accumulated across countless previous episodes to scaffold new explicit learning, and that this could be critically related to his preserved extra-hippocampal structures in the temporal lobe. Indirect support for this idea came from the dissociation observed in patient KA between intact context-free learning for meaningful objects and severely impaired context-free learning for abstract, meaningless visual patterns (see Experiment 2). Thus, the material-specific effect observed in preserved learning abilities for patient KA (see also Cipolotti et al., 2006; Bird et al., 2007) could be related to the semantic status of the materials (for recent evidence along this line, see (Brady, Alvarez, & Sto, 2019; MacKenzie, Alexandrou, Hancock, & Donaldson, 2018)). We investigated this hypothesis by adapting the design of Experiment 3b for patient KA.

Materials & methods

Participants

Patient KA and 16 healthy controls provided their informed consent to participate. Controls data were taken from Experiment 3b, to match as closely as possible regarding age, gender (all males) and education with the patient.

Procedure

The procedure was the same as described in Experiment 3b. Briefly, in the *familiarization* phase, participants were first presented with a set of unknown faces associated with a random occupation, and had to rate whether the association was plausible or not. No learning instruction was given and subjects were told that the test investigated subjective aspects of face perception. Each face-occupation association ($N=32$) was presented three times in a fully randomized order. After a 25 minutes break, the study task involved 96 face-scene association trials, again presented in a random order. Along with the 32 familiarized faces (Experimental Knowledge or EK condition), the 64 remaining trials involved 32 entirely unknown faces (Novelty condition) and 32 famous faces (Pre-Experimental Knowledge or PEK condition). For each face-scene association, subjects were asked to imagine that they were walking into the scene and meeting the person depicted at the centre of the screen, then to rate how pleasant or unpleasant this situation would be. Emphasis was put on the need to answering on the basis of both the scene and the face, not only on either element of the “episode”. After a 10 minutes break, the recognition memory test started. It involved 23 distractor faces for each condition, namely 46 unknown faces and 23 famous faces that had not been presented before. Subjects first made an Old/New judgment on the face, then to rate their confidence for the Old/New response. For each correct “Old” response, subjects were then presented with the face together with two scene pictures, the target scene that was previously paired with the face, and a scene previously associated with a different face. Participants had to make a source memory judgment, then to rate their confidence for this judgment. Finally, after a 10 minutes break, subjects performed a fame judgment task involving all the faces stimuli used in the recognition test. For each item, they were asked to decide whether the face was famous or not. Items yielding an incorrect response

(famous face judged unknown or unknown faces judged famous) were further discarded from the analyses, on an individual basis.

Statistics

Our interest was in comparing the performance of one single patient with the group of matched healthy controls, on recognition memory performance for faces and for face-scene associations. We thus focused on the indexes of Accuracy, Hits & FAs rates, Source Memory and we further reported on high-confidence ratings Hits as an estimate of subjective recollection. A Bayesian approach developed for single cases study was used and provided a Point Estimate (PE) with 95%CI of the likelihood of the patient's scores in the normal population (Crawford & Garthwaite, 2007a). This approach was used to directly compare patient KA with controls. Moreover, given our hypothesis that prior knowledge resulting from conceptual processing may trigger similar improvement in patient KA than in controls, we used the regression method proposed by Crawford & Garthwaite, (2005) to provide a regression-based predicted score in the PEK condition in patient KA based on his score in the Novelty condition. Our reasoning was that if the patient benefits from PEK at least as well as controls, then we should find evidence for the null hypothesis when contrasting his actual score with the predicted score in the PEK condition.

Results

Patient KA was slightly older than controls (35 years old vs. 27.8 +/- 6.9), but the difference was not significant ($p=0.08$; PE=83.9%; %95IC=[66.5 – 95.1]); similarly patient KA underwent fewer years of formal schooling than controls (9 vs. 13.7 +/- 2.4), which again did not reach convincing evidence for the alternative hypothesis ($p=0.32$; PE=4.16%; %95IC=[0.3 – 14.3]).

Across prior knowledge conditions, patient KA performed at the level of controls regarding recognition accuracy for faces ($p=0.40$; PE=19.9%; %95IC=[7.1 – 38.2]), response bias ($p=0.22$; PE=88.9%; %95IC=[73.4 – 97.6]) or Source Memory ($p=0.38$; PE=19.2%; %95IC=[6.7 – 37.3]).

We could not find evidence supporting any difference between KA and controls, be it for Novelty, EK or PEK conditions, including when considering Source Memory and High-confidence Hits (see *Figure 65* & *Figure 66*). No comparison reached significance (two-sided, $\alpha=5\%$). Note however that regarding FAs, patient KA was in the upper range of controls.

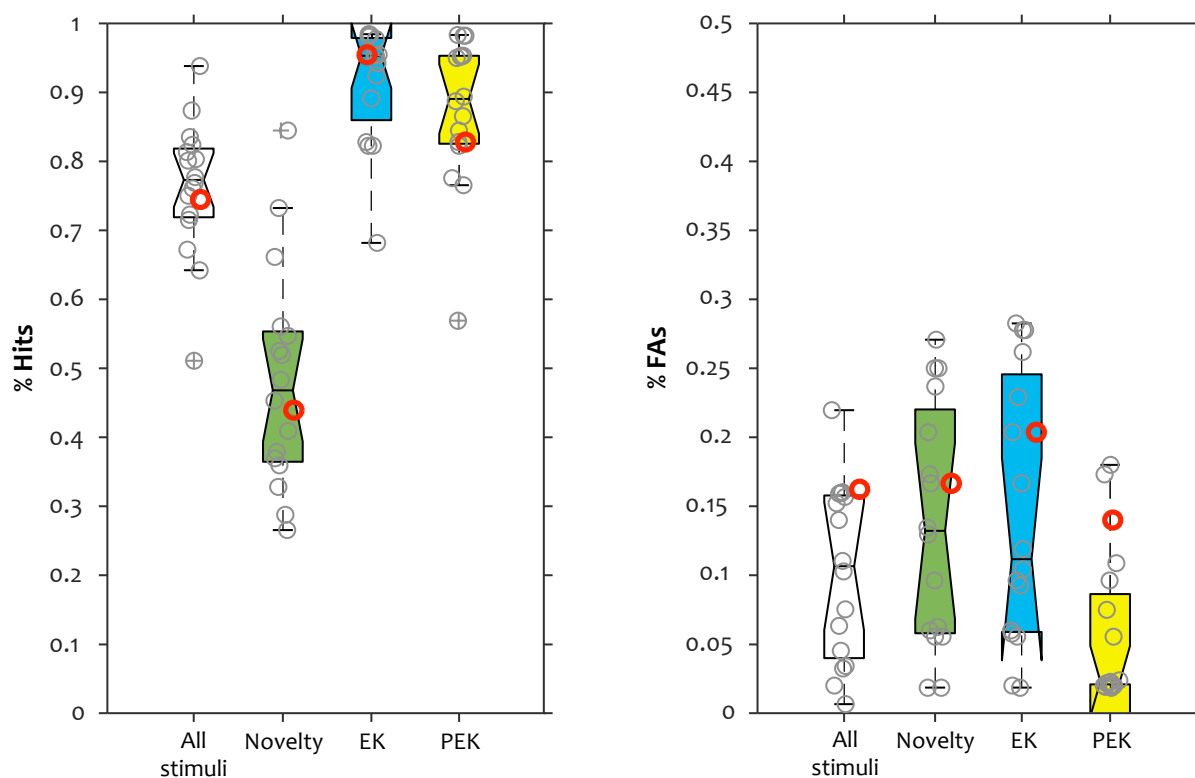


Figure 65. Performance of patient KA and 16 matched controls for the Hits and FAs rates.

Consistently with prior findings from Experiments 3a & 3b, healthy controls performed better in PEK than Novelty conditions, be it for recognition accuracy for faces ($BF_{10}=1.433e^7$), Source memory ($BF_{10}=9.811$), or high-confidence Hits responses ($BF_{10}=1498.4$). Spearman's correlation coefficient between Novelty and PEK was 0.094 ($p=0.718$) for accuracy scores, 0.331 ($p=0.210$) for Source Memory, and 0.665 ($p=0.005$) for High confidence Hits. This yielded predicted scores for KA of 0.92, 0.70, and 0.90 for recognition accuracy, source memory and high-confidence Hits, respectively, given his performance during the Novelty condition. He actually obtained corresponding scores of 0.855, 0.58 and 0.92, which did not differ from the prediction (corresponding PEs=18.1, 20.3 and 36.7%, with respective %95ICs of [5.0 – 38.3], [5.9 – 41.8] and [16.0 – 60.9]).

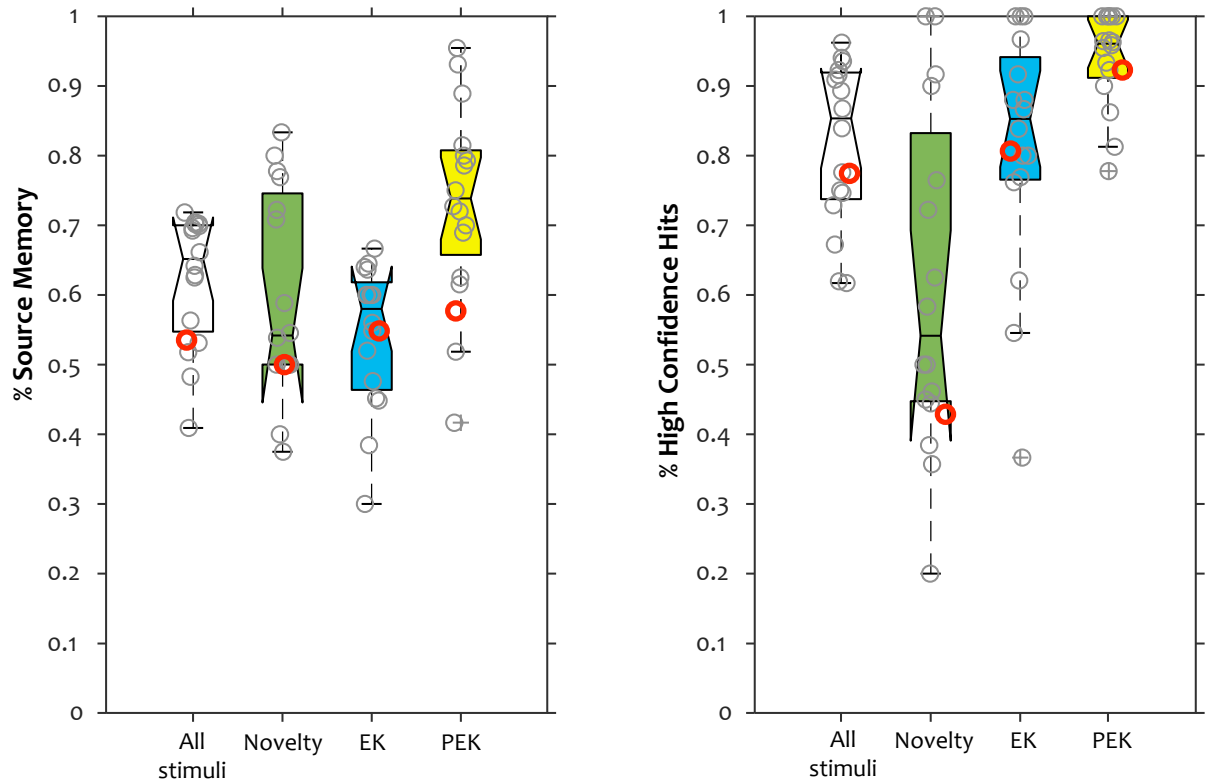


Figure 66. Performance of patient KA and 16 matched controls for Source Memory and Hits responses with High confidence.

Discussion

In this study, we compared patient KA with severe developmental amnesia to healthy controls in a recognition memory task for faces and face-scene associations. Faces were either entirely unknown to the participants (Novelty condition), unknown but familiarized before the study phase (EK condition), or famous (PEK condition). We replicated prior findings of normal item recognition memory in developmental amnesia (e.g. Vargha-Khadem et al., 1997), since patient KA performed in the full normal range with this respect. Moreover, this adds to several studies showing preserved recognition memory for faces after bilateral damage to the hippocampal formation (Cipolotti et al., 2006; Bird et al., 2007; Bird et al., 2008; Bird & Burgess, 2008; Smith et al., 2014; see also Bird, 2017). However, we also found that patient KA could benefit PEK as much as healthy controls regarding faces recognition, and we extended this pattern to source memory and to subjective recollection as estimated through high-confidence Hits. These findings are broadly consistent with the idea that prior knowledge at encoding can trigger learning

processes that largely operate independently of the hippocampus. Nonetheless, they also differ from several prior reports, as we will discuss below.

Our findings of preserved recognition memory for unknown faces in KA fit with prior reports, including in developmental amnesia (Smith et al., 2014; Cipolotti et al., 2006; Bird et al., 2008; see Bird, 2017 for review, but see patient JC, Bird et al., 2007). However, findings of preserved recognition memory for famous (and familiarized) faces in KA are at odds with the prediction that recognition of familiar materials should be impaired after hippocampal damage (Bird, 2017). The author grounded this prediction notably upon a study by Smith et al. (2014) who thoroughly investigated recognition memory for famous vs. unknown faces in a sample of 5 amnesic patients. In sharp contrast with our own findings, they reported that Old/New recognition memory for famous faces was impaired, and only for the faces correctly identified as famous by the patients. In our view, several differences in our study vs. Smith et al.'s (2014) are relevant here.

First, we must mention that the authors compared 5 amnesic patients with a smaller sample of controls (8) than ours (16). Moreover, the authors had to exclude 2 control subjects who did not identify a sufficient number of famous faces as famous in a familiarity judgment task, thus leaving with 6 controls. Figure 4B from their article further suggests that the amnesic patients actually performed very well (around 80% accuracy) by comparison with the controls (around 94%). Despite a larger number of items in their experiment (50 targets vs. 32 in our study), our controls reached a similar level of accuracy (92%), and so was the case for patient KA (85%). Given the high inter-individual variability reported in the Smith et al. (2014) study (estimated through the standard error of the mean displayed in figure 4B), and our use of a different and more conservative statistical approach, this could partly explain the discrepancies.

Second, as already mentioned in the introduction section, detailed MRI analyses for the hippocampus and extra-hippocampal structures are not available for these 5 patients, and the aetiology of the amnesic syndromes also remained unclear in some cases (i.e. 2 cases of drug overdose, 1 case of ischemia plus toxic shock, 1 case lacking any identifiable cause, 1 case of anoxia following cardiac arrest). Moreover, slight volume reduction in parahippocampal gyrus is reported in at least 4 patients. Finally, all 5 patients were aged 50-75 years old, and no detailed neuropsychological background is reported. One possibility therefore that cannot be ruled out is that at least some of these patients may have presented with some extra-hippocampal abnormalities, and / or some level of

cognitive decline, since they have been tested years after serious medical conditions. By contrast, here we contrasted performance of patient KA with a larger sample of healthy controls, without any medical history and free of any memory impairment. In addition, the selective damage to the hippocampal system with clear preservation of extra-hippocampal structures in KA was established with several independent imaging techniques.

Considering source memory and estimates of subjective recollection, we also found that patient KA was unimpaired. However, an important limitation of the present study lies in the floor effect observed in controls for source memory in the Novelty and EK conditions, therefore making impossible further interpretation of the patient's performance. In the PEK condition however, KA performed in the low but normal range, and importantly, the discrepancy between his scores in the Novelty and PEK conditions also fell in the normal range. Moreover, we found that KA's high-confidence ratings for Hits responses to famous target faces were similar to controls. Our task design does not however allow to stating on whether true recollection or familiarity contributed to the patients' performance.

Altogether, these findings therefore support the idea that extra-hippocampal structures can support pre-experimental knowledge guided memory, including memory for face-scene associations. While unitization could be a candidate process, especially given the study instructions emphasizing the integration of the face and the background, further investigation is needed to address this outstanding issue. Another possibility could be that high face-scene congruency with existing memory schemas about the famous faces would have triggered faster consolidation, independently of the hippocampus, as proposed in the SLIMM framework (Van Kesteren et al., 2012). For now, an interesting perspective could be to assess whether familiarity-based recognition memory, which is preserved in KA, can support recognition memory for famous faces. While some authors have argued that this could hardly be the case (e.g. Smith et al., 2014), it has never been tested to the best of our knowledge. The Speed and Accuracy Boosting procedure we used in Experiment 1 could be particularly well suited for that purpose, and we have started pilot experiments with patient KA.

General Discussion

General Discussion

Foreword: A thesis as a professional journey, personal summary

Before discussing the findings reported during this this, I wish to make an assessment of my own goals through this work, both for those who made it possible and for myself. As a neuropsychologist for around 15 years, I have run several researches mainly grounded on the atypical profiles of brain-damaged patients, together with their unsatisfied needs regarding cognitive disabilities. The main goal of this work, to me, was to get the opportunity to focus on a series of questions, all related to patient KA, and try to move some steps forward. This is hardly doable when you work as a full time neuropsychologist with limited time devoted to research. The other goal for me was basically to learn about one neuroimaging technique, which finally happened to be task-based functional MRI. This was because we have the privilege at the Rennes University Hospital to host a MRI scanner that is dedicated to research, and what we need is sufficient knowledge and skills to use it. So my hope was that this thesis might give me the required background to further apply for grants, and thus keep on running neuroimaging studies.

About four years later and 345 participants involved in the experiments reported in this work, I have to say that these goals were largely exceeded.

First and as I discuss below, I think this work will contribute to our understanding of memory disorders, their neural and cognitive substrates.

Second, working with patient KA has led to several new projects, many of which are reported in the following discussion. I plan to continue seeking for preserved learning processes in patient KA, and I will hopefully start next summer a project involving the Neurinfo imaging platform of Rennes University Hospital, the Empenn research unit that hosted me for the neuroimaging part of my thesis in Rennes, and a post-doc student from the Liège Cyclotron research group, Gabriel Besson. We will address the issue of the contribution of within-MTL functional connectivity to familiarity-based recognition. Another project that should start shortly relates to how the work presented here can contribute to a better diagnosis and rehabilitation of patients with developmental amnesia. This condition is likely underestimated, as the story of KA dramatically illustrates. Jointly with patient KA, we decided a short movie inspired by his everyday life,

with the intention to raise awareness among medical doctors and professionals in the field of education about this syndrome.

Third, I have acquired several critical skills for scientific research.

For example, I learned a lot not only on task-based fMRI, but also on various MRI techniques and their limitations as well, so that I feel confident in designing new experiences, and especially regarding the difficulties associated with imaging the MTL. Similarly, I have acquired some basic coding skills (MatLab), and also how to use several imaging or statistical tools (ITK-snap, xjview, ASHS, volBrain, JASP, GIMP, SPM, FSL, GPower, among others).

Finally, I also have learned a lot about how to share results in the scientific community, with great opportunities to attend to important international conferences like ICOM-6 (Budapest, 2016) or “LearnMem” (Irvine, CA, 2018).

Together with intensive teaching for undergraduate students as well as numerous conferences for the general public (around 300 hours during my thesis and over 1000 hours since I started in 2002), I think that I have gained further legitimacy to apply for a university position (in psychology or in neurosciences departments). However, I would like to keep a clinical position as well, since clinical neuropsychology remains to me at the heart of my scientific interests.

Let's now discuss our main findings

Our objectives in this thesis were twofold. First, we aimed at investigating whether explicit memory acquisition and retrieval could occur despite severe amnesia following bilateral damage to the hippocampal system. We have argued that one critical gap in the current state-of-the-art was the lack of demonstration that such learning abilities could occur in conditions similar to controls, i.e. as fast as healthy subjects, rather than following dedicated learning techniques. Second, based on the surprising findings of a material-specific effect in new learning abilities after hippocampal amnesia, we aimed at investigating the role of prior knowledge in declarative learning. With this respect, we have underlined the inconsistencies across models putting forward the role of novelty or of familiarity detection in triggering long-term memory encoding. Similarly, we have outlined the surprising lack of knowledge regarding how aging and Alzheimer's disease could affect novelty or familiarity-based declarative learning.

Following on from the neuropsychological tradition, the present work has therefore unfolded along the findings brought by the case study of patient KA. Basically, our findings can be divided in **two sections, following our objectives and hypotheses**. One section is **more focused on the results with patient KA and relates to how learning can occur without remembering**. Issues to be discussed are the cognitive and neural routes for such learning, which should account for both the acquisition of new explicit memories and the large amount of knowledge KA has built. The other section relates to the question **of how prior knowledge impacts new learning**. Critical issues to be discussed are the candidate cognitive processes and neural substrates for prior knowledge-dependent learning, the impact of aging and of Alzheimer's disease on such learning. We further discuss these two lines of issues in turn.

All along the discussion, we have highlighted in green some of the key contributions of this thesis, in our opinion, and the text highlighted in red illustrates experimental perspectives, some of which had already been addressed (see Appendixes A & B).

Patient KA: The case for learning without remembering

The series of experiments reported with patient KA (Jonin et al., 2018) have brought strong evidence for little, if any, residual episodic learning abilities. KA presents with one of the lower scores ever reported at the Rivermead Behavioural Memory Test, and scores below the first centile for virtually any long-term episodic standard measure. Besides, consistent evidence for his inability to acquire new associations in long-term memory was also reported (e.g. arbitrary associative learning in the paired associates subtest of the Wechsler scale, object-location combinations in a recognition test). Thus, apart from item recognition memory and standard measures of short-term memory, patient KA looks totally unable to recall new information from episodic memory or to form new arbitrary associations in long-term memory, which are defining features of amnesia.

These findings are of utmost importance, since explicit learning and memory of new facts or of new episodes (i.e. self-experienced events) constantly interact together in everyday cognition. It follows that as put forward by Squire & Zola, (1998), provided sufficient, residual episodic abilities may well support new semantic learning, although with enough repetition and efforts. In the case of patient KA, the findings of supranormal semantic knowledge are therefore unlikely to result from residual episodic abilities. Of equal importance are our results of superior semantic, or context-free, knowledge stored in KA's long-term memory. From a cognitive perspective, prior cases with developmental amnesia (DA) could not rule out the "residual episodic memory" account either because of the existence of some residual episodic learning capacities, or because of the findings of low-to-normal semantic memory aptitudes. Given that we cannot predict the level of semantic knowledge that is supposed to be reached for a given level of episodic learning abilities, Squire & Zola (1998) argued that this low-to-normal achievement regarding semantic memory could well, again, have resulted from slow and effortful learning resulting from the residual episodic abilities.

Strikingly, this core issue for the neuropsychological models of declarative memory and the episodic-semantic distinction had not been directly addressed before. Following Squire & Zola (1998)'s point, what would be unexpected under the unitary declarative memory account is a situation where semantic performance would exceed that of healthy controls despite compromised episodic memory. Yet, this is exactly what we found in patient KA who, as an example, can discourse extensively on French History, and even more specifically on the Napoleonian period, or giving you by heart the titles and

corresponding years – including sometimes the album title – of famous French music hits. In our opinion, an important contribution of this thesis is that we provide the first strong evidence for “learning without remembering”.

Box 1. The residual episodic memory account of learning preservation in developmental amnesia does not hold in patient KA

Probably the most robust evidence that semantic learning can occur despite a severely compromised episodic system comes from cases reports of developmental amnesia. Still, prior reports have mostly limited the assessment of semantic memory to academic achievements tests, and have shown low-to-normal performances, and sometimes slight impairments. Moreover, prior cases reports have also outlined some preserved episodic learning abilities in typical standardized tests. The “residual episodic memory” account therefore states that, with sufficient time and efforts, some fair level of semantic memory performance could have been achieved (Squire & Zola, 1998). This would remain compatible with the unitary, declarative memory view. In this thesis, we have brought strong arguments against this view. Patient KA presents with little, if any, residual episodic learning abilities, and still outperforms controls in some semantic memory tasks, as extensively assessed far beyond the domains of academic achievements (i.e. vocabulary or information subtests of the Wechsler scales). Our report thus strongly supports the idea that learning can occur without remembering.

Candidates mechanisms for learning without remembering: cognitive processes

The multiple system view: preserved semantic memory system?

The typical interpretation of the cognitive profile of patients with DA relates to the SPI model from Endel Tulving (1995). Namely, DA was taken as strong evidence for the existence of two separate memory systems within declarative memory, i.e. semantic and episodic memory. Along this view, early bilateral damage to the hippocampus would prevent the episodic memory system from normally developing but preserved subhippocampal structures would still support semantic memory. Thus, the learning of new facts, the acquisition of conceptual knowledge would entirely rely upon the

semantic store, viewed as a separate biological entity. Several arguments against this view must be put forward here.

First, as we have extensively argued in the introduction section (see Chapter II & III) evidence from experimental psychology and cognitive neuropsychology rather speaks for **distinct encoding and retrieval processes in the service of different knowledge systems** (e.g. Nadel, 2008). For example, relational processes are considered by some authors to be at the heart of episodic memories, and episodic remembering will result from relational processing. However, this does not imply the existence of a specific kind of representations with specific properties (i.e. episodic). This only suggests that relational processing will bind together separate elements to allow reconstructing an episodic memory.

Second, our results **do not allow to state that KA's semantic memory (i.e. context-free memory representations) is normal**. The fact that KA shows supranormal semantic knowledge in some domains, and that under certain circumstances he can access such knowledge faster than controls, may indicate that either he is more efficient than controls in the use of retrieval processes, or that the organization of semantic knowledge in KA differs from that of controls. In fact, recent evidence has supported the view that semantic knowledge organization is not normal in DA, both in terms of contents and of structure (Blumenthal et al., 2017). The authors have studied the well-documented case of patient HC, and showed that she generated less extrinsic features for object concepts than matched controls. Importantly, they suggested that this might result from hippocampal injury, since the acquisition of concepts that are tightly dependent upon the integration of external features would be more relying on relational binding processes. For example, to acquire the concept “knife”, you might need to bind separate contexts and usages across time (i.e., along several distinct life events), which allows the integration of distinct extrinsic features (i.e. can be used at the butcher's, during a picnic, by an artist in a circus, etc.). By contrast, patient NB with selective damage to the left rhinal cortices (perirhinal and entorhinal cortices) due to surgery underwent at age 26 (Bowles, Duke, Rosenbaum, McRae, & Köhler, 2016) was unimpaired.

Third, recent theoretical frameworks of concept acquisition emphasize the **convergence between concept formation and episodic memory**. Concept acquisition requires that across multiple occurrences of unique episodes, we are able to extract the features that are common to a given concept and also the features that differentiate between concepts (Mack et al., 2018). This requires pattern separation, pattern completion and

integration processes, to allow formation of new concepts in semantic memory. Yet, such processes are tightly linked to episodic memory, and highly dependent upon the hippocampus. The building of distinct representations for similar experiences is associated with pattern separation, and the retrieval of an entire episode given an appropriate cue is associated to pattern completion. It is therefore hard to see how the processes underlying the formation of new conceptual knowledge could occur in an independent system (semantic), isolated from the system supposedly supporting memory for individual experiences. In controls, each and every interaction between recollected life events and existing conceptual knowledge can support new learning and memory-guided behaviour. However, in patients like KA, a more restricted number of efficient learning processes is available, and they always lacked the experience of remembering to do so. It is therefore unsurprising that their semantic organization is found abnormal, reflecting the close relationships between conceptual knowledge acquisition and episodic learning. Overall, the results we obtained with patient KA regarding a striking contrast between episodic memory and semantic knowledge should point towards preserved explicit *learning processes*, rather than preserved *memory system*, which nature needs to be determined.

What kind of learning processes could account for the pattern of preserved functions reported in KA? These processes should meet at least three criteria. First, they should allow ***rapid learning and retrieval***, since we found that KA did not differ from controls when he had to acquire and retrieve new explicit knowledge about prior occurrence of object pictures. Second, they should ***allow binding together different elements*** of information. This is because the impressive amount of conceptual knowledge available in patient KA has unlikely been learned without associative – and generalization – processes. Typically, reporting on the Battle of the Pyramids featuring Napoleon in 1798 requires stored associations within long-term memory. Finally, these processes should operate ***without an efficient hippocampal system***.

The contribution of familiarity and unitization

Which kind of cognitive process may allow rapid learning and binding in long-term memory? Familiarity-based retrieval, or the sense of prior exposure, could be pointed out

since it has been shown to critically rely upon the perirhinal cortex that is clearly preserved in KA as in previous patients with DA. This is in line with the dual processes approach as well, and also would fit with the assumption that familiarity is a fast and automatic process (Yonelinas, 2002). However, long-term memory binding of separate information is typically assumed to depend on hippocampal computations, as long as it involves associative processes. It therefore seems **unlikely that familiarity-based retrieval on its own may support concept formation.**

Yet, some models have pointed out situations where associative encoding could actually be achieved at a subhippocampal level. For example, the relational theory suggests that perceptual “blends” could be acquired and retained without hippocampal processing, but at the cost of an inability to further update these rigid representations. A related proposal is the idea of **unitization**. The BIC model assumes that under circumstances where separate elements can be processed as a whole, further retrieval does not require pattern completion and can therefore be performed through subhippocampal structures (perirhinal and lateral entorhinal cortices, or parahippocampal and medial entorhinal cortices). Therefore, one could speculate **that patients like KA use unitization strategies at encoding, which allow them to further recognize new associations on the basis of familiarity.** Along the repetition of single episodes, this might lead to actual concept formation.

As a consequence, one would expect unitization to be a possible candidate to account for concepts acquisition in DA, and recent reports in patient NC have indeed shown how a unitization strategy could circumvent relational memory impairments (D’Angelo et al., 2015).

Box 2. Unitization as a candidate mechanism for preserved learning in developmental amnesia.

To account for preserved acquisition of conceptual knowledge in patient KA, candidate mechanisms must meet at least the following requirements: 1) allow rapid acquisition and retrieval; 2) allow the binding of separate elements to form new associations; 3) be independent of the extended hippocampal system. **One such candidate could be unitization,** which allows separate elements to be processed as a whole, and further retrieval to be based on familiarity.

However, the boundaries of unitization are unclear (i.e. why and how unitization can take place, and whether “top-down” or “bottom-up” unitization is effective, see Tibon et al., 2014). Unitization may also depend on the representational domain of the information processed as suggested by the representational account from Davachi et al. (2006). Here, it is suggested that unitization-based learning would remain doable as long as within-domain representations must be bound, not in the case of between-domains binding. A related proposal comes from the Domain Dichotomy framework (Mayes et al., 2007) stating that associative encoding can be achieved through perirhinal computations as long as the representations of the individual features to be bound are close enough in the ventral stream. Close representations would better converge at the perirhinal level and thus be bound without further hippocampal involvement at retrieval (e.g. object entity involving, say, a red apple). By contrast, representations more distant from each other would require hippocampal computation to be bound within long-term memory (e.g. object-location association). Thus, here, unitization may occur in the case of close, but not distant, representations of the individual features at encoding.

These possible boundaries for unitization can be related to the issue of abnormal organization of semantic knowledge in patients with DA. As stated above, patient HC was especially impaired for extrinsic, not intrinsic, concept features (generation task), and for non-living as opposed to living objects (typicality ratings), the former being more related to extrinsic features (Blumenthal et al., 2017). It could be the case that extrinsic vs. intrinsic features of object concepts is an instance of impossible vs. possible unitization strategy. Indeed, the formation of concepts with high extrinsic features would more likely involve across-domains binding, while concepts with high intrinsic features would conversely require more within-domain binding. If we take the above example of the “knife” concept, acquiring this concept might require the accrual of various features across several episodes that are extrinsic to the object (where, how we use it, with which other objects, etc.), thus requiring between-domains features binding. By contrast, the acquisition of the concept “Zebra” might essentially involve within-domain (i.e. within-object) features, most being intrinsic to the object (e.g. its shape, colour, etc.). Thus, unitization in DA could support concept formation only when within-domain associations are critical. As a consequence, semantic knowledge might be preserved only for the concepts which formation did not critically depend on binding separate elements across domains, i.e. elements that are encoded distantly in the visual stream.

Perspective 1. Highlighting dissociations within semantic memory in developmental amnesia

To what extent unitization can support concept formation in DA therefore remains an open question. One testable prediction is that conceptual knowledge depending on the integration of spatial and verbal features, for example, should be much less preserved, or even impaired, by comparison with conceptual knowledge depending on within-domain features. For example, patients with DA should show poor performance when asked to retrieve geographical landmarks on maps, whereas they may well have a normal amount of knowledge about the countries depicted on the same map.

In any case, we need further research to identify the circumstances that could trigger effective unitization. What we know is that damage extended to the neocortex might prevent from benefiting unitization (Ryan et al., 2013), which reinforces the possibility for KA who has preserved bilateral perirhinal cortices to use such encoding strategy. However, as we further discuss, our findings of a material-specific effect for new learning in KA may contribute addressing this issue.

Material-specific learning in KA: prior knowledge as a boundary for unitization?

A striking finding of the present thesis is that KA totally failed at learning new abstract shapes, while he performed just fine with objects. In our opinion, this finding might shed some light on the circumstances where unitization might or not take place at encoding. Material-specific effects have already been reported in several cases of amnesia. A consistent pattern that emerged was the impairment of topographical and words memory while recognition of unknown faces remained preserved. Importantly, this pattern was similar considering either recollection or familiarity estimates. The famous patient Jon, for example, was unable to perform recognition tasks involving scenes while he did well with unknown faces (Bird, 2017; Bird, Vargha-Khadem, & Burgess, 2008; Cipolotti et al., 2006; see also Lacot et al., 2017 for a contrast between single items and scenes). Moreover, ROCs curve analyses of Jon's performance suggested that both familiarity and recollection estimates were unremarkable for faces, but an aberrant model involving two recollection parameters uniquely accounted for ROCs data for scenes recognition, suggestive of idiosyncratic strategies. Here we contribute this

literature in showing that a speeded recognition memory task that mainly taps on familiarity-based retrieval (see Besson et al., 2012) yields a clear dissociation depending on the stimuli used. Thus, **the perspective grounded on dual processes views that successful recognition for any kind of materials should be possible**, even after hippocampal damage, as long as the task can be performed on the basis of familiarity, is **not supported in patient KA**.

One possibility to account for this material-specific effect would be to consider that the building of long-term representations for abstract shapes may require additional relational, or associative processing that are not needed for familiar objects.

Our speeded recognition tasks required subjects to decide whether an item was presented or not during the study phase. In the case of real objects, it implies that the particular object displayed had been processed up to the conceptual level, so that when shown a target picture (e.g., a balloon), the subject can decide whether this concept was recently experienced or not. Here, conceptual fluency may help to make fast and accurate response as the ones provided by KA. In the case of abstract patterns, however, three critical differences arise. First, there is no prior knowledge, or pre-existing representations, for abstract patterns. Second, as a consequence, conceptual processing is not possible. Third, and similarly, distractors cannot be rejected based on conceptual processing, so that accurate discrimination between targets and lures critically relies on the resolution of the representation built at encoding. Conceptual fluency won't occur, and perceptual fluency might not be sufficient either. Indeed, considering that the abstract shapes we used were more perceptually similar than the real objects, one would expect a high-resolution binding to be required for correct memory discrimination (see p. **Erreur ! Signet non défini.**). Such high-resolution binding in the case of our stimuli clearly involves configural integration of shapes, colours and spatial features, and we suggest that such integration may rely on computations performed at the entorhinal or hippocampal level (e.g. Barense, 2005; Bussey, Saksida, & Murray, 2003; Cowell, Bussey, & Saksida, 2006; Lee et al., 2005; Yonelinas, 2013). Importantly, since we have brought evidence for atrophy of the right entorhinal cortex in KA, the patient would be unable to encode these stimuli with the resolution required for further retrieval.

Thus, this is an instance where unitization may not occur, because of the level of perceptual integration required by the task, and because, as already suggested before, unitization might need conceptual processing to occur (e.g. see Tibon, Gronau, Scheuplein, Mecklinger, & Levy, 2014). Indeed, prior reports have suggested that

conceptual processing at encoding may favour integration or unitization processes (Ahmad, Fernandes, & Hockley, 2015; Graf & Schacter, 1989; Tibon et al., 2014).

Box 3. Material-specific familiarity-based recognition in developmental amnesia: the limits of unitization.

Evidence for a material-specific effect on familiarity-based recognition memory in patient KA may point towards an important boundary for the process of unitization. When targets and lures cannot be discriminated on the basis of conceptual processing, and are perceptually very similar, high-resolution intra-item binding might be required to achieve accurate recognition. Such binding might not be supported by unitization, since unitization may require conceptual processing to take place.

Perspective 2. Modulation of familiarity-based recognition memory after hippocampal damage.

Along this line, one would predict this material-specific effect to disappear if, for example, perceptually and conceptually similar objects would have been used in the “real objects” condition. Conversely, the use of perceptually dissimilar abstract patterns should also reduce, if not cancel, the material-specific effect. Alternatively, using a 2-alternate forced choice testing format should also alleviate the deficit, since at least perceptual fluency could be helpful here. However, increasing the number of lures should act as increasing the perceptual similarity between targets and lure and thus would not be beneficial.

Support for these ideas can be found in the recent case study of patient JMG, with damage to bilateral MTL with the notable exception of the right hippocampus (Barbeau et al., 2011; Lacot et al., 2017). JMG was impaired in a Old/New recognition test involving abstract patterns, which is presumably due to damage to the right subhippocampal structures. Importantly, JMG was also impaired in a recognition test involving abstract patterns but in a 5-alternate forced choice format. This can be contrasted with normal performance of KA for abstract shapes within a 3-alternate forced choice format (see Jonin et al., 2018, Table 4). Finally, performance of the patient FRG, with intact right entorhinal, perirhinal and parahippocampal cortices but destroyed right hippocampus and left MTL is also relevant, since this patient successfully performed a series of three Old/New recognition memory tasks involving abstract patterns (Barbeau et al., 2005;

Barbeau et al., 2011, Table 2). A recent study also used abstract patterns and found a positive relationship between intra-item configural processing and the volume of the lateral entorhinal cortex (Yeung et al., 2017). This strengthens the idea that encoding of previously unknown stimuli, made of separate elements and thus requiring some level of binding across several features (i.e. shape, colour, spatial) might not be achieved through perirhinal computations, but rather might need at least the involvement of the entorhinal cortex. By contrast, in the case of stimuli for which existing conceptual knowledge is available, such level of binding may not be necessary to allow further accurate recognition.

Box 4. Material-specific familiarity-based recognition in developmental amnesia: support for the representational-hierarchical view of the MTL

Our suggestion is therefore that the material-specific effect observed in patient KA may be interpreted within the representational-hierarchical models whereby recognition tests that require items to be processed as single entities can be successfully performed through rather early computations in the ventral stream (actually preserved in KA). The representation of abstract patterns, however, would require additional, later computations presumably sustained by the entorhinal cortex, or even the hippocampus, depending on the discrimination demands placed on the test.

In the case of KA, evidence for damage to the right entorhinal cortex and hippocampus could therefore account for this pattern of results, and also point towards a boundary for unitization. Unitization at encoding could take place as long as prior knowledge is available, allowing conceptual processing at encoding. In these situations, as stated before, unitization might be an interesting candidate to account for preserved concept formation in KA. However, when prior knowledge is not available at encoding, like in the case of unknown stimuli made of separate elements (arbitrary associations could be another instance of stimuli lacking prior knowledge), relational processing would be mandatory for the binding operations.

If true, a way to move forward would be to investigate whether distinct binding processes that operate at encoding could be differentially affected following damage to the hippocampus or to subhippocampal structures.

Perspective 3. Does short-term memory binding at encoding dissociate within the MTL?

An interesting possibility would be to contrast binding of features that are intrinsic to the object (i.e. “conjunctive binding”) with binding of extrinsic features (i.e. “relational binding”). These forms of binding have already been contrasted in long-term memory (Mayes et al., 2007), however, an interesting possibility would be to investigate whether they also dissociate within working memory, i.e. during the study phase of a recognition paradigm. Following our proposal, it could be the case that preserved conjunctive binding processes may support preserved explicit learning in KA, in spite of disrupted relational binding. We have explored this idea in a fruitful collaboration with Dr Mario A. Parra, as presented in Appendix B (Jonin et al., 2018).

In summary, we have suggested that unitization might be a candidate mechanism susceptible to account for the preservation of semantic learning in patient KA. However, we have acknowledged that unitization might take place at encoding only when pre-existing representations, or prior knowledge, is available. This of course leaves us with an unresolved issue, namely how KA could have acquired conceptual knowledge in the first place?

Towards an account for the acquisition of knowledge despite amnesia

A relevant clinical observation here in KA is that he has consistently shown intense interests for some domains of knowledge, and, as stated before, he has likely become kind of an “expert” in it. We have cited the example of his intense interest for History, but he also has an impressive amount of knowledge regarding firemen and all the stuff associated with this domain. This and other domains of relative “expertise” in KA (e.g. French music hits), according to his relatives, often takes the form of obsessions, in that KA seems to lack curiosity for things that differ from his major interests. This kind of behaviour was termed “**intense conceptual interests**”, and it has been increasingly described and investigated in the last two decades, becoming a central topic in educational-psychology and cognitive development literature (Alexander, Johnson, Leibham & Kelley, 2008; DeLoache & Simcock, 2007; O’Keefe & Garcia, 2014; Rotgans &

Schmidt, 2017; 2014;). About one-third of young children would present that kind of intense interests, associated with the development of an impressive amount of knowledge in children below 6 years old, and it might be more frequent in boys. Intense interests are supposedly beneficial for the cognitive development, regarding attention, increased learning and deeper levels of processing (Alexander et al., 2008). Interestingly, retrospective studies in adults experts show how early in life their interest grew up for the domain of expertise (Ericsson & Crutcher, 1990). Intriguingly, intense conceptual interests do not last for many years. Rather, after a period typically lasting from a few months to a few years, children seem to forget a large part of this (or these) domain-specific knowledge (e.g. Chi & Koeske, 1983). The typical age range for children to develop these intense interests is generally around 3 years old, according to studies of parents' reports (DeLoache, Simcock, & Macari, 2007). Interestingly, by age 6, children master thousands of words and their meanings, and this is achieved in a very limited time windows in the development, an observation often attributed to the phenomenon of "**fast-mapping**" (Carey, 2010). Fast-mapping refers to an incidental associative learning procedure that allows to create "novel word-referent links in as little as one exposure" (Samuelson & McMurray, 2017). However, and importantly, these novel associations learned through "fast-mapping" incidental procedures do not seem to be retained on the long-run, unless novel exposures or "**extended mapping**" can take place (for a recent review, see also Cooper et al., 2018). Recently, a study has shown that adults with acquired amnesia could perform better than controls in an associative learning task (picture – name associations) under a "fast-mapping" procedure (Sharon, Moscovitch, & Gilboa, 2011). Note however that this result has never been replicated so far either in late-onset amnesia (Cooper et al., 2018) or in a series of three patients with developmental amnesia (Elward et al., 2019).

Perspective 4. Do fast-mapping, extended-mapping and intense conceptual interests relate each other in early cognitive development?

An exciting possibility, that has never been investigated as far as we know, is that fast-mapping, extended-mapping and intense conceptual interests could be related in the service of the early development of learning abilities. In the case of patient KA, we could speculate that, like many other children, he may have developed such intense interests quite early in life, as suggested by the clinical reports with him and his relatives. Whether fast-mapping could have been involved in the development of these interests of course remains to be investigated. This should be easily doable by contrasting children with and without “intense conceptual interests” on fast-mapping learning procedures for items belonging to their domains of interest or not, for example.

One could nonetheless speculate that the reason for the absence of convincing evidence for rapid learning through fast-mapping in cases of DA so far (i.e. only one study) could be that patients are tested too late: so far, fast-mapping studies in healthy adults consistently revealed that this procedure was less efficient than the typical “episodic encoding” condition for subsequent memory (Cooper et al., 2018).

Now, considering our proposal that prior knowledge available at encoding may be critical to trigger unitization strategies, which in turn makes further recognition possible in amnesia, we could speculate on a possible account for KA’s profile. It seems to us possible that, if an amnesic patient were highly – abnormally – dependent on prior knowledge for subsequent memory, it would make sense that he would develop much more self-interest-guided behaviours than his pairs, just because this gives him more chance not to forget. Thus, it may have been the case that his actual intense interests, and comparatively superior knowledge in some domains, may in fact reflect the continuous development of such learning strategies. That is, by focusing on a restricted set of conceptual domains, preserved learning through unitization may take place, giving the patient more chance to keep the track of his on going activities. As an example, it has been demonstrated that patients with damage limited to the hippocampus could perform like controls in learning combinations between grocery items and their prizes, but only when the combination was congruent with existing (i.e. real) prizes. Moreover,

this was not observed in patients with damage extending to structures of the parahippocampal gyrus (Kan et al., 2009).

Box 5. Intense conceptual interests first, then unitization triggered by existing knowledge?

Therefore, it is conceivable that patient KA has, along his development, started to focus on the only “intense conceptual interests” for which he had successfully acquired knowledge, because this may increase the likelihood of memory formation, in kind of a “virtuous circle”: prior knowledge triggers unitization which allows associative recognition which, along multiple episodes, leads to concept formation.

Future research is needed to better characterize whether pre-existing representations in long-term memory (i.e. prior knowledge) alone can benefit subsequent associative memory, or whether *congruency* with prior knowledge is the key factor. In the last case, theories putting forward the role memory schemas would be strongly supported (e.g. SLIMM framework), while in the other case, older accounts like the levels-of-processing framework should be considered (for example, patient Jon was shown to benefit from depth-of-processing manipulation with words, see Gardiner, Brandt, Vargha-Khadem, Baddeley, & Mishkin, 2006). In the same vein, we need more investigations of the boundaries between unitization and conceptual elaborative encoding. So far, only one study has brought evidence suggesting that these processes may correspond to distinct cognitive form of learning (Parks & Yonelinas, 2015). Noteworthy, this investigation found that unitization especially enhanced associative learning involving faces-word pairs (Expt. 4), which again support this mechanism as an important candidate to account for the pattern reported in patient KA.

What could be the brain substrates for preserved concept formation in patients like KA?

The Anterior Temporal network may support rapid neocortical learning

Our imaging results in KA have contributed addressing the issue of what could be such preserved learning processes. We have brought evidence that in DA, brain damage may well extend beyond the hippocampal formation. This confirmed prior reports of damage to diencephalic structures, and extended the findings to the whole hippocampal system.

That is, for the first time to the best of our knowledge, a case report provided data suggesting not only that there is some degree of hippocampal atrophy in that syndrome, but also that each and every structure connecting the subiculum to the anterior thalamic nuclei has abnormal features. This reinforces the idea that this system has some functional specificity, and also makes it unlikely, at variance with prior studies, that preserved structures within the circuit could be responsible for the remaining learning abilities in KA. Of greater interest here is the status of extra-hippocampal structures. We found very robust evidence for the preservation of the parahippocampal gyrus and entorhinal cortices, exception made of a right entorhinal volume loss. Moreover, cortical thickness and volumes segmentation revealed an unexpected higher grey matter density in the medial temporal pole, broadly encompassing Brodmann's areas 38 and 36. Paralleling other cortical thickness reports in neurodevelopmental conditions, these results are highly suggestive of a reorganization of the MTL following early injury, which has never been reported in DA. We can only speculate that the particularly severe hippocampal atrophy in KA, by comparison to previous cases, encompassing all subfields, might have triggered such functional reorganization. Although controversial, animal studies previously suggested that more severe hippocampal damage would in fact result in a more efficient functioning of extra-hippocampal structures, maybe due to the absence of interference from the residual hippocampal system.

Box 6. The case for two learning pathways within the PMAT framework

Our suggestion therefore would be that at least two explicit learning pathways coexist within the MTL. In line with the proposal from the PMAT framework (Ranganath & Ritchey, 2012; Ritchey & Ranganath, 2015), one pathway would mainly rely on the Anterior Temporal (AT) network including the perirhinal cortex as a core node; the other pathway would depend on the Postero Medial (PM) network including the parahippocampal cortex as a core node. In the case of KA, beyond the hippocampal injury, damage to most of the PM network is most likely, which could have favoured a differential development of the AT network as reflected in our cortical thickness measures (see Gogtay et al., 2007; Huttenlocher, 1990; Khundrakpam, Lewis, Zhao, Chouinard-decorte, & Evans, 2016; Shaw et al., 2008).

Of great relevance here are recent findings of thinner temporal poles cortices in the syndrome of Highly Superior Autobiographical Memory (HSAM) (LePort et al., 2012; for a

recent review see Palombo, Sheldon, & Levine, 2018). These subjects have very superior abilities of autobiographical memory recall, while they cannot be discriminated from normal controls on standard tests of episodic and semantic memory.

Perspective 5. The case for a neurodevelopmental continuum regarding explicit learning
One promising perspective would thus consist in considering the syndrome of DA and of HSAM on a continuum with respect to the PMAT framework. While early injury to the hippocampal system would have shifted further synaptogenesis and synaptic pruning towards favouring the AT network in DA, unknown atypical developmental condition in HSAM might have shifted brain maturation towards favouring the PM network. In the case of HSAM, very recent support for this idea has just been reported in an task-based fMRI studies revealing that most of the PM regions display higher activity during autobiographical memory retrieval in HSAM than in controls (Santangelo et al., 2018). Similarly, the lack of autobiographical recollection in a subject with “Severely Deficient Autobiographical Memory” (SDAM, Palombo, Alain, Söderlund, Khuu, & Levine, 2015) has recently been associated with reduced neural synchrony in the gamma band, a MEG marker of recollection in normal controls (Fuentemilla, Palombo, & Levine, 2018). We thus have preliminary but consistent evidence showing that in HSAM, the PM network may be abnormally efficient, while comprehensive cognitive assessment does not reveal any specificities regarding semantic knowledge. Conversely, in SDAM, neural markers of recollection are apparently lacking. An hypothesis that needs further investigation is whether in DA, a pattern closer to the one observed in SDAM but opposite to the one reported in HSAM could be highlighted, as long as early damage to core regions of the PM network were severe enough to, as we speculate, lead to a reorganization favouring the efficiency of the AT network. This could account for the superior semantic knowledge observed in KA, and for his particularly fast responses when dealing with famous faces discrimination.

Perspective 5. Characterizing the network underlying familiarity for famous vs. unknown faces in KA and controls.

A related issue would be the investigation of whether KA presents with an abnormal discrepancy between familiarity-based recognition for famous vs. unknown faces, as compared to controls, and whether this could be related to the reorganization of his AT network. We have started a behavioural experiment using the speeded recognition paradigm to collect preliminary data, before we can hopefully design an fMRI experiment for that purpose.

Altogether, we have completed the first series of objectives of this thesis by bringing additional data supporting the existence of a rapid learning pathway outside the hippocampus. In doing so, we did confirm the hypothesis that semantic knowledge can be acquired and retrieved despite no residual episodic learning abilities, and with no need of dedicated learning techniques. Furthermore we also have verified the assumption that such learning processes are unlikely to be the result of residual functioning in the extended hippocampal system. However, we brought evidence for a material-specific effect in a recognition procedure mainly tapping on familiarity, in contradiction with the dual processes framework. Among the possible accounts for these findings, we suggest that pre-existing representations available at encoding could be responsible for this material-specific effect favouring meaningful stimuli. How prior knowledge affects new learning was the second main goal of this thesis, which we further discuss below.

Prior knowledge, not stimulus novelty, is a powerful learning enhancer

When the to-be-learned stimuli carry **pre-existing representations**, we have brought evidence that it **considerably increases the likelihood of long-term memory formation**. Around 20% improvement was reported when comparing famous with unknown faces, which represents a very large benefit due to an experimental manipulation that was incidental to the encoding task: the orienting tasks we used did not differ across novel or familiar stimuli.

This result extends numerous prior studies suggesting that familiar items yield better memory than unknown ones, again highlighting to us an overlooked fact, namely that **our learning processes may be biased towards the acquisition of new memories about memoranda that we are familiar with**. An original contribution that is added by the present work is that, by directly contrasting novel with familiarized or famous faces, our result help resolving prior contradictions in the literature. As noted by Poppenk et al. (2010), there was a sharp contrast between the acknowledged role of stimuli repetition in learning and proposals putting the emphasis on novelty detection as a critical factor in triggering long-term memory encoding (e.g. Tulving & Kroll, 1995). We have extended the findings from Poppenk et al. (2010) who used written proverbs to demonstrate that familiar, but not novel, items were better remembered, and obtained similar findings using more relevant materials for everyday cognition, that is face-scene associations. Besides, the use of faces also allowed us to make sure that novel stimuli had never been experienced before, which is a confounding factor that cannot be ruled out with words. We do not take our results as evidence against the models predicting that novelty should increase memory performance; in fact we only demonstrate that such prediction does not apply to absolute stimulus novelty. Refinement of the definition of novelty (see Bastin et al., 2019) is needed to clarify inconsistent reports regarding the issue of memory enhancement. Similarly, we need to better characterize the sources of familiarity, or prior knowledge, if we are to better understand the relationship between knowing and learning. The present thesis aimed at doing so by contrasting two main forms of prior knowledge, as we will discuss below.

One of our objectives was to contrast stimulus novelty and stimulus familiarity in the same learning task where the status of the items in memory would be carefully checked, where the availability of prior knowledge at encoding would be incidental and irrelevant for the task instructions, and where the testing format (source memory judgment) would

circumvent the confounding factor due to differential retrieval demands. By doing so and using materials that are relevant for everyday cognition (face-scene associations), and that further reduce the inter-individual variability regarding perceptual expertise, **our data helps resolving the contradictions related to how both novelty and familiarity could enhance long-term memory.**

An important result that we think we have brought here is actually a negative finding: when novelty is operationalized as stimulus novelty (i.e. a previously unseen face), it does not lead to better memory formation than familiar stimuli (i.e. already experienced faces). Besides, this was true even for item memory, suggesting a robust advantage for famous faces because considering items recognition alone in fact should yield more False Alarms for famous faces than for unknown faces, which was not the case. An implication of this finding is that novelty detection processes known to trigger efficient long-term memory encoding may have more to do with our ability to process errors of prediction than novelty per se. That is, neurocognitive accounts like the PIMMS model (Predictive Interactive Multiple Memory Systems, Henson & Gagnepain, 2010) assume that memory-guided behaviours result from the dynamic interaction between memory systems, and that backwards flow of information within the MTL hierarchy may provide predictions (e.g. based on contextual processing) that are compared to the actual sensory input processing. This may result in signalling an error of prediction that, when large enough, could trigger additional long-term encoding mechanisms.

Box 7. Contextual novelty, not stimulus novelty, may drive the novelty effect on subsequent memory

Thus, and in accordance with recent proposals suggesting that contrasting conceptual novelty (an unexpected combination of familiar elements) with conceptual familiarity (an expected combination of familiar elements) should be helpful in resolving the discrepancies (Reggev et al., 2017), our results suggest that the role of novelty should be considered as related to isolation, bizarreness, or incongruent effects rather than as a lack of prior knowledge.

Along this line, it could well be the case that both relative novelty (i.e. as a result of broken expectations, or large prediction error) and prior knowledge (i.e. pre-existing representations congruent with the incoming information) drive learning enhancement, as predicted in the SLIMM framework (Van Kesteren et al., 2012). This perspective has

very recently found support in a series of behavioural experiments using visual discrimination learning to generate memory for rules (considered as memory schemas) and testing memory for trials either congruent or incongruent with the learned rule against unrelated trials (Greve et al., 2019). The authors found increased event memory for both incongruent and congruent trials by comparison with the unrelated, baseline trials, and further argued for their results to reflect distinct learning processes that would support either congruency-based memory or non-congruent-based memory. This illustrates more generally how prediction error models may gain influence in future research, as they reflect the utmost importance of considering the dynamic interactions between what we know and how we learn to gain further insight into the understanding of learning mechanisms.

In that context, a remarkable result of this thesis is that **standard memory measures used in clinical settings displayed differential relationships with our assessment of stimulus novelty- or stimulus-familiarity based learning.** The fact that some universally used testing procedures like the Logical Memory subtest of the Wechsler Memory Scale may tap on prior knowledge-based, but not novelty-based, learning is of great matter. Because we have shown that stimulus novelty yields lower long-term memory performance, it implies that **current neuropsychological assessment may underestimate memory impairments at least in some patients.** We will come back to this idea later.

Beyond Levels-Of-Processing: benefits of conceptual and perceptual knowledge

One way to account for the benefit of prior knowledge is to consider the levels-of-processing framework (LOP), which assumes that deeper (i.e. semantic) encoding will result in a higher probability of successful learning. However, and as stated in section VI.I, p. 147, one weakness of the framework is that depth of encoding is actually hard to define.

Typically, it has been operationalized using orienting tasks at encoding that stress either semantic or perceptual processing, showing that the former exceeds the latter in terms of subsequent memory. In an effort to further investigate the hypothesis derived from this framework, we contrasted two kinds of prior knowledge in the same task design. Following Poppenk et al. (2010), “Experimental Knowledge” (EK) was operationalized as

pre-study familiarization with previously unknown faces; “Pre-Experimental Knowledge” (PEK) was operationalized with the use of famous faces. While the former results from recent exposures, and is therefore unlikely to trigger conceptual processes when encountered again at study, the latter results from countless exposures over the lifetime, and triggers conceptual processing at study. We have therefore argued that experimental knowledge resulting from recent exposures would mainly yield perceptual knowledge, potentially triggering perceptual fluency during the study phase. By contrast, famous faces are expected to yield both conceptual and perceptual fluency at study. We thus consider that our task may help isolating the specific benefits associated with conceptual processing (associated with both identification and reactivation of a large knowledge network, and conceptual fluency during study).

Following the LOP framework, we would expect PEK to generate more Hits than EK. Moreover, given that correct rejection of famous faces used as lures (PEK condition) is more demanding than correct rejection of unknown faces (EK & Novelty conditions), we would expect to see an increase in the rate of FAs in the PEK condition. A famous paradigm in psychology has repeatedly shown this pattern of FAs: the Deese-Roediger-McDermott (“DRM”) paradigm. Several accounts have been advanced for the finding of high FAs rates to critical lures, but a common feature of these models is the idea that conceptual similarity between the lure and the encoded representations of the targets at study will increase the probability to endorse a lure as studied (i.e. Activation Monitoring Theory, Roediger, Watson, McDermott, & Gallo, 2001; Fuzzy Trace Theory, Brainerd & Reyna, 2002).

In contradiction with these frameworks, we found that the PEK condition generated fewer FAs than EK, while Hit rates were similar in both conditions. We replicated the result in an independent sample, which strengthens in our opinion this conclusion. In our view, this pattern means that conceptual processing (i.e. semantic, or “deep” encoding) might not be required to massively improve item recognition, since recent exposures (i.e. perceptual knowledge) seems sufficient. However, conceptual processing seems to be mandatory to correctly reject associated lures, so enhancing the efficiency of retrieval processes. In addition, the fact that high-confidence Hits were more frequent for famous faces seems to reinforce this idea of enhanced retrieval efficiency, and so did the findings of a selective increase in recognition memory for the context in the PEK condition.

Box 8. Challenging the Levels-Of-Processing framework?

A core prediction of the LOP framework is that semantic processing should increase memory formation, but also should yield higher false alarms in recognition memory. The findings of increased Hits to similar levels for stimuli with both Pre-Experimental Knowledge and Experimental Knowledge, and the findings of fewer False Alarms for stimuli with Pre-Experimental Knowledge than Experimental Knowledge contradict the LOP prediction.

In line with prior proposals (Gagnepain et al., 2008; Gagnepain et al., 2011; L. M. Reder et al., 2013; Reder, Liu, Keinath, & Popov, 2015) we have suggested that processes outside the range of learning mechanisms *per se* could account for this pattern of results.

When facing with familiar stimuli, perceptual and conceptual fluency refer to the ease of processing of these stimuli, due to past experiences (Oppenheimer, 2008). Generally, increased fluency causes inflation in Hits and FAs rates (Whittlesea, 2002), because fluency on its own is not systematically attributed to recent exposures. However, given that fluency by definition generates a subjective experience of increased ease of processing, our suggestion is that it can modulate the other cognitive processes involved at encoding. In the case of face-scene associations, increased fluency for face may free-up attentional and working memory resources that are necessary to fulfil the task instructions, namely imagining an event where the participant himself would meet the person depicted by the face, in the background that is displayed as a landscape. Such a task typically requires the binding of separate elements to further make a pleasantness judgement (see Experiments 3a & 3b), which cannot be achieved without the involvement of attention and working memory. Thus, we suggest that fluency triggered by the face displayed at the centre of the screen may have favoured these binding processes. When successful, they should ideally result in the building of a representation that is distinctive enough to resist interference. This account would predict that **more fluency at study would yield a more distinctive representation that would therefore support higher recognition for the face-scene association.**

Coming back to the comparison between EK and PEK, familiarized faces (EK condition) are expected to yield mostly perceptual fluency, while famous faces (PEK condition) should trigger both perceptual and conceptual fluency. Therefore, associative binding for famous faces is expected to be more successful than associative binding for familiarized faces. We have brought evidence that increasing stimuli distinctiveness by using a

different background scene for each faces indeed improved associative memory, but only for the PEK condition, in accordance with our proposal. Furthermore, increased distinctiveness of the materials resulted in an overall decreased accuracy in item recognition that did not interact with the different prior knowledge conditions. Again, this is supportive of our view pointing towards the role of fluency and working memory / attentional resources allocation, since changing the study contexts at each trial unsurprisingly would leave fewer attentional resources for the processing of the face only.

Box 9. The role of fluency, attention and working memory resources

In an associative memory task, increasing the distinctiveness of the paired stimuli increased source memory and decreased item memory, leaving the pattern of prior knowledge benefits unchanged. We suggest that more fluency (perceptual and / or conceptual) at study, due to prior knowledge, may free-up attentional and working memory resources for context processing. This might enable more efficient item-context binding, thus increasing the distinctiveness of the association.

Perspective 6. Testing the role of working memory in associative binding processes during encoding.

A testable prediction from the above proposal is that a dual-task paradigm should reduce the advantage associated with prior knowledge for associative memory. For example, in a condition where subjects would perform a visual span task while encoding face-scene associations, prior knowledge should not yield superior source memory.

Interestingly, in a recent investigation of the impact of unitization on recollection and familiarity, it was reported that increased unitization could improve associative memory, leaving item memory unchanged (Parks & Yonelinas, 2015). The authors manipulated levels of unitization or word pairs (Expt. 1), essentially manipulating how the emphasis was placed on the semantic relationship between individual words in a pair at encoding. These findings are in line with the proposals that prior knowledge at encoding, and especially in the form of large semantic knowledge accumulated over the lifetime, may trigger learning processes that augment long-term memory item-context binding.

The highly dynamic view of how pre-existing representations, processing fluency, item and associative encoding interact together in the service of learning clearly needs further investigations. One possible avenue could be to further investigate the benefits of perceptual vs. conceptual fluency at encoding, for example by manipulating the number of exposures prior to the study phase. One could contrast single vs. multiple prior exposures of unknown faces to increase perceptual fluency. We would predict that repeated prior exposures should allow associative memory for unknown faces to get closer to the level of associative memory for famous faces.

Finally, an important experimental perspective resulting from our results in Experiments 3a & 3b is that source memory assessment within classical designs might well underestimate performance.

Box 10. The limitations of source memory paradigms

Source memory tasks typically use lists of individual items that are presented at study bound with a limited number of contexts, most often two (e.g. 2 different colourful backgrounds, 2 different task instructions, 2 different voices associated with the target item, 4 spatial locations, etc.). In the present thesis, we have shown that using as many different contexts as the number of individual items yielded a significant increase in associative memory, and also impacted item memory. We believe this should be taken into account and investigated further.

Prior knowledge triggers age-resistant learning processes

The present work has also brought strong evidence, across two independent studies, that **the benefits of prior knowledge were age-resistant, and this was also true considering associative memory.**

This is a striking result given the well-acknowledged associative deficit hypothesis in aging (Naveh-Benjamin, 2000), stating that memory for association is particularly sensitive to aging. As stated above, due to floor effects in our tasks, our findings should be taken with caution, and this especially holds since we did not replicate the associative deficit expected in elderly subjects, for novel stimuli. Still, a consistent result was that

elderly subjects benefit from pre-experimental knowledge as well as their youngest counterparts, including when considering source memory associated with high confidence ratings. Similarly, Hits rates associated with high-confidence ratings, often considered as mainly reflecting recollection-based retrieval, benefited from pre-experimental knowledge to the same extent in young and elderly participants. Again, given the relative frailty of recollection processes in aging, these findings look of great matter to us.

First, as we discuss below, they suggest that new declarative learning supported by prior knowledge of semantic nature may depend on neural substrates that are relatively spared by physiological aging.

Second, as some authors recently suggested (Parra, 2017), we need memory tasks that show little sensitivity to aging if we are to discover novel cognitive markers of neurodegenerative diseases associated with age, like Alzheimer's disease. In the present work, we have made one step forward in that direction.

Perspective 7. Benefits of Pre-Experimental Knowledge as a cognitive marker of abnormal memory decline with aging?

A promising perspective here is to build a recognition memory task allowing to quantify the degree of benefits associated with pre-experimental knowledge, in other words a task inspired by our design that could provide a standard measure of the expected discrepancy between memory for novel vs. familiar stimuli. Given that this index should have only little, if any, dependency on age, it may provide a very useful score to discriminate elderly patients with genuine memory impairments. More specifically, as discussed below, one testable prediction could be that incident Alzheimer's Disease might be detected through a reduced discrepancy between source memory for unknown but familiarized faces, and famous faces.

The fMRI study described in Experiment 4 replicated the finding of increased source memory for famous over unknown but familiarized faces in an independent sample of carefully screened healthy elderly. Importantly this time, the task design did not contaminate the data with floor effects. Yet, we observed on average a 15% increase in source memory in the PEK condition, which is strikingly close to the results we had in the behavioural studies. Again, this critically confirms that when semantic knowledge is

available for an item at encoding, the benefits for subsequent memory extend from item to context recognition.

However, **in our sample of patients with early Alzheimer's disease, the benefit of prior knowledge did not hold anymore.** This, to us, may represent **an important step towards a novel cognitive marker of Alzheimer's disease well before the dementia stage.**

Third, our results fit with an emerging literature suggesting that the elderly may disproportionately benefit prior knowledge (Badham et al., 2012, 2015; Castel, 2005; Naveh-Benjamin et al., 2003; Umanath & March, 2014). Still, recent efforts to demonstrate how associative memory deficits could be alleviated when separate elements share a semantic relationship at encoding have sometimes failed (e.g. through unitization, (Delhaye & Bastin, 2016; Delhaye, Tibon, et al., 2018). Further research is therefore required to better characterize the boundary conditions for prior knowledge to enable better associative memory.

Fourth, and as suggested before, our findings speak for a more thorough consideration of how prior knowledge may play a role in the usual psychological tests used in clinical settings. Considering that existing long-term memory representations clearly help the elderly to increase associative and item memory, the large number of tests that use meaningless, previously unknown, materials (think of the Rey Complex Figure, but also visual memory subtests of the Wechsler Memory Scale, the Warrington Memory Test, in French most visual subtests of the “Batterie d’Evaluation de la Mémoire” from J.L. Signoret, etc.) might lead to overestimate memory impairments. Conversely, as we discuss below, other tests involving familiar materials may underestimate memory performance.

Thus, one **important perspective regarding clinical neuropsychology** is that **the lack of consideration for the role of prior knowledge** in new learning may result in **increased type I or type II errors** when neuropsychologists interpret their patients' scores on memory tests.

Neural routes for prior knowledge-based declarative learning

Our work with patient KA has provided clues for the neural basis of prior-knowledge based declarative learning. We have suggested that these learning processes enabling

better item and source memory in controls and in KA may not rely upon the hippocampal system. One possibility that we have discussed above is that prior knowledge, and especially in the form of an existing conceptual network (a notion rather close to the concept of schema), would trigger unitization processes, thus favouring binding operations in long-term memory that would not be dependent on hippocampal operations. This account can in our view be strengthened by our findings that long-term memory binding of famous faces with their spatial (scene) context was preserved in aging, despite the acknowledged deleterious effects of age on the hippocampus. Prior studies have suggested that memory for stimuli that are congruent with existing knowledge could be preserved as long as the anterior sub hippocampal structures are preserved, even in case of bilateral hippocampal damage (e.g. Kan et al., 2009). More recently, it was shown that item familiarity due to recent exposures as well as familiarity resulting from lifetime accumulated knowledge (quite similar to the EK and PEK condition that we used in this thesis) could be encoded within the perirhinal cortex (Bowles et al., 2016; Duke, Martin, Bowles, Mcrae, & Köhler, 2017). We believe this reinforces our hypothesis that prior knowledge may increase (conceptual) fluency during encoding, in turn facilitating unitization (or binding) operations, and this would allow further recognition of the association to rely on familiarity (Parks & Yonelinas, 2009, 2015). One important prediction however is that any damage to the perirhinal cortex should result in an inability to benefit prior knowledge in new learning. We actually have reported evidence consistent with this idea in our fMRI experiment (Experiment 4). In fact, we found that patients with early Alzheimer's disease and relatively slight cognitive impairment, not demented, totally failed to increase memory performance in the PEK (famous faces-scene combinations) condition. Moreover, the patients lacked the BOLD signal observed in controls as predicting associative memory. Yet, such activity in controls was correlated with source memory performance.

Box 11. Perirhinal cortex damage as observed in early Alzheimer's Disease prevents from benefiting Pre-Experimental Knowledge.

We have brought fMRI evidence for the involvement of the perirhinal cortex in subsequent associative memory effects for stimuli carrying Pre-Experimental Knowledge. This effect was lacking in early AD patients. These findings support the idea that early memory symptoms might have more to do with subhippocampal structures than hippocampal dysfunction, and that memory for highly familiar items may be particularly vulnerable. This is strikingly congruent with the patients' complaints, namely day-to-day memory losses for personally relevant, daily routine activities.

These results are important because it is well acknowledged that early tau pathology in Alzheimer's disease first occurs in the rhinal cortices (Braak & Braak, 1991; Delacourte et al., 1999). Not only this pattern of results fit with the idea that sub hippocampal structures may, together with other structures possibly within the "Anterior Temporal" network (Ritchey & Ranganath, 2015), support new learning when pre-existing semantic representations are available, but also they suggest that **we probably underestimate the memory impairments in early Alzheimer's disease**. Given that most of the testing procedures used involve multiple-trials learning, typical assessment thus imply gradual familiarization with initially unfamiliar materials, which broadly corresponds with the EK condition we have used. In that condition, patients actually performed fairly well, while they showed severe impairment in the condition involving pre-experimental knowledge. **This aspect of the present thesis dramatically highlights how prior knowledge and beyond, the kind of prior knowledge involved in memory tasks, truly matters.**

Beyond memory disorders: the role of retrieval processes in new learning

The case study that launched the present work brought evidence for the existence of an efficient learning process that does not depend on the hippocampal system. We have argued that MTL reorganization following early injury can have triggered a neurodevelopmental shift favouring the Anterior Temporal system that in turn may be the foundation for unitization processes at encoding in the service of familiarity-based recognition memory. As we suggest, this would occur only if existing long-term

knowledge representations might be reactivated at encoding, thus being responsible for the triggering of an automatic, fast and efficient learning pathway.

While this may occur in patients with developmental amnesia, there is no reason why these learning processes could not take place in healthy subjects as well.

A second thought on what is learning, as extensively presented in the introduction section, suggests that memory-guided behaviours must result from fast and rather automatic processes, instead of slow “episodic recollection”, at least in many of our daily routines. **Learning is therefore much more about what we know than what we don't.**

If learning is supposed to basically refer to our ability to detect environmental regularities, our work so far has contributed to the theoretical frameworks that emphasize the role of existing representations (i.e. regularities detection) in learning. Therefore, what we need is to focus on the processing approaches that aim at predicting how knowledge and learning interacts in the service of behaviour, rather than furthering the structural approach that has provided useful heuristics (i.e. semantic-episodic distinction), but little mechanistic accounts for explicit learning. As an example, a promising perspective could be to consider that during learning, acquisition and retrieval processes largely overlap. When dealing with familiar stimuli, we have suggested that perceptual processing up to the level of e.g. the entity (a face, an object, etc.) may trigger additional retrieval processes, in that current sensory inputs match with existing representations. It is well acknowledged that these retrieval processes are associated with increased long-term memory (i.e. **retrieval practice effect or “testing effect”**, Roediger & Karpicke, 2006). Thus, an outstanding issue to further address is whether retrieval processes involved during prior knowledge-based learning contribute to improve further remembering, and on which neural grounds.

Perspective 8. The role of repeated retrieval in new learning

Prior knowledge dramatically enhances new learning. The impact of prior knowledge implies that during learning, sensory input “matches” to some extent with existing long-term representations. This is a defining feature of successful memory retrieval, which, when repeated across time, is known to enhance long-term retention, an effect called “retrieval practice” or “testing effect”. An interesting perspective would therefore be to investigate whether the testing effect can occur under circumstances that are favourable even for patients with amnesia, i.e. during recognition memory. Put simply, can repeated successful recognition yield better long-term memory retention?

We have started examining this question as shown in Appendix A. Complementary experiments are currently running, but preliminary results suggest so far that repeated retrieval as it occurs in recognition memory tests does improve long-term retention. Furthermore, data speak for a retrieval practice effect even when retrieval processes are highly constrained and likely to be limited to fast, familiarity-based recognition. This may hopefully bring new perspectives to alleviate memory disabilities in hippocampal amnesia, and also to optimize teaching techniques in the field of educational.

Limitations

As for any experimental research, several limitations must be outlined here. One major limitation of our work is that the tasks we designed in Experiments 3a and 3b, proved too difficult regarding the associative memory component. This is why we should consider the above interpretation with great caution, since they await further replication in larger samples and with maybe fewer target stimuli. Nonetheless, we wish to underscore that our effort to replicate, in a larger independent sample, our first findings was successful, so that our conclusions, while not definitive regarding associative memory, can be considered as robust for item recognition. Moreover, behavioural findings from Experiment 4 largely replicate the advantage of pre-experimental over experimental knowledge in healthy elderly, thus reinforcing the idea that the nature of prior knowledge does matter. A related limitation is that we failed to replicate the associative deficit expected in older participants, which again may relate to issues regarding the

optimal number of trials. This is an important caveat and we should keep in mind that stronger evidence for the role of prior knowledge in aging might arise in further studies that could demonstrate prior knowledge benefits above and beyond observed deficits associated with age, on an intra-individual basis. Another limitation is that we only asked participants in Experiments 3a, 3b, 4 & 5 to make a fame judgment on all the faces involved in the experiment. This was further used to discard from analyses the items for which inaccurate fame judgments were performed. While this represents an important methodological effort that has generally not been completed in prior studies, it does not allow to completely rule out outliers responses. For example, a correct fame judgment made on a famous face does not prevent from situations where, in fact, the subject incorrectly identified the face (e.g. confusion between two celebrities). To circumvent this limitation, we could have better tested the actual knowledge of the participants for each famous face. Use of a quantitative scale would furthermore allow, with sufficient trials, to investigate whether the amount of semantic knowledge about a face could modulate the benefits of prior knowledge on subsequent memory.

Regarding studies with patient KA, a critical limitation of our work is that we could only speculate on the brain basis for his particular profile, rather than drawing direct inferences on this issue. This is because we did not manage to run an appropriate experimental design involving e.g. task-based fMRI with patient KA. This was something we planned to do, however, with accumulated knowledge on these techniques, it soon appeared that gathering BOLD signal data in a single case vs. a control group with the hope of elucidating brain-behaviour relationships is a very hard challenge. We therefore plan, as stated before, to run a rs-fMRI experiment hopefully this summer that may give us some preliminary findings. In the meantime, inferential reasoning like in the tradition of neuropsychology was the best we could use.

Finally, regarding our fMRI study with early AD patients, sample size is a main concern, and it was really challenging to get this number of participants. This is why we will publish the article as a preprint first, together with hopefully a full open access to our data, so that further replications or meta-analysis might be doable. Moreover, our conclusions regarding the lack of involvement of the perirhinal cortex in the subsequent memory effects in AD must also be taken with caution. It is well acknowledged that even in the earliest stages of MCI due to AD, tau pathology extends far beyond the rhinal cortices, so that any generalization about the relationships between this region and prior knowledge-based learning cannot be taken at face value. We believe an interesting promising

complementary approach would be to investigate possible correlations between perirhinal cortices volumes and an index of the PEK vs. EK discrepancy for source memory, as suggested in Perspective 8 above, in a sample of elderly participants with various degrees of cognitive decline.

Conclusion

In this work, we have put forward the utmost importance of existing knowledge for new learning in declarative memory. Pre-existing representations profoundly affect the way we encode, consolidate and retrieve our experiences. In our opinion, this is an overlooked fact in the field of memory research and, accordingly, only recent theoretical frameworks aim at accounting for such influence.

We suggest that prior knowledge could trigger a rapid learning route for conscious memories that is largely independent from the hippocampal system. With this respect, we have provided very strong evidence in patient KA for the existence of such learning pathway. Further neuropsychological studies with amnesic syndromes of various aetiologies should clarify the boundaries of this learning route. We propose that focusing on the relationships between “fast-mapping” and intense conceptual interests in a developmental cognitive perspective might prove very insightful. More research is warranted here, given the deep impact this may have for memory-impaired patients.

Under some circumstances, we also have shown that prior knowledge can alleviate the impact of age on memory, whereas patients with early Alzheimer’s Disease proved totally unable to benefit prior knowledge. We believe that this is a major contribution of our work. Not only it opens perspectives for new cognitive markers of the disease, but also it suggests that neuropsychological assessment of learning and memory may well be riddled with type I and type II errors. Taking into account prior knowledge in the development of new assessment tools, and in current interpretations of test scores, could be an important guideline following the present thesis. Similarly, we report on the possible underestimation of associative memory performance in the literature using typical source memory paradigms, which again should be taken into account from now on.

Finally, and hopefully, this work could also be fruitful regarding the field of education, emphasizing on some critical factors involved in the acquisition of new knowledge.

Overall, our learning system may well be biased towards the acquisition of new memories about what we already know rather than about what we ignore.

“Case studies continue to illuminate the cognitive neuroscience of memory”

Rosenbaum, Gilboa, & Moscovitch, 2014, Annals of the New York Academy of Sciences

“Je pense que je l’ai vu, mais je suis pas certain, pas sûr... non, je peux pas dire”

Patient KA, July 2017.

[English translation:

“I think I saw it already, but I am not certain, not sure...no, I can’t tell.”]

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Appendix A: Experiments 6a & 6b. Does repeated recognition memory result in a testing effect?

Scientific valorisation

Poster presented at the “Journée de printemps de la Société de Neuropsychologie de Langue Française”, Liège, Belgique, May 2016

Poster presented at the International Conference on Learning and Memory, Irvine, CA, USA, July 2018

Oral communication at the “Forum d’hiver de la Société de Neuropsychologie de Langue Française”, Paris, France, December 2017

Oral communication at the International Conference on Memory (ICOM 6), Budapest, Hungary, July 2016.

Retrieval practice based on recognition memory:

A test of the retrieval effort hypothesis

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Abstract

Retrieval of information from memory yields better long-term retention than mere restudying the very same information, a finding called “testing effect” or “retrieval practice effect”. While the testing effect has been the target of intensive research in recent years, there is no agreement on its theoretical underpinnings. A core prediction of the dominant retrieval effort hypothesis has received very little attention. Indeed, retrieval practice should not be beneficial for further retention if retrieval is based on effortless, automatic processes. In this study, we aimed at testing this prediction in two experiments using recognition memory tasks. In the first experiment, learning schedules were manipulated between participants, contrasting repeated studying, repeated testing and alternate Study-Test phases. In the second experiment, we aimed at ruling out the contribution of recollection to retrieval with a speeded recognition memory paradigm, which allowed contrasting the effect of repeated study vs. repeated testing on further retention. In both experiments, we found an advantage for testing schedules, despite less exposure to the learning material. The second experiment importantly yielded equivalent retention after 6 months for Study and Test intervening conditions, even when retrieval practice was largely based on familiarity. We therefore failed to verify an important prediction of the retrieval effort theoretical framework.

Keywords: testing effect; retrieval practice; retrieval effort; recognition memory; familiarity

Introduction

Retrieval of information from memory leads to better long-term retention than merely restudying the same information, a finding called “testing effect” or “retrieval practice effect” (Bowles et al., 2016; Köhler et al., 2017). Importantly, the testing effect occurs even when the number of tests and study events is equated, so that it cannot be explained by a simple effect of extra-re-exposure to the material (Carrier & Pashler, 1992). Beyond the great variability in the experimental designs used across previous studies, the testing effect is usually observed using a three-step procedure. First, during an initial encoding phase, to-be-remembered stimuli are presented. Second, during an intervening learning phase, either encoding is repeated (intervening study trials) or, in the experimental condition, memory for the stimuli is tested (intervening test trials). Third, after a variable delay, a final test assesses memory for the previously learned information. As long as exposure to the material is equivalent between test and study trials, observation of a better memory after an intervening phase of test trials is the key finding that characterizes the retrieval practice effect. This finding was replicated many times with different kinds of materials (for a recent meta-analysis, see (Carrier & Pashler, 1992)). The retrieval practice effect represents a major move forward in our understanding of the factors contributing to successful learning, as it points toward a break in the typical paradigm used in learning and memory research. Indeed, the testing effect clearly suggests that testing can serve as a learning event, and thus, that learning does not occur only during study phases.

Surprisingly, despite an impressive surge in research with more than 40 studies on the topic over the last 3 years, we still lack a consensual account of the mechanisms driving the testing effect. Furthermore, among the numerous theories proposed, not all proved testable or, alternatively, can only be tested using specific experimental material (e.g., word pairs, Carpenter, 2011; Pyc & Rawson, 2009). The present study, therefore, aimed at testing a core prediction of one of the most influential accounts for the testing effect, namely, the retrieval effort hypothesis.

An influential account for the retrieval practice effect states that the difficulty of the initial retrieval is responsible for the effect (Carpenter & Delosh, 2006; Glover, 1989). This account is derived from the desirable difficulty framework (Bjork, 1994), but the idea that the difficulty of learning may result in better retention can be tracked back to Ebbinghaus' seminal studies: "what is learned with the greatest difficulty is best retained", (as cited in(Bjork, 1994). The general idea is that retrieval from memory during the intervening phase implies an active updating of the memory trace together with the creation of multiple retrieval routes. This is supposed to increase the probability of further recall by contrast with passive restudying (Roediger & Butler, 2011). Whereas the kind of elaborative processes and mechanisms involved remain to be fully specified, much evidence has supported this influential account for the testing effect. For example, manipulating the amount of letters available as cues in a stem-completion paradigm during the intervening phase led to an inverse relationship between final test performance and the amount of cues needed during intervening retrieval (Roediger & Butler, 2011). In another study, participants had to learn target words presented in a cue-target words pairs paradigm where researchers manipulated the strength of the association between cue and target. As hypothesized, they found better performance at final test for weak pairs by comparison with strong pairs (Carpenter, 2009), supporting the idea that maximizing the effort associated with retrieval will increase the benefits of testing (i.e., retrieval effort being stronger for weak pairs like "Basket – Bread" than strong pairs like "Toast – Bread"). Former research manipulated the testing format used during the intervening tasks, and demonstrated that free recall led to better performances at final test than cued recall, which in turn gave rise to better performances than recognition (Glover, 1989); again supporting the idea that more elaborative processes involved during the critical test trials may increase the effect of testing. The retrieval effort hypothesis therefore assumes that controlled, elaborated, effortful retrieval processes during the intervening phase are responsible for the retrieval practice effect. Conversely, a core prediction of these theories is that automatic, effortless retrieval processes should not lead to a testing effect.

While free or cued recall procedures generally used in the testing effect literature strongly rely upon recollection of the context associated with the learning event, recognition memory (i.e., the judgment of prior occurrence) involves more automatic retrieval processes, distinct from contextual recollection (Glover, 1989). Indeed, in a typical recognition memory task, subjects are asked to discriminate between lures and targets by reference with the study phase. Being presented with the target information during target trials, subjects can rely on familiarity judgment to give a correct answer, thus retrieving prior occurrence of the stimuli through automatic processes. More specifically, visual recognition memory in humans has been characterized as a very efficient system, with a massive storage capacity. For example, single-trial learning of 10 000 pictures for 5 seconds each yielded an impressive recognition memory accuracy over 80% after a 2 days delay (T. F. Brady, Konkle, Alvarez, & Oliva, 2008; Standing, 1973). One can therefore wonder whether recognition memory-based retrieval practice may be of benefits for long-term retention. Again, because recognition memory retrieval is supposed to be achieved through rather effortless, automatic, processes, the dominant retrieval effort hypothesis predicts that it should not be the case. As briefly reviewed below, we suggest that evidence is not conclusive with this respect.

Previous studies brought some evidence, although limited, that alternate-forced choice recognition testing during the intervening phase may lead to a testing effect (T. F. Brady, Konkle, Alvarez, & Oliva, 2008; Standing, 1973); but see Duchastel, 1981). These studies used multiple-choice testing during the intervening phase while final test formats were based on either free or cued recall. Importantly however, Roediger & Marsh (2005) also showed that the positive testing effect due to prior testing under multiple-choice format came at some cost. Indeed, the lures used in the intervening testing phase were often chosen as wrong answers during the final cued recall test (see also Odegard & Koen, 2007). Consequently, it is generally assumed that when recognition memory is used as the intervening task, this may at best lead to a very limited testing effect, and at the cost of false memories which overall tend to discard any eventual benefit of

recognition memory-based retrieval practice on long-term retention (see also Kang, McDermott, & Roediger, 2007; McDaniel & Masson, 1985).

It is worth noting that exception made of Carpenter & DeLosh (2006)'s study who used words lists, these studies used prose passages as material to be learned, a common material across testing effect studies. Use of prose passages implies the elaboration of rather complex alternate forced choice recognition memory tests, for example asking to complete the following statement: "In the last stage before a blackhole is formed, a detonation occurs, known as a: 1) starbust; 2) explosion; 3) blastula; 4) supernovae" (Meyer & Logan, 2013). The cognitive processes involved in such a task cannot be taken as examples of automatic, effortless retrieval processes like the one involved in simple Old/New recognition memory tasks, even if elaborative processing required here remains limited by comparison with a typical free recall task (Meyer & Logan, 2013). Supporting this view, it has been shown that when multiple-choices recognition tasks are built to intentionally trigger elaborative, controlled retrieval processes, they may give rise to testing effects even larger than after cued recall procedure during the intervening phase (Glover, 1989). These data are therefore broadly supportive of the retrieval effort hypothesis, and would suggest that a testing effect driven by simple Old/New recognition memory procedures is unlikely.

Little work has been done to constrain the intervening tasks to very simple, automatic retrieval tasks, and then assess whether a testing benefit still holds. We are aware of only three studies, the most cited being (Little et al., 2012) (experiment 4). However, since the authors did not use a study-only control condition, their conclusions are difficult to align with more recent controlled studies on the testing effect. However, in a more recent report, Carpenter and DeLosh (2006) orthogonally manipulated the type of intervening tasks within participants (restudying, free recall, cued recall and Old/New recognition) and the type of final test between participants (free recall, cued recall and Old/New recognition) to highlight potential benefits of retrieval practice for lists of nouns (experiment 1). They failed to find any interaction between the intervening task and the final test type, suggesting that the retention across the different types of final test was not

modulated by the kind of intervening task. Nonetheless, an important result was that when an intervening recognition task was used, no testing effect was found. By contrast, an earlier study using nouns found that a simple Old/New intervening recognition task did increase both recall and recognition performances during final tests (Mandler & Rabinowitz, 1981), but at the cost of an increase in false alarms rate. One important difference between these studies lies in the delay before final test, which lasted 5 minutes in Carpenter and DeLosh's experiment (2006) versus 1 week for Mandler & Rabinowitz's (1981). Given that retrieval practice effects are generally observed after long delays but are sometimes absent at short delays (Mandler & Rabinowitz, 1981), this might explain the discrepancies. Furthermore, it is noteworthy that in the Mandler & Rabinowitz's study, recognition memory accuracy during the intervening phase was very high with a Hit rate around 90% and a discriminability index d' superior to 2.5. This is not surprising given that participants were tested on 50 items only, including 25 targets items, which is far from the large storage capacity of recognition memory in humans, as stated above (in the case of recognition memory for words, see (Roediger & Butler, 2011)). Such a high accuracy during the intervening learning phase actually suggests that the participants in that study were far below their learning possibilities. Such a ceiling effect in the intervening learning phase may have led to underestimate the benefits associated with recognition memory-based testing. The same comment applies to Carpenter & Delosh's study (2006) where intervening testing via recognition memory involved successive blocks where 8 targets nouns were to be circled among 8 distractor nouns. That brief review of the use of recognition memory tasks during intervening phases suggests that we lack experimental data to determine whether or not effortless, automatic, retrieval processes can drive a testing effect.

In summary, while the testing effect has been the target of intensive research in recent years, there is still no agreement on its theoretical underpinnings. A core prediction of the dominant retrieval effort hypothesis, which is that retrieval practice should not be beneficial for further retention (if retrieval is based on effortless, automatic processes) has received little attention.

Our aim here was, therefore, to assess whether recognition memory-based retrieval can or cannot lead to a testing effect. In a first experiment, we adapted a typical learning schedule from the testing effect literature, with intervening tasks and final test based exclusively on Old/New recognition tests. In a second experiment, we adapted a speeded recognition memory task known as the “Speeded and Accuracy Boosting procedure” (Besson, Ceccaldi, Didic, & Barbeau, 2012) to further assess whether or not familiarity-based retrieval practice could overcome repeated study regarding retention at short (i.e., 25 minutes) and long-term (i.e., 6 months) delays. Finally, it is noteworthy that despite the importance of pictures in learning, either in educational settings or in everyday lives, there is a dearth of studies using that kind of stimuli in the testing effect literature (but see Carpenter & Pashler, 2007; Tse, Balota, Moynan, Duchek, & Jacoby, 2010; Wartenweiler, 2011; Wheeler & Roediger, 1992). This is why pictures of objects were used as stimuli in the following experiments.

Experiment 1

Methods

Stimuli

930 photographs of objects were taken from the Bank of Standardized Stimuli (Brodeur, Guérard, & Maria, 2014), then resized to 390x390 pixels and reformatted in an uncompressed format (i.e., .bmp). 210 pictures were randomly sampled across participants to serve as targets, and 210 to serve as distractors. All stimuli were presented on a grey background.

Experimental setting

Stimuli were presented on a laptop computer screen, using E Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA). Subjects responded by left-clicking on the button below the track pad, and response accuracy was always emphasized in the instructions.

Experimental design and procedure

An initial encoding phase and a final test phase were common to all participants. During the initial encoding phase, participants were instructed that they would have to memorize a series of photographs for further recognition. Each stimulus was presented for a fixed duration of 700ms, with a 250ms inter-stimuli interval. The 210 targets were presented in a random order, across three blocks of 70 stimuli with a self-paced break between blocks. During the final test phase, participants were explained that they would be presented a series of Old and New stimuli. They were instructed to respond as fast as possible for an Old item (Go response), and to not respond in case of a New item (No Go response). The 420 stimuli were presented for 700ms each, with a jittered inter-stimulus interval ranging from 100 to 500 ms. Subjects were provided with an immediate visual feedback for their response accuracy, lasting 600 ms, after each recognition trial. Correct No Go and correct Go responses were followed by the word “Bravo” presented at the center of the screen, incorrect responses by the word “Incorrect”; and “Too late” appeared whenever no response was recorded within the 700 ms delay. 6 successive blocks of 70 stimuli were used, with a self-paced pause between blocks, the order of presentation being fully randomized across participants.

Three different learning procedures were administered during the intervening phase: the Study-Test (ST) procedure, the Study (S) procedure and the Test (T) procedure. Each participant was randomly assigned to one group (ST, S or T) in a cross-sectional design. An overview of the

experimental design is provided in Figure 1. In the ST group, a learning cycle consisted in a Study phase identical to the initial encoding phase, followed by a Test phase, identical to the final test phase described above. In the S group, a learning cycle consisted in a Study phase identical to the initial encoding phase. In the T group, a learning cycle consisted in a Test phase identical to the final test phase. Within each group, two successive learning cycles were administered. For each recognition memory phase of the experiment (either during learning cycles or for the final test), a different set of foils was used. This means that $3 \times 210 = 630$ stimuli were randomly sampled from our original set of stimuli to be used as distractors in the Study-Test group and Test group, while only 210 stimuli were required for the Study group. Importantly, for each group, a 3 minutes cartoon randomly selected among a set of 12 cartoons was presented as a distracting task, after the initial encoding phase and between each learning cycle.

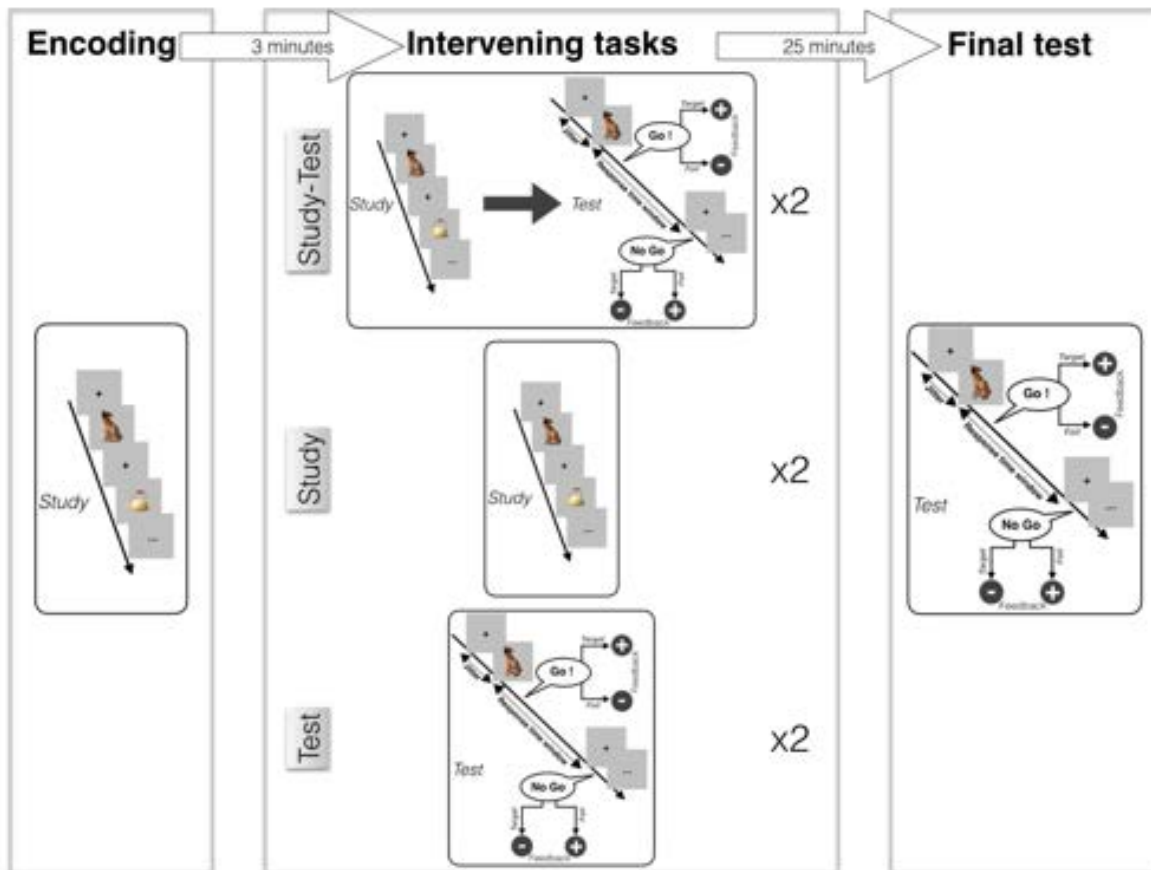


Figure 1. Experiment 1, design overview. After an initial encoding phase common to all participants, three groups (Study-Test, Study, Test) received distinct learning schedules. In the Study-Test group, a study phase preceded a test phase, this study-test cycle was repeated once; in the Study group, learning consisted in two successive study phases; in the Test group, participants received a recognition memory test twice. After a fixed delay of 25 minutes, every participant was administered a final recognition memory test.

Our design allowed us to contrast three learning procedures: (1) In the Study-Test group, learning was tested through a typical alternation of encoding and retrieval phases, as it occurs in most of the multiple-trials learning tests, except that retrieval trials consisted in a recognition memory test, instead of the free or cued recall procedures usually used across testing effect literature; (2) in the Study group, repeated encoding phases imitates the “Study” condition usually administered in the typical testing effect experiments; (3) in the “Test” group, we replaced the typical repeated free recall trials used in prior testing effect studies with recognition memory trials. Critically, this design implies a strong difference in study duration between groups. Whereas the total time spent explicitly studying the stimuli was set at 7.35 minutes in the Study-

Test and Study groups, it was highly restricted to 2.45 minutes in the Test groups. That is, time spent by participants to explicitly study the to-be-learned stimuli for further memory testing was three times less important in the Test group.

After the last learning phase and during the delay before the final test phase, participants completed a general health questionnaire and the McNair cognitive difficulties scale (McNair & Kahn, 1983), the French version of the National Adult Reading Test (Mackinnon & Mulligan, 2005), and the Logical Memory subtest of the Wechsler Memory Scale, 3rd Ed. (Wechsler, 2001). These tasks filled a fixed delay of 25 minutes between the last learning trial and the final test.

Hypotheses

Following the retrieval effort hypothesis, retrieval from memory derived from repeated recognition memory tasks (i.e., correct discrimination between Old and New items) should not benefit final testing, because judgment of prior occurrence theoretically does not typically involve effortful retrieval processes. Thus, we expected performance at final test to be positively influenced only by the time spent encoding stimuli as well as the global exposure duration to the material.

Participants

90 healthy young subjects, undergraduate students from Rennes University provided written informed consent for their participation to the study, which was conducted in compliance with the Declaration of Helsinki. The health questionnaire revealed recent psychiatric condition and / or psychoactive medication in 10 cases. 2 participants apparently lacked motivation, resulting in very poor performances. 1 participant scored significantly below expected performance from

available norms at both immediate and delayed trials of the Logical Memory subtest. Finally, a software bug resulted in the loss of one participant's data. This resulted in the final inclusion of 76 healthy participants (57% females), with normal memory functioning and free of any medical or psychological condition. Overall, participants were aged 19-30 years old (median = 22), had completed 10-20 years of education (median = 15), and had a median full-scale estimated IQ of 107 (ranging from 91 to 124) (see Table 1 for socio-demographic, questionnaires and logical memory data).

Groups	Sex ratio %Female	Age	Years of education	f-NART FSIQ	CDS	Immediate Recall	Delayed Recall
Study-Test, N=27	63	.15 (.4)	15.04 (2.3)	106.47 (6.4)	48.85 (15.4)	12.37 (2.9)	12.37 (3.0)
Study, N=24	68	.25 (.8)	15.08 (1.6)	107.17 (6.36)	52.04 (15.3)	12.08 (2.7)	12.00 (2.9)
Test, N=25	44	.56 (.1)	14.20 (2.0)	106.31 (3.73)	52.40 (13.4)	12.12 (2.9)	11.48 (2.6)

Table 1. Experiment 1. Sociodemographic and psychometric background of participants. Means are displayed above standard deviations (in brackets). F-NART FSIQ= French version of the National Adult Reading Test, estimated Full-Scale IQ ; CDS= Cognitive Difficulties Scale ; Immediate & Delayed recall are expressed as scaled scores from Wechsler Memory scale, 3rd Ed. The three groups were matched for Age, Sex ratio, Education, FSIQ, CDS, immediate & delayed verbal recall (Bayes Factors well below 1, BF₁₀ range= [0.121 - 0.880]).

Statistical analyses

Accuracy at final test was operationalized through signal detection theory analyses, with the following dependent variables: Accuracy (percentage of correct responses), Hits (percentage of Go response to targets) and FAs (percentage of Go responses to foils).

We tested our hypothesis within a Bayesian probabilistic framework rather than using the standard frequentist approach (Null Hypothesis Significance Testing), given the acknowledged limitations in the use and interpretation of p-values (see (Brodeur, Guérard, & Maria, 2014)). We therefore computed Bayesian factor values (BF₁₀) using the JASP software v. 7.5.6. (Love et al.,

2015; for very recent similar approach in experimental psychology, see e.g., Kelly & Heit, 2017). The Bayes Factor (BF₁₀) provides an odds ratio for the alternative vs. null hypotheses, with values < 1 favoring the null hypothesis and values > 1 favoring the alternative hypothesis. Importantly, because Bayes factor is a probability ratio (i.e., ratio of the likelihood of data under the alternative vs. the null hypotheses), it allows comparing the respective likelihoods of a testing effect (after recognition memory intervening tasks) or its absence, rather than simply considering the likelihood of the absence of testing effect under these conditions. To give a concrete example, an estimated BF₁₀ of 0.4 would indicate that data are 2.5 times more likely to occur under the null hypothesis than under the alternate hypothesis, and more generally, an estimated BF₁₀ value of 30 – 100 is considered very strong support for the alternative hypothesis. Robustness analyses for the estimation of the Bayes factor were also performed with JASP software, allowing qualifying the degree of evidence for either hypothesis (Jeffreys, 1961).

Results of experiment 1

As illustrated in Table 1, group assignment resulted in 27 participants in the Study-Test group (ST), 24 in the Study group (S) and 25 in the Test group (T).

As described in the methods section, S and ST groups critically differed from T group in terms of the total duration devoted to explicitly studying the to-be-learned stimuli. Indeed, participants in the group T explicitly encoded the items during the initial encoding phase only, thus leading to a total duration of $210 \times 700 \text{ms} = 2.45$ minutes; while participants from the groups ST and S, due to two extra study trials, spent 7.35 minutes studying the pictures. We also computed the total exposure time to stimuli (Roediger & Karpicke, 2006b) to compare the different learning schedules, taking into account response times during recognition trials administered before the final test. Participants in the ST group were exposed to the items during 11.03 minutes (s.d.= 0.23)

on average, versus 6.39 minutes (s.d.= 0.18) on average for T group. In the S group, that value was fixed by design at 7.35 minutes.

A series of Bayesian ANOVAs with group entered as a between-subjects variable yielded BF_{10} estimates > 1000 for Accuracy and Hits, corresponding to a very strong level of evidence for the hypothesis of a group effect on the final test performance (see Figure 2). Further independent sampled t-tests confirmed our expectations of superior performances in the ST group vs. S group (Accuracy, $BF_{10} > 1000$; Hits, $BF_{10} \Rightarrow 1000$) as well as a superiority of the ST group over T group (Accuracy, $BF_{10} = 119$; Hits, $BF_{10} = 16$). Robustness analyses suggested that evidence favoring ST group over S and T groups was decisive or very strong for the comparison ST vs. S (median effect sizes for Accuracy = 2.033, 95%CI=[1.341, 2.742]; Hits = 1.847, 95%CI=[1.178, 2.522]), while it was decisive or strong for the comparison ST vs. T (median effect sizes for Accuracy = 0.929, 95%CI=[0.360, 1.527]; Hits = 0.697, 95%CI=[0.190, 1.277]).

However at odds with our hypothesis, final test performances proved better in the T group by comparison with the S group (Accuracy, $BF_{10} = 0.092$; Hits, $BF_{10} = 0.063$), and robustness analyses suggested either decisive or strong level of evidence (median effect sizes for Accuracy = 0.059, 95%CI=[0.001, 0.271]; Hits = 0.061, 95%CI=[0.002, 0.307]).

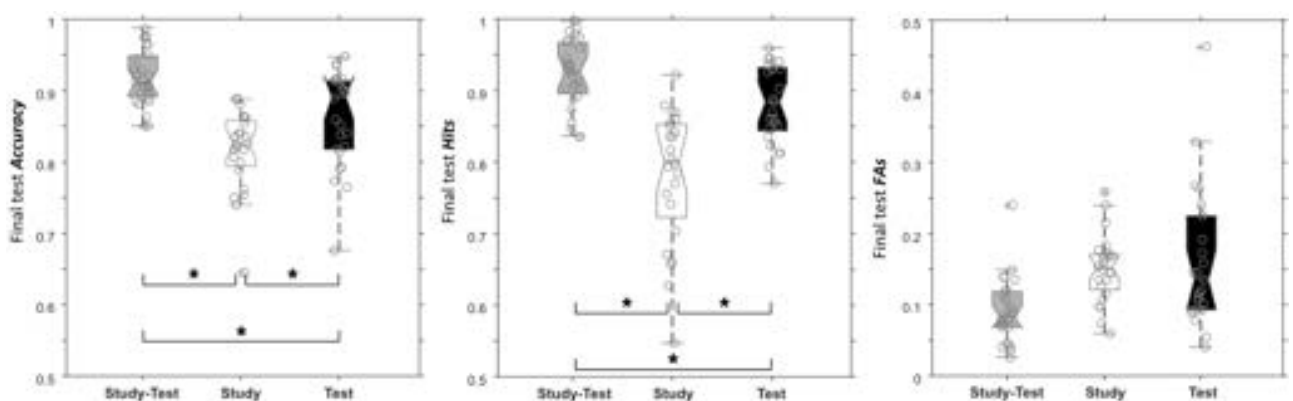


Figure 2. Experiment 1. Notched boxplots for final test results. Asterisks indicate estimates of the Bayesian Factor $BF_{10} \neq 1$ for t-tests planned comparisons between groups. Each circle represents one observation, notches represent the 95% Confidence Interval of the median.

The gain observed in final accuracy measures at final test in the T group by comparison with the S group came with substantial changes in response bias (we used the non parametric B'' response bias index after Grier [1971]) and median response times. Estimates of BF₁₀ made under the hypothesis of a difference between groups reached 114 for B'' (median effect size = 1.030, 95%CI [0.426, 1.651]) and was superior to 1000 for the median response times for Hits (median effect size = 1.385, 95%CI [0.755, 2.036]). Evidence suggesting that participants in the T group adopted a more liberal response bias and were faster in making accurate Go responses was decisive or strong and decisive or very strong, respectively. However, and importantly, the two groups did not differ regarding the false alarms rate (BF₁₀= 0.320) (see Figure 2) and evidence supporting a difference between groups for the median response times for false alarms was only positive or substantial (BF₁₀= 5, median effect size = 0.659, 95%CI [0.100, 1.231]), with T group participants being faster.

Discussion of experiment 1

To sum up the results of experiment 1, final test data only partly confirmed our hypothesis of a group effect. Final test accuracy measures were found to be superior in the ST group. However, T group participants obtained a better accuracy and hit rate than S group participants, without any cost in terms of false alarms rate. This occurred despite significantly less total exposure time to targets and a time spent at explicitly studying stimuli three times less important in the T group. Furthermore, T participants were also faster in making hits, overruling the possibility of a trade-off effect between hits and reaction times.

Thus, to the best of our knowledge, experiment 1 provides the first evidence for a testing effect following recognition memory-based retrieval practice, which is at odds with our main hypothesis derived from the retrieval effort theory of the testing effect. However, it is well acknowledged that recognition memory relies upon two distinct processes, recollection and familiarity (Mandler,

1980; Yonelinas & Jacoby, 1994). While recollection is defined as the retrieval of qualitative information about the study episode (contextual retrieval), familiarity is defined as an acontextual sense of prior exposure (Yonelinas, 2002; Yonelinas, Aly, Wang, & Koen, 2010). In experiment 1, we used a typical Old / New recognition memory paradigm that does not allow the estimating of the respective contributions of recollection and familiarity to performance. This is important since recollection “involves the recovery of qualitative associations prompted by a critical cue” (Eichenbaum, Yonelinas, & Ranganath, 2007, p.124). In other words, the contribution of recollection to recognition memory matches the controlled, effortful processes described in the retrieval effort hypothesis, and it follows that the contribution of recollection to retrieval practice in experiment 1 may explain our finding of a testing effect. To further explore whether a testing effect may occur due to effortless, automatic, retrieval processes, one should therefore rule out the contribution of recollection-based retrieval to focus on familiarity-based retrieval. This is what we attempted to in experiment 2.

Experiment 2

Methods

Experiment 2 aimed at testing whether memory retrieval practice associated with familiarity-based recognition memory may lead to a testing effect. For that purpose, we adapted the Speed and Accuracy Boosting (SAB) procedure recently introduced by Besson et al., (2012) for each testing phase of experiment 2. Since familiarity is supposed to be a rapid and automatic process by contrast with the slow, controlled processes that support recollection (Brown & Aggleton, 2001; Yonelinas, 2002), the SAB procedure is assumed to mainly rely on familiarity (Sauvage, Beer, & Eichenbaum, 2010; Besson et al., 2012; 2015).

The Speed and Accuracy Boosting procedure

The Speed and Accuracy Boosting (SAB) procedure constraints participants to use their fastest strategy and has been used in several studies (Barragan-Jason, Besson, Ceccaldi, & Barbeau, 2013; Besson, Ceccaldi, Tramoni, Felician, Didic, Barbeau, 2015; Besson et al., 2017). Based on a classical Go/NoGo task, the SAB procedure requires participants to provide a go response to targets within a given response time deadline following stimulus onset. Based on previous studies, the deadline was set at 500ms in the present experiment. A go response before this response deadline was followed by an audio-feedback, positive if the item was a target (hit), negative if the item was a distractor (false alarm). Similarly, a no-go response was followed by a positive (correct no-go response for a distractor, i.e. correct rejection) or negative (incorrect no-go response for a target, i.e., omission) audio-feedback. Before presentation of each item, a fixation cross was displayed with a jittered duration ranging from 300 to 600ms. Stimuli were then presented and participants had up to 500ms to give their answer. The SAB procedure is a very demanding task, thus two training blocks of 10 target stimuli, to be recognized among 10 distractors, were administered before the experiment. These items were not used in the subsequent trials. A schematic diagram provided in Figure 3 illustrates the SAB procedure.

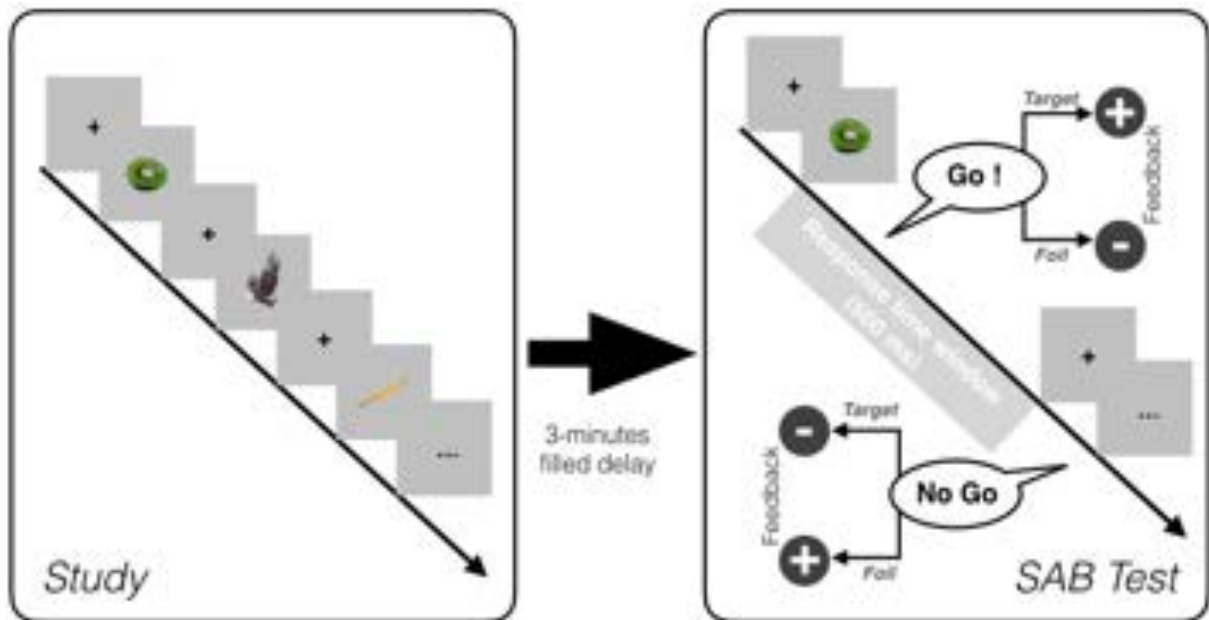


Figure 3. Experiment 2. Speed and Accuracy Boosting (SAB) procedure overview. After a typical study phase, a speeded Go / Nogo task required participants to provide Go responses for targets only, within a short response deadline (500 ms). After each response, an audio-verbal feedback was provided.

Stimuli

795 photographs of real objects were taken from the web (mean $\sim 379 \times 345$ pixels, SD $\sim 107 \times 92$ pixels), without any context, reformatted in an uncompressed format (i.e., .bmp) and displayed on a grey background. The required number of targets and distractor pictures was randomly sampled across participants, and different sets of distractors were used for successive test phases (see below).

Experimental setting

For all experiments, stimuli were presented on a CRT computer screen, using E Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA). Subjects responded by raising their fingers from a dedicated infrared response pad, and response speed was always emphasized in the instructions.

Experimental design and procedure

Figure 4 provides an overview of the design of experiment 2. During Study phases, stimulus presentation was self-paced, with minimal presentation duration of 2 s, and with a 500ms inter-stimuli interval. Two learning conditions were used in a cross-sectional design: the “Study” condition, further labeled “S”, and the “Test” condition, further labeled “T”. Both learning conditions included 4 encoding blocks intermixed with 4 test blocks. In both learning conditions, encoding instructions emphasized the memorization of a series of photographs for further recognition.

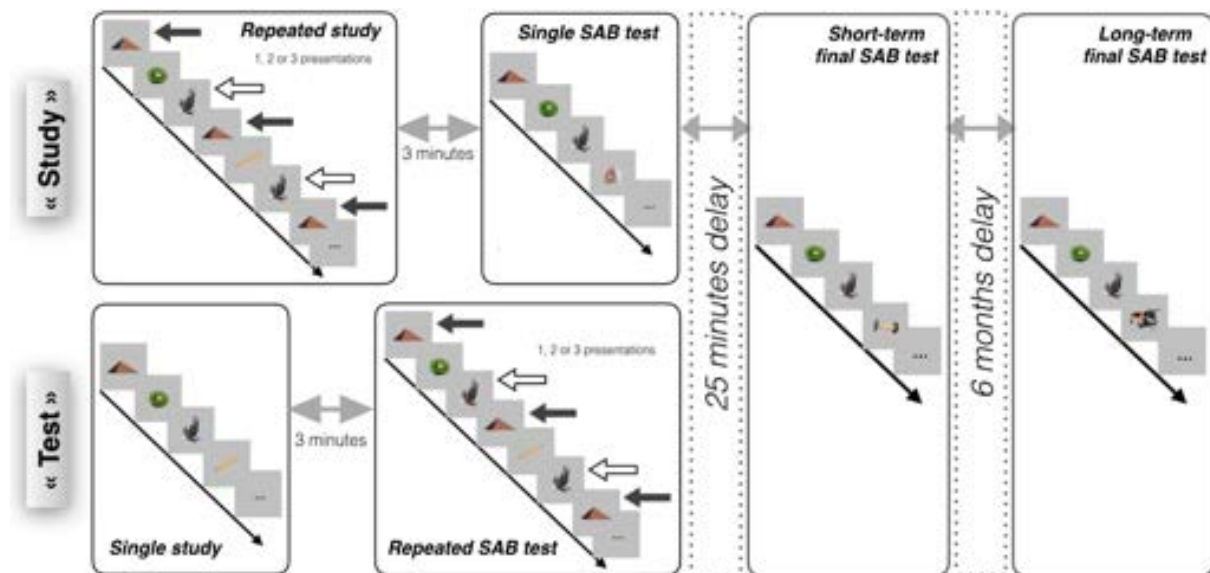


Figure 4. Experiment 2. Design overview. “SAB” refers to the Speed and Boosting Procedure described in the methods section. Top row: “Study” condition; Bottom row: “Test” condition. In the Study condition, two thirds of the items were repeatedly studied but tested only once before final tests procedure. In the “Test” condition, items were studied only once but two thirds were further repeatedly tested. For the sake of clarity, ISIs are not displayed.

In the S condition, during the study phase, a third of the 156 targets (i.e., 52 items) were presented only once, another third twice and the last third three times. Presentation order was

pseudo-randomized across participants, so that three different items at least separated two consecutive occurrences of identical pictures. After each encoding block, a three-minute cartoon was displayed as an interference task, randomly taken from a series of 12 videos. Thereafter, a test block started. Each test block consisted in a recognition memory test administered under the speed and accuracy boosting procedure (SAB), where an equal number of foils were randomly intermixed with target pictures, with a jittered 100-500ms inter-stimulus interval. During the delay before the final short-term test phase, participants completed the same tasks and questionnaires as in experiment 1, for a fixed 25-minute delay before the final test. The final test was also based on the SAB procedure, though with a different set of 156 distractors than during the previous test phases.

In the T condition, the 156 target items were presented in the same manner as in the S condition, except that items were presented only once. Instructions were the same, i.e., to memorize a series of photographs for further recognition. After the three-minute interference phase filled with a cartoon as described above, a recognition memory test was administered under the SAB procedure. During the test blocks, one third of the target items were presented once, one third twice, and one third were presented three times. Participants therefore had one, two or three opportunities of target retrieval within the test blocks. During the delay before the final short-term test phase, participants completed the same tests and questionnaires as described for the S condition, and the final test phase started automatically after 25 minutes. That phase was identical to the one described above for the S condition.

In both groups, participants were not aware that they would be asked to come back to the laboratory for a long-term final test. 6 months after the final short-term test phase took place, we contacted the participants and asked them to come back for a long-term test phase, using the same procedure as during the short-term final test phase, except that a new set of distractors was used. The practice trials were administered again to train participants for this very demanding recognition memory paradigm. A 6-month delay was chosen because prior studies

suggest that long-lasting memories can be highlighted by use of recognition memory tasks (Dolcos, LaBar, & Cabeza, 2005; McCullough & Yonelinas, 2013; Milton et al., 2011).

Our design, therefore, allowed us to contrast the effect of repeated study versus repeated familiarity-based retrieval on short- and long-term retention. Importantly, the same testing procedures were used during the intervening phases and at final tests, either short- or long-term. This was intentionally done by reference to the Transfer-Appropriate Processing (TAP) theoretical framework, stating that the testing effect magnitude may be optimized when the processing demands involved during initial and final testing closely match (Dolcos, LaBar, & Cabeza, 2005; McCullough & Yonelinas, 2013; Milton et al., 2011). Because our goal in experiment 2 was to explore whether or not a testing effect may occur when retrieval practice is mostly based on familiarity, and possibly being resistant to a 6 months-delay, we reasoned that using the same testing procedures during learning and final testing limited the risk of a type II error (i.e. a false absence of the effect).

Hypotheses

Recognition memory under the SAB procedure yields very short response times, and it has been showed that responses up to 420 ms reflect familiarity-based responses (Morris et al., 1977; Roediger & Butler, 2011). Our first hypothesis, thus, was that minimal reaction times estimated during the intervening phases should remain in that range, a sine qua non condition for any further interpretation in terms of familiarity-based retrieval practice. Furthermore, following the core prediction of the retrieval effort hypothesis, we hypothesized that retrieval practice based on such automatic, effortless processes should not lead to a testing effect. In other words, final testing performances were expected to be mainly driven by the time spent explicitly studying the material, which was up to three times more important in the S group. Indeed, participants in the S

group studied the items either once (for items presented only once), twice or three times while participants in the T group studied items only once. Across participants, this resulted in total study duration of 23.5 minutes in the S group versus 13.6 minutes in the T group. Meanwhile, the mean time spent studying each picture did not differ between groups (S group, mean= 4.5 s, range [3.2 – 6.7]; T group, mean= 5.2 s, range [3.8 – 7.4]). Further, the test trials also exposed participants to the target stimuli for a maximum time of 78 seconds in the S group vs. 156 seconds in the T group. Overall, this resulted in a total exposure to target information far less important in the T group (24.8 vs. 16.2 minutes). Finally, we expected delay to influence performances in both groups (i.e. forgetting at 6 months-delay), but no group X delay interaction was hypothesized, because the same pattern of S group advantage was expected at both short- and long-term delays.

Participants

41 healthy young subjects, undergraduate students at Toulouse University, signed informed consent forms for their participation, and were paid for their time. Technical issues with the infrared response pad made 4 learning datasets unavailable, 2 participants scores significantly below norms at recall tests on the Wechsler memory scale, and 5 other participants failed to reach a minimal level of performance either during the first training session or the first recognition block, reflecting the very demanding nature of the task. This resulted in the final inclusion of 30 healthy participants (16 included in the group T and 14 in the S group) (see Table 2 for socio-demographic, questionnaires and logical memory data). At 6 months, only 9 participants from each group proved reachable and consented to perform the long-term final test.

Groups	Sex ratio %Female	Age	Years of education	f-NART FSIQ	CDS	Immediate Recall	Delayed Recall
Study « S »	79	22.79 (3.5)	13.86 (1.5)	105.68 (5.9)	48.21 (16.5)	44.93 (7.9)	31.21 (6.2)
Test « T »	69	24.69 (4.0)	14.50 (1.9)	108.26 (5.4)	46.73 (13.2)	45.32 (7.0)	31.69 (5.5)

Table 2. Experiment 2. Sociodemographic and psychometric background of participants. Means are displayed above standard deviations (in brackets). F-NART FSIQ= French version of the National Adult Reading Test, estimated Full-Scale IQ ; CDS= Cognitive Difficulties Scale ; Immediate & Delayed recall are expressed as scaled scores from Wechsler Memory scale, 3rd Ed. The groups did not differ for Age, Sex ratio, Education, FSIQ, CDS, immediate & delayed verbal recall (Bayes Factors well below 1, BF₁₀ range= [0.348 - 0.690]).

Statistical analyses

The SAB procedure provides a continuous distribution of responses times, which allows the estimation of the minimal processing time required for each task, through the computation of a minimal reaction time (min RT). After dividing RT distributions in bins of equivalent width (20 ms), across-participants minimal reaction times were computed by determining the first of three consecutive bins for which the number of Hits started to significantly outnumber the number of FAs (Fischer's exact test, $p < 0.05$). To increase statistical power and better reflect each group's behavior in terms of min RT, we also pooled together all trials from all participants and computed across-trials min RT for each group. Across-trials min RT were defined as the middle of the first of three consecutive bins where Hits rate significantly outnumber FAs rate, using χ^2 -tests, $p < 0.05$.

The same analyses as in experiment 1 were used to compute recognition memory performances.

Results of experiment 2

As illustrated in Table 2, group assignment resulted in 14 participants in the Study group (S), and 16 in the Test group (T).

Minimal reaction times during the intervening phase

Estimates of the minimal processing time required to accurately recognize a target across participants were in the expected range (group T, mean minRT = 345 (+/- 26.8) ms, range [320 - 400]; group S, mean minRT = 390 (+/-15.2) ms, range [380 - 420]). However, across-trials min RT revealed very similar profiles in the temporal dynamics of responses. As can be seen in Figure 5, across-trials min RTs were very similar between groups.

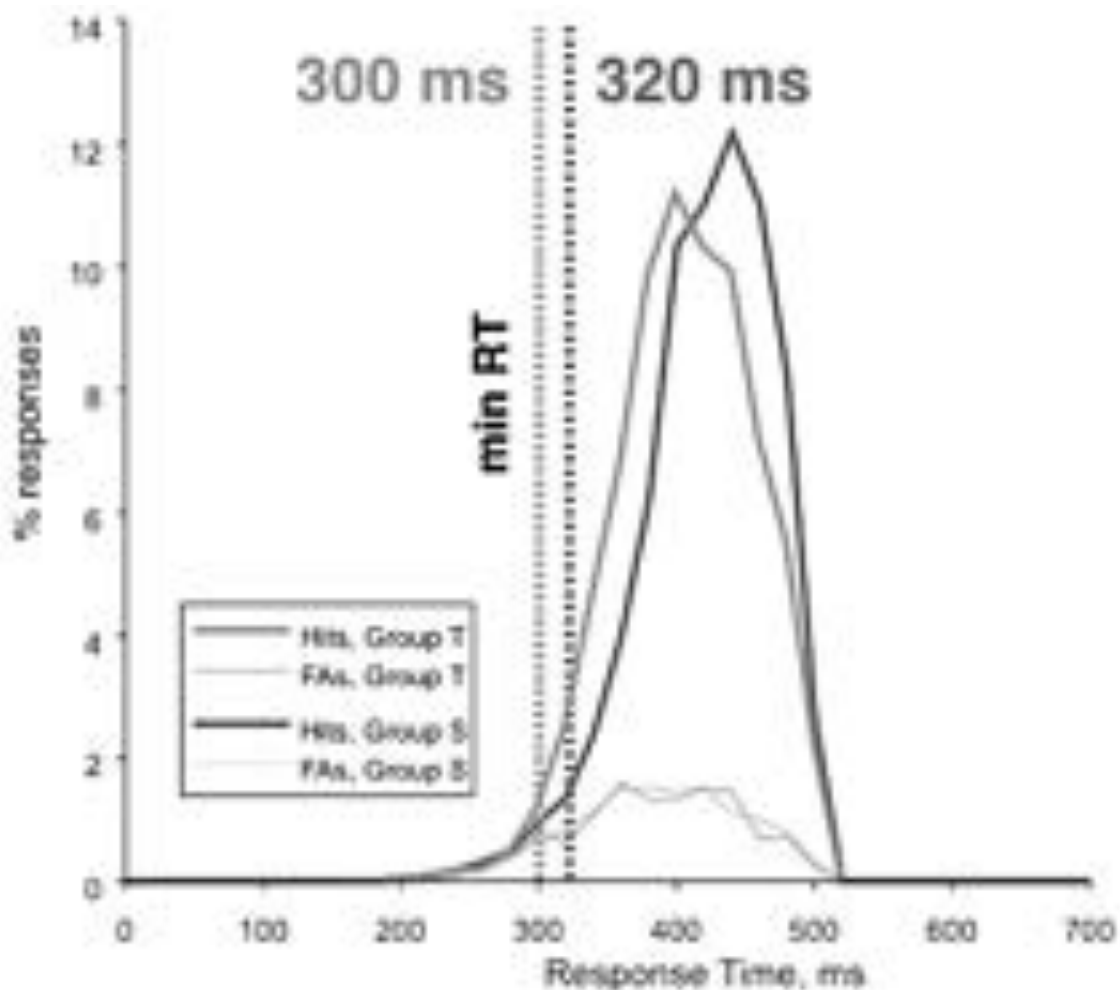


Figure 5. Distribution of the reaction times during the intervening phase in groups S & T, across-trials. The minimal reaction times (vertical lines) were computed as the first moment when hits significantly outnumber false-alarms (FA) rate.

Altogether, minimal reaction times analysis confirmed that participants chiefly used fast and automatic, presumably familiarity based, recognition processes.

Short-term final test

The alternative hypothesis being that group S outperforms group T regarding accuracy at final test did not receive support from an independent Bayesian t-test (Accuracy, $BF_{10} = 0.668$), and the robustness analysis yielding a moderate level of evidence favoring the null hypothesis (median effect sizes for Accuracy = 0.313, $95\%CI = [0.018, 0.881]$). Regarding Hits rates, a mixed Bayesian ANOVA with group as a between factor and number of items presentations (i.e., 1, 2 or 3) as a within-subjects factor brought evidence for a main effect of the number of presentations ($BF_{10} > 1000$), but we did not find any contribution of the main effect of group ($BF_{10} = 0.444$), and the group X number of presentation interaction did not add value to the model ($BF_{10} = 0.261$). As expected, a very strong level of evidence was found for the effect of the number of presentations (median effect sizes for 1 vs. 2 presentations = -1.321, $95\%CI = [-1.823, -0.831]$; 2 vs. 3 presentations = -0.754, $95\%CI = [-1.162, -0.364]$).

A planned comparison further focused on the items presented three times, thus benefiting from 3 study events but only one test event in the S group, and conversely three test events but only one study event in the T group. Independent t-tests yielded moderate evidence for the null hypothesis (Accuracy, $BF_{10} = 0.407$; median effect size = 0.234, $95\%CI = [0.011, 0.761]$; Hits, $BF_{10} = 0.579$; median effect size = 0.285, $95\%CI = [0.016, 0.864]$). Figure 6 summarizes short-term final test results.

Interestingly, we found moderate evidence favoring the absence of a group differences for Bias and False Alarms measures (Bias: items presented only once, $BF_{10} = 0.341$; items presented twice, $BF_{10} = 0.340$ and for items presented three times, $BF_{10} = 0.342$; False Alarms: $BF_{10} = 0.340$). Likewise, median reaction times (RTs) for Hits and FAs were similar in both groups (Hits median RTs, S group: 421ms [403 - 454], T group: 418ms [402 - 454], $BF_{10} = 0.398$; FAs median RTs, S group: 402ms [351 - 456], T group: 398ms [352 - 426], $BF_{10} = 0.345$). Hits RTs were also similar for targets presented only once, twice or three times, respectively. Across-trials minimal reaction times were estimated at 300 and 340 ms in the S group and the T group, respectively, thus being in the same range and well below the expected upper limit of 420 ms.

Altogether, these results indicate that short-term retention increases with repetition of the material during the learning phase in both groups. However, one single study event coupled with three test events yielded equivalent short-term retention than three study events coupled with one single test event, despite the total time spent looking at the stimuli being much shorter. Moreover, learning associated with repeated familiarity-based retrieval yielded equivalent Bias and False alarms rate at final test.

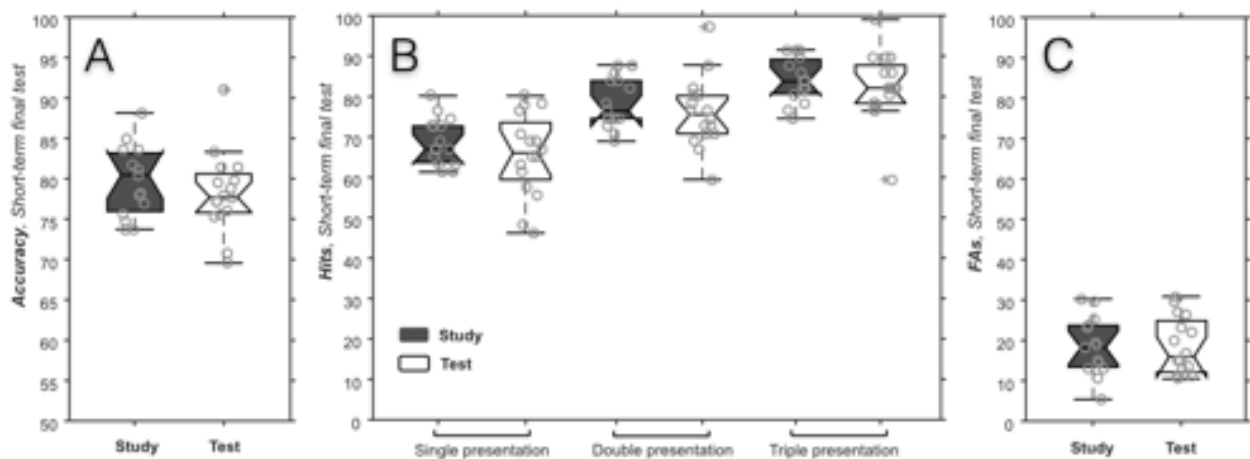


Figure 6. Experiment 2. Notched boxplots for Short-term final test. (A) Accuracy; (B) Hit rates for items presented once, twice or three times either at study or at test during the intervening phase; (C) False Alarm rates. Each circle represents one observation, notches represent the 95% Confidence Interval of the median.

Long-term final test

Figure 7 summarizes the long-term final test results. Only two participants from the S group failed to outperform the chance level at 6 months, confirming that visual recognition memory paradigms allow to evidence long-lasting memories. Removing data from these two subjects did not affect the results presented below. We found moderate evidence for an absence of group effect on Accuracy (BF₁₀ = 0.426; median effect size = 0.254, 95%CI=[0.012, 0.878]). Focusing on the items being presented three times, we found moderate or anecdotal evidence in the same

direction (Accuracy, $BF_{10} = 0.229$; median effect size = 0.157, 95%CI=[0.007, 0.637]; Hits, $BF_{10} = 0.591$; median effect size = 0.314, 95%CI=[0.016, 1.006]).

We found moderate or anecdotal evidence for similar Bias and False Alarms rate in both groups (Bias: items presented only once, $BF_{10} = 0.286$; items presented twice, $BF_{10} = 0.250$ and for items presented three times, $BF_{10} = 0.223$; False Alarms: $BF_{10} = 1.219$). Reaction times (RTs) analysis for Hits and FAs yielded the same pattern as the one found for short-term final test, with very similar results between groups. Finally, across-trials minimal reaction times were fast (260 and 320 ms in the S group and the T group, respectively), again suggesting the involvement of very fast and automatic retrieval processes.

Taken together, these results suggest that one single study event associated with three test events led to the same long-term retention, and with a similar retrieval speed, than three study events associated with a unique test event. Learning thus clearly occurs very efficiently during repeated familiarity-based retrieval, and not only during study events. Importantly, we found that these findings are not associated with any difference in response Bias or in the rate of False Alarms.

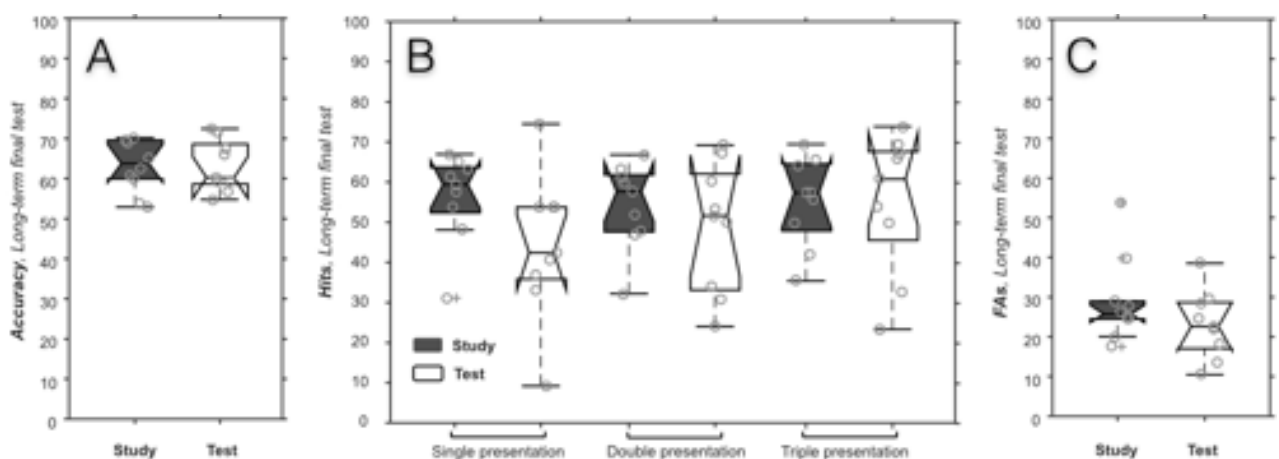


Figure 7. Experiment 2. Notched boxplots for Long-term final test. (A) Accuracy; (B) Hit rates for items presented once, twice or three times either at study or at test during the intervening phase; (C) False Alarm rates. Each circle represents one observation, notches represent the 95% Confidence Interval of the median.

Spacing effects

The between-subjects design used in experiment 2 introduces an important difference between groups. During the intervening learning phases, because items can be repeated across recognition trials in the T group but not in the S group, and because we had to keep the probability of target occurrence constant between groups (i.e., 50%), there were twice as many distractors in the T group than in the S group. In the S group, recognition test during the intervening phase included an overall number of 156 targets and 156 distractors. By contrast, in the T group, 52 targets were presented only once, 52 were presented twice, and 52 three times, thus leading in the use of 312 distractors. It follows that the number of items separating two successive presentations of the same picture (further labeled “Lag”) may inherently be greater in the T group, thus introducing a spacing effect during the learning trials that could advantage the T group. However, it was recently demonstrated that spacing effects interact with testing effect up to the cancellation of the retrieval practice effect when the learning schedules control for differences in lags between conditions (Soderstrom, Kerr, & Bjork, 2016).

Based on the inspection of the distributions, each item with a lag superior to 60 items was removed (leading to similar lags means of 22 items across study trials in the S group vs. 28 items across test trials in the T group). We ran the same analysis as the ones presented above after removing these items. Results were identical to the pattern described before for short- and long-term retention. Briefly, we found moderate to strong evidence for a main effect of the number of presentations at short-term only ($BF_{10} = 61.429$), decisive evidence for a main effect of delay ($BF_{10} > 1000$ for both delays), but no effect of group, and interactions did not either add value to the models.

Discussion of experiment 2

Experiment 2 provides the first evidence of learning and long-term retention of object pictures after familiarity-based recognition memory practice. Indeed, minimal reaction times analysis suggested that both groups made use of familiarity-based retrieval during the intervening learning phases, with a range of minimal reaction times falling well below 400 ms. This confirms the very fast and automatic, effortless, processes engaged in the task. However, at odds with our hypothesis of a better retention in the S group, due to the higher number of study events, we found that increasing the number of study events did not make any difference at both 25 minutes and 6 months delay. At first sight, these data may not speak for a testing effect strictly speaking, *i.e.*, when defined as a better retention following intervening retrieval trials than following the same amount of intervening study trials. Yet, participants in the T group benefited from only one study event per item, while up to three study events occurred for participants in the S group. Moreover, in the Test condition, participants initially learned (*i.e.*, encoded) the pictures much faster since they spent only 13.6 minutes looking at the stimuli whereas 23.5 minutes were required, on average, in the S condition. We thus argue that results of experiment 2 provide clear evidence that a strong learning effect arises from effortless retrieval practice. Despite spending considerably less time in learning, and being exposed less frequently to the material at study, participants in the T condition retained as much information at short- and long-term delays as in the S condition.

General discussion

Decades of research have established that retrieval processes are not neutral for learning: memory retrieval by itself can enhance future retrieval, a finding called the retrieval practice effect. The present study is the first investigation of the retrieval practice effect using Old/New recognition memory paradigms for pictures both during intervening and final test phases.

Another originality of our study is that we tested retention at final test after a 6 month delay, which is considerably longer than the delay usually used in most prior studies (but see (Soderstrom, Kerr, & Bjork, 2016)). Following the retrieval effort hypothesis, an influential account of the testing effect, we hypothesized that the automatic, effortless retrieval processes involved in recognition memory, should not be beneficial at final test. The results from experiment 1 were at odds with that prediction, highlighting better retention after repeated retrieval under Old/New recognition memory conditions than after repeated studying. Experiment 2 constrained retrieval practice to familiarity-based recognition memory, which produced similar retention at both short- (25 minutes) and long-term (6 months) delays than repeated study. Overall, these results speak for the involvement of very efficient learning processes during recognition memory-based retrieval, even when such retrieval involves minimal effortful processes.

Old/New recognition memory as a learning paradigm

To date very little attempts had been made to assess whether retrieval based on simple Old/New recognition memory paradigms could trigger a testing effect. One reason for this is probably the frequent reference to educational settings, where implementation of the retrieval practice effect is more likely to involve multiple-choice or recall formats. However, some methodological challenges may also explain the lack of such studies. First, because recognition memory is very efficient in healthy subjects, the trade-off between avoiding ceiling effects with a high number of stimuli (typically hundreds), and an acceptable duration of the experiment for the participants may require a long piloting phase. This also highly constrains the experimental plan, because within-subjects designs are made quite unlikely due to the need for twice as much stimuli as for a between-subjects designs. Second, recognition memory paradigms imply that target items will be presented again at retrieval, after initial encoding, in the experimental or testing condition. This is a critical difference with the usual testing effect designs where recall format is used (either cued

or free recall), so that after initial encoding, target items are presented again only in the study-only condition, during the intervening phase. We dealt with these constraints by closely matching the number of study and test events across conditions in both experiments, and by using a study-only condition in experiment 1. In experiment 2, we manipulated the ratio of study vs. test trials by presenting items either once, twice or three times either during study or test phases. Besides, the study condition included a test trial immediately after the study period and before the final tests, so that any difference between groups should be associated not with retrieval *per se*, but with retrieval practice (retrieval repetition).

Prior studies using Old/New recognition paradigms

As already presented in the Introduction, we are aware of only three prior studies using an Old/New recognition memory format during the intervening phase. The study by Glover (1989) has methodological limitations. In the second study by Carpenter & Delosh (2006), no testing effect was found after recognition memory testing, whereas the third study from Mandler & Rabinowitz (1981) found such an effect, but at the cost of a significantly higher false alarms rate during final recognition test.

We avoided ceiling effects during the intervening phase by greatly increasing the number of stimuli used in both experiments, which is a pre-requisite given the acknowledged efficiency of visual recognition memory in humans. We also examined final retention at 25 minutes (Experiments 1&2) and 6 months (Experiment 2) post learning (vs. 5 minutes in Carpenter & Delosh, 2006 and 1 week in Mandler & Rabinowitz, 1981), and final retention was assessed through recognition memory conditions only. These differences may explain our divergent findings. Results from experiment 1 showed a striking advantage for repeated testing over repeated studying, even when testing relies on fast, simple, recognition processes, and despite a time devoted to explicit encoding three times less important in the Testing condition. These

results are at odds with predictions from the retrieval effort framework, because it's central claim is that effortful, controlled retrieval processes are responsible for the effect. Here we found strong level of evidence suggesting that rather automatic and effortless retrieval processes do benefit long-term retention by comparison with a study-only condition. Importantly, we also found that this advantage of repeated recognition memory-based retrieval came with no cost in terms of false alarms, but with an increased speed of processing because participants in the experimental group presented with shorter reaction times overall.

Can familiarity-based retrieval trigger a testing effect?

In an effort to further constraint retrieval under Old/New recognition memory paradigm to familiarity-based processes, experiment 2 tapped the fastest responses of participants through the use of a Speed and Accuracy Boosting procedure. In contrast to experiment 1, we failed to highlight any difference between repeated study and repeated testing at both short- and long-term final tests. However, we bring two lines of arguments that actually speak for a positive effect of retrieval practice.

First of all, in the repeated study condition, participants had up to three opportunities to explicitly encode the material, whereas only once in the repeated test condition. Moreover, test occurred also in the repeated study condition because in our design, after initial encoding, a recognition task was administered. Our procedure therefore allowed us to directly compare the effect of repeated testing events after a single study to multiple study events associated with a single testing event, each test trial being completed under the same format. In such a design, we therefore believe that an absence of testing effect should have led to better retention in the repeated study condition, due to extra-exposure to the stimuli, both in terms of frequency of study events and in total time spent studying.

Second, as pointed out by Karpicke, Lehman, & Aue (2014), one must consider that retrieval also occurred during repeated study trials, (so-called “Study-phase retrieval”). Indeed, repeated study trials provided up to three opportunities of retrieving 100% of the material, without any interference due to extra-list stimuli. By contrast, participants in the repeated Test condition had up to three trials to accurately retrieve target items (*i.e.*, recognize an Old item), but an equivalent number of trials were made of extra-list items. In other words, whereas in the Study condition, the critical encoding phase allowed subjects to perfectly retrieve 100% of the material up to three times, without any interference, subjects in the Test conditions had to discriminate, up to three times, between Old and New stimuli. In the end, this clearly favored the restudying condition where no extra-list item can interfere at encoding, and where twice less foils were used at test, thus reducing the opportunities of inaccurate recognitions. This is, therefore, a very constraining paradigm, where an absence of testing effect would predict that the number of study events should mainly drive retention, thus leading to a clear advantage of the repeated studying condition.

At odds with this, our findings revealed that one extra test trial was sufficient to boost retention up to the level achieved through repeated studying, even when comparing three study events with only two tests events (see results section and Fig. 6 B), and the effect remained after 6 months. By reference to the seminal report from Tulving (1967), the surprising result in experiment 2 comes from the fact that participants in the study condition did not reach better short-and long-term retention than participants in the test condition (see also Roediger & Karpicke, 2006a, 2006b). This finding of learning effects just as efficient following repeated familiarity-based retrieval, *i.e.*, a fast, automatic and effortless retrieval, as following repeated studying clearly challenges in our view the retrieval effort hypothesis.

Limitations

Two limitations of the present study must be mentioned, however. First, because we aimed at testing participants after a 6 months delay in experiment 2, without leaving any opportunities to rehearse the study material during that delay, this resulted in a very small sample size at long-term final test. More generally, results from experiment 2 should be replicated with larger samples. Yet, among the participants who performed the long-term test, only two failed the task, both pertaining to the “Study” group. This confirmed that visual recognition memory is a very efficient system, with above-chance performances reachable after 6 months following one single study event in the case of the “Test” group.

Second, the use of Old/New recognition paradigms in both experiments made it mandatory to use feedback after each recognition trial. Karpicke et al. (2014) have argued that a feedback approach may be unsatisfactory because it can on its own drive some testing effect that cannot be teased apart from the main effect of retrieval *per se*. Indeed, in our study, the benefit of retrieval we observed is a combination of direct (retrieval success) and indirect, or mediated, effects (feedback post recognition trials). Nonetheless, in the particular case of recognition memory, participants in the test condition are presented with both targets and lures, so that false alarms are as likely to occur as hits. It follows that without any feedback, not only participants in the test condition would be disadvantaged because of the massive interference generated by extra-list items, but also this would drop the successful retrieval rate far from the study-phase successful retrieval rate, where only targets are presented. In addition, the study condition in experiment 2 also involved a test condition including feedback, like any other test phases used in the experiments. Thus, any positive effect of feedback should have benefited participants in the study groups as well. Taken together, these considerations do not rule out a contribution of feedback *per se* to our findings, but make it less likely than the main contribution of recognition memory-based retrieval processes.

Conclusions and future directions

An influential account of the testing effect, the retrieval effort hypothesis, predicts that effortful, controlled, retrieval processes are responsible for the effect. Our findings of a testing effect triggered by recognition memory based retrieval are not consistent with that prediction, and, if replicable, may call for a revision of that account. However, that hypothesis is by no mean a mechanistic account for the testing effect, which is still lacking (but see Karpicke et al., 2014). As suggested earlier (Chan & Mcdermott, 2007), studies crossing testing formats both during intervening and final test phases are required, and with respect to the present study, a design allowing to test whether familiarity-based recognition can enhance cued or free recall, for example, would be appropriate. Furthermore, it would be insightful to cross designs allowing the investigation of transfer effects (*i.e.*, whether or not the testing effect may generalize to unstudied materials) with experimentally controlled procedures allowing to assess core predictions of the emergent mechanistic accounts for the testing effect. As an example, the recent “automatization account” from (Chan & Mcdermott, 2007) suggest that learning after retrieval practice may share properties with skill-learning. If so, generalization after retrieval-based learning should be rather limited. Otherwise, important clinical perspectives may arise from our findings. If indeed effortless retrieval processes proves to trigger a testing effect, brain-injured patients with impairments in controlled processes but preserved automatic processes may take advantage of retrieval practice methods. There is already some evidence that retrieval practice effects can efficiently serve as a rehabilitation technique in severe amnesia following traumatic brain injury (Pastötter & Bäuml, 2014; Sumowski et al., 2010; Sumowski, Coyne, Cohen, & Deluca, 2014). Our hope is that future work may help determine whether such effortless learning processes as the one used in the present study, far easier than successive recall schedules in clinical settings, could be of some rehabilitation interest.

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Appendix B: Experiment 8. Relational and conjunctive binding in visual short term memory dissociates within the medial temporal lobe



Special issue: Research report

Refining understanding of working memory buffers through the construct of binding: Evidence from a single case informs theory and clinical practise

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ABSTRACT

Binding operations carried out in working memory enable the integration of information from different sources during online performance. While available evidence suggests that working memory may involve distinct binding functions, whether or not they all involve the episodic buffer as a cognitive substrate remains unclear. Similarly, knowledge about the neural underpinnings of working memory buffers is limited, more specifically regarding the involvement of medial temporal lobe structures. In the present study, we report on the case of patient KA, with developmental amnesia and selective damage to the whole hippocampal system. We found that KA was unable to hold shape-colours associations (relational binding) in working memory. In contrast, he could hold integrated coloured shapes (conjunctive binding) in two different tasks. Otherwise, and as expected, KA was impaired on three relational memory tasks thought to depend on the hippocampus that are widely used in the early detection of Alzheimer's disease. Our results emphasize a dissociation between two binding processes within working memory, suggesting that the visuo-spatial sketchpad could support conjunctive binding, and may rely upon a large cortical network including sub-hippocampal structures. By contrast, we found evidence for a selective impairment of relational binding in working memory when the hippocampal system is compromised, suggesting that the long-term memory deficit observed in amnesic patients may be related to impaired short-term relational binding at encoding. Finally, these findings may inform research on the early detection of Alzheimer's disease as the preservation of conjunctive binding in KA is in sharp contrast with the impaired performance demonstrated very early in this disease.

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1. Introduction

Since its introduction in 1974, the Working Memory (WM) model proposed by Baddeley and Hitch (Baddeley & Hitch, 1974) has undergone revisions and refinements. A cognitive construct which has driven substantial amount of research and revisions of the model is binding, understood as the function that enables the integration of information from different sources during online performance (Zimmer, Mecklinger, & Lindenberger, 2006). To account for such an operation in WM, Baddeley proposed the episodic buffer, arguing that this may be the locus of binding functions (i.e., chunking) that were hard to accommodate in short-term memory (STM) buffers proposed earlier (Baddeley, 2000). This new component attracted considerable amount of attention leading to new questions about the structure and functions of WM and its neurobiological underpinnings (Baddeley, 2007a, 2007b; Baddeley, Allen, & Hitch, 2011). This paper reports on the study of a single case, patient KA, whose pattern of performance can shed new light on the ongoing debate about the function, structure, and neural substrate of WM as a workspace wherein different binding functions operate. Before we report on KA's history and assessment, we will briefly review the role that the construct of binding has played in shaping our understanding of WM. We will then address the literature reporting on neuroimaging and clinical studies that have sought evidence on the neural correlates of functions attributed to the episodic buffer and their vulnerability to brain damage and cognitive ageing. We will then introduce the current study emphasising the contribution that the evidence presented here can make to both understanding of the functional architecture of WM and refinement of memory assessment.

2. What has the construct of binding taught us about the functional organization of WM?

Baddeley (Baddeley, 2000, 2007a, 2007b) thought of the episodic buffer as a temporary store that integrates incoming information from other STM buffers and that retrieves them from long-term memory as unitary multimodal representations. Once formed, such bound representations become available to conscious awareness (Baddeley et al., 2011; Loge, 2011; Rogers & Baddeley, 2006). Rogers and Baddeley (2006) postulated that features held by the episodic buffer are stored in unitary representations either as integrated objects or as chunks (see Cowan, 2001; Cowan, 2010). Baddeley, Allen, et al. (2011) and Baddeley, Jarrold, et al. (2011) argued that the episodic buffer has a central role in providing a multidimensional medium, allowing binding together chunks or features from different sources either visual or verbal, a process that requires executive control. In the verbal domain, Jefferies, Lambon Ralph, and Baddeley (2004) reported that under dual task conditions, recalling strings of unrelated sentences (i.e., scrambled words) was more disrupted than recalling random word lists, although on subsequent learning trials recall of the latter was also disrupted. These dual task effects were not observed for meaningful short stories. The authors concluded

that whereas the requirement to integrate phonological with long-term linguistic information is not attentionally demanding, the integration of unrelated concepts is effortful. The processes supporting sentence recall reflect the contributions from both automatic linguistic functions and controlled binding functions operating on an attentionally limited WM component i.e., the episodic buffer. Vogel, Woodman, and Luck (2001) and Luck and Vogel (1997) investigated whether the integration of visual information in WM was cognitively demanding. Searching for evidence about the unit of representation of visual WM (i.e., integrated objects or individual features), the authors found that holding features integrated within unified object representations was not costlier than holding individual features. They suggested that temporarily storing in visual WM objects defined by multiple features is a cost-free process, in as much as it does not consume additional WM capacity, and therefore the unit of representation of visual WM would likely be integrated objects. Wheeler and Treisman (2002) challenged this view by manipulating the change detection task in a way that required binding (i.e., swapping features between objects rather than adding new feature values as previously done by Vogel et al. (2001) and Luck and Vogel (1997). Under this task conditions binding in visual WM proved costly and such a cost varied depending on whether resources (i.e., feature dimensions) were drawn from the same or different pools (see Olson & Jiang, 2002 for further testing of this hypothesis). Allen, Baddeley, and Hitch (2006) decided to use the paradigm of dual-task interference to investigate whether binding in visual WM features drawn from different pools (i.e., colour and shape) was an automatic or a resource demanding function. Through a well-designed series of experiments (Allen, Hitch, & Baddeley, 2009; Allen et al., 2006; Karlsen, Allen, Baddeley, & Hitch, 2000), the authors demonstrated that this form of feature binding does not require executive resources above and beyond those needed to process single objects. This evidence was in line with the suggestions made by Vogel et al. (2001) and Luck and Vogel (1997) thus questioning the hypotheses that the episodic buffer is the seat of binding operations carried out in WM. Following this evidence, Baddeley, Allen, et al. (2011) and Baddeley, Jarrold, et al. (2011) revised the WM model to propose that this form of low-level feature binding may occur in other WM buffers such as the visuo-spatial sketchpad.

Allen et al. (2006) acknowledged that there are many different types of binding, depending on what stores, memory domains, or forms of representation are involved, and that visual feature binding is just one particular type. In fact, more recent studies have investigated whether other forms of binding which had been well characterised in long-term memory (e.g., associative learning or relational long-term memory binding; Mayes, Montaldi, & Migo, 2007; Moses & Ryan, 2006) would operate in WM under the same cognitive constraints. This research has demonstrated that forms of memory binding well investigated in long-term memory seem to share functional properties when carried out in WM. Single case and neuroimaging studies have consistently demonstrated that two forms of memory binding, namely relational and conjunctive, known to dissociate in long-term memory (Mayes et al., 2007; Moses & Ryan, 2006), also dissociate in WM.

When the features to be bound share internal relationships (features are part of the same object, e.g., coloured shape), conjunctive binding is involved, whereas relational binding refers to the processes linking features that share external relationships (i.e., features to be bound are part of distinct objects, e.g., face-name). These findings have shed new light on the neuroanatomical organization of brain networks subserving WM binding buffers. We review this evidence in the next section.

3. Neuroanatomy of WM buffers mapped through the construct of binding

The distinction between relational and conjunctive binding made in long-term memory (Moores & Ryan, 2006; Olson, Moores, Riggs, & Ryan, 2012) has also been investigated in WM. For example, Prabhakaran, Narayanan, Zhao, and Gabrieli (2000) investigated relational binding in WM by asking participants to remember arrays of letters presented in different locations or just letters and locations while being scanned using fMRI. The authors found that a network involving frontal, parietal, and temporal regions supported task performance. They reported a neuroanatomical dissociation for features and bindings whereby the right frontal region was preferentially involved in the maintenance of integrated representations in WM, and posterior brain regions were preferentially involved in the maintenance of individual features. Baddeley (2000) acknowledged that this network would well be the neural correlate of the episodic buffer. It is well known that in addition to frontal and parietal region, relational binding functions carried in WM also rely on medial temporal lobe (MTL) structures such as the hippocampus. For instance, Piekema, Rijpkema, Ferrander, and Kessels (2010) found that intrinsic intra-item binding (a form of conjunctive binding) did not yield activation of medial temporal lobe (MTL) structures whereas inter-item binding (a form of relational binding) did. Parra, Della Sala, Logie, and Marcon (2014) reported that holding conjunctions of features in WM did not recruit the hippocampus but regions forming a frontal-parietal-occipital-temporal network (i.e., left dorsal premotor cortex/middle frontal gyrus, left inferior parietal lobule, and left fusiform gyrus). Taken together these findings and the proposal by Baddeley, Allen, et al. (2011) and Baddeley, Jarrold, et al. (2011), one could argue that different binding functions carried out in WM may rely on different networks subserving different buffers. For instance, while a frontal-parietal-MTL network could be the neural correlate of the episodic buffer (Baddeley, Jarrold, & Vargha-Khadem, 2001; Prabhakaran et al., 2000), the parietal-occipital-temporal network could be the correlate of the visuo-spatial sketchpad (Parra et al., 2014; Shafritz, Gore, & Marsch, 2002; Todd & Marsch, 2005; Xu & Chun, 2006).

Studies of single clinical cases have supported this view. Baddeley, Allen, and Vargha-Khadem (2010) investigated patient Jon who suffered from bilateral atrophy of the hippocampus from birth and have shown preserved conjunctive binding function in WM. Parra et al. (2015) reported on case AE who after a right hippocampal infarct, which caused amnesia, presented with a dramatic deficit to hold relations of features

in WM but completely normal abilities to hold feature conjunctions.

While these studies might suggest that some forms of STM binding could rely on the hippocampus (see also Bird & Burgess, 2008; Ezzyat & Olson, 2008; Finde et al., 2008; Hannula, Tranel, & Cohen, 2006; Hartley, Bird, Chan, Opolotti, Hassain & Vargha-Khadem et al., 2007; Kan, Giovanello, Schroyer, Makris, & Verfaellie, 2007; Nichols, Kas, Verfaellie, & Gabrieli, 2006; Olson, Page, Moore, Chatterjee, & Verfaellie, 2006; Piekema et al., 2010), it remains unclear why, in other MTL damaged patients, objects-locations or drawings-locations binding maintenance at short delays have consistently been reported as preserved (Denson, Moulden, & Squire, 2010; Jernison & Squire, 2011; Jernison, Winstead, Hopkins, & Squire, 2012; Strager, Kirwan, Hopkins & Squire, 2008; see also Squire, 2017 for an example in the verbal domain). These authors suggest that as long as the task procedure does not exceed WM capacity, patients with amnesia do not present any WM binding deficit (Denson & Squire, 2011), a view more compatible with the typical contrast between impaired long-term but preserved STM performance in amnesia.

However, the hypothesis of a dissociation between the active maintenance of conjunctions versus relations of features in WM found support in research on cognitive ageing. For instance, older adults present with relational binding deficits in both long-term memory (Naveh-Benjamin, Bray, & Levy, 2007; Naveh-Benjamin, Guez, Klib, & Reedy, 2004; Old & Naveh-Benjamin, 2008) and WM (Cowan, Naveh-Benjamin, Klib, & Saults, 2006; Mitchell, Johnson, Raye, & D'Esposito, 2000; Peterson & Naveh-Benjamin, 2005). However, they seem to retain the ability to process conjunctions features until late in life (Brockmole, Parra, Della Sala, & Logie, 2008; Hoofvangers, Gonzalez, Magnolia, & Parra, 2017; Parra, Abrahams, Logie, & Della Sala, 2008). This dissociation has been explained by the atrophy that the hippocampus undergoes with ageing (Mitchell, Raye, Johnson, & Greene, 2006; Mitchell et al., 2000). Monti et al. (2015) highlighted the important contribution that the hippocampus makes to relational memory processing across a broad range of tasks that span multiple domains. However, regions of the brain that appear to support conjunctive binding functions in LTM (i.e., entorhinal and perirhinal cortices; Mayes et al., 2007) remain unaffected by age (Frazzetta et al., 1995). From these perspectives, conjunctive binding functions may be more reliable to inform about abnormal ageing variants than relational binding functions.

Parra and collaborators have thoroughly investigated this hypothesis. They have found that indeed conjunctive binding functions separate normal ageing from mild stages of dementia due to Alzheimer's disease (AD) earlier and more accurately than relational binding functions (Ruppura et al., 2015; Parra, Abrahams, Logie, & Della Sala, 2013). Hence, considering that the visuo-spatial sketchpad appears to host automatic, low-level WM binding functions which are subserved by age-resistant brain regions, while the episodic buffer hosts relational binding functions which require the contribution of the hippocampus, a structure known to shrink with age, assessment of functions supported by the former buffer may offer better opportunities to contribute to the early detection of AD than of those supported by the latter buffer.

Despite this evidence, consensus papers continue to recommend relational binding tasks, particularly long-term associative memory tasks, as markers for the early detection of AD (e.g., Free and Cued Selective Reminding Tests, Costa et al., 2017; but see Della Sala, Kozlova, Starnate, & Farra, 2017). This position follows the long-standing view that relational forms of episodic memory (e.g., associative learning) which are supported by the hippocampus are the earliest memory functions affected by this form of dementia (but see Džić, Barbescu, Fečican, Tramošić, Guedj & Poncet et al., 2011). The evidence supporting this notion is rather scattered in the literature and no one single study has brought together these methodologies to test patients with hippocampal damage. Such research is needed to demonstrate if those relational memory functions assessed by tests recommended by guidelines do indeed rely on the hippocampus while conjunctive binding as assessed by the STM binding test does not (Peters, Abraham, Logie, & Della Sala, 2014).

4. The present study

The contribution that studies of patients with brain lesions has made to shaping our understanding of the functional architecture of WM has been widely acknowledged (Baddeley, 2007c). This paper addresses the question of whether neuropsychological evidence drawn from a single case could inform about the functional organization of WM buffers, which host different binding functions. The aim of the paper is twofold. A theoretical aim focuses on investigating the hypotheses that dissociations of memory binding functions can be observed in patients with hippocampal damage, and that such dissociations would allow further assessment of recent hypotheses regarding the anatomo-functional architecture of WM buffers (Baddeley et al., 2011). An applied aim focuses on further investigating the hypothesis that memory tests which assess conjunctive binding functions of WM buffers – which are preserved in healthy ageing and severely affected in the pre-clinical stages of AD – do not tax the function of the hippocampus, whereas those which assess relational or associative binding functions do. To test these hypotheses, we chose a battery of neuropsychological tests, which are being recommended by recent guidelines and consensus papers as useful markers for the early diagnosis of AD (Costa et al., 2017). As we noted above, such tests have never been used before together within a common assessment protocol. We predicted that the study of patient KA (see Joliet et al., 2018 for an in-depth case report) who we introduce next, would allow us to gain new insights about the dissociable nature of WM binding buffers, their neuroanatomical underpinnings, and the implications of such evidence for the assessment of age-related diseases such as AD. To investigate these hypotheses, we assessed KA with two sets of memory tasks. First, we selected a series of three memory tasks consistently reported as tapping hippocampal-dependent processes. These tests were also chosen because of their diagnostic value in identifying early AD. Second, we assessed KA's ability to perform two experimental STM binding tasks designed to further dissociate relational and conjunctive binding functions. In the next section, we describe the case of patient KA, together with a detailed

examination of the radiological findings. We then provide the description of the tasks used together with the rationale for their selection and the overall experimental procedure.

5. Materials & methods

5.1. Case description

KA is a right-handed man who was 36 years-old at the time of assessment. This patient was first seen in the memory clinic of Rennes University Hospital in 2009, when he complained of memory deficits since he was a child which was corroborated by his family. His only and notable antecedent was severe neonatal hypoxia, and his neurological examination proved unremarkable. However, clinical observation revealed obvious limitations in moment-to-moment memory: KA often repeats himself without any awareness and cannot orient himself in an unfamiliar environment. Initial neuropsychological assessment confirmed very severe and selective memory impairment, without any other cognitive deficit (see Table 1, and see Joliet et al., 2018 for details). A 44 points discrepancy was found between Intelligence and Memory Quotients (IQ & MQ), KA scoring 97 and 53, respectively. Patient KA received different neuropsychological assessments between March 2009 and July 2015 without any notable change. A psychometric confirmation of his severe amnesia finally came from his performance on the Rivermead Behavioural Memory Test, patient KA scoring 5 (profile score), which is twice lower from previously well-known cases of early-onset amnesia (e.g., Rosenbaum, Carson, Abraham, Bowles, Ewan, Köhler et al., 2011).

5.1.1. Radiological findings

Visual examination of MRI scan (see Fig. 1) revealed bilateral atrophy of the hippocampal formation, together with severe atrophy of the fornix and bilateral anterior thalamic nuclei. The mammillary bodies as well as the mammillo-thalamic tract remained unidentifiable, an extremely rare condition across the literature.

To further examine patient KA's hippocampus, a dedicated high-resolution (375⁰×375² mm) proton-density-weighted MRI sequence was acquired on a 3T-scanner perpendicular to the long axis of the hippocampus. That sequence allowed to segment hippocampal subfields (CA1, Subiculum, and "other subfields", i.e., CA2-3-dentate gyrus) according to a published protocol (La Joie, Fouquet, Mézenge, Landeau, Villain, Mevel et al., 2010) that was developed based on anatomical atlases (Duvernoy, 2005; Harding, Haliday, & Kri, 1998) and successfully applied to neurodegenerative disorders (La Joie, Ferrat, de La Sayette, Egret, Desjardis, Belliard et al., 2017). Patient KA's volumes were compared to a group of 20 healthy males who were matched for age (mean: 28.4, SD: 3.4), but more educated than KA (years of education, mean: 14.5, SD: 3.0), after normalizing for total intracranial volume. This confirmed a severe bilateral hippocampal volume loss (volume loss exceeding 55%, z-score = -5.6), which was marked in every segmented subfield in both hemispheres, in particular in the CA1 and subiculum regions (see Fig. 1).

Table 1 – Patient KA's neuropsychological background. For the sake of clarity, raw scores were converted to percentile rank scores based on available normative data.

Cognitive domains/tests	Raw scores	Percentile Ranks
French National Adult Reading Test		
Raw score, mean = 40	21	
Estimated Full Scale IQ (mean = 100, SD = 15)	100	50
Estimated Verbal IQ (mean = 100, SD = 15)	100	50
Estimated Performance IQ (mean = 100, SD = 15)	100	50
Intelligence/Wechsler Adult Intelligence Scale, III		
List of subtests		
Vocabulary	36	50
Information	22	73
Comprehension	20	37
Similarities	23	63
Digit Span	13	36
Letter Number Sequencing	8	9
Arithmetic	13	37
Picture Completion	22	62
Digit Symbol - Coding	62	26
Block design	29	6
Matrix reasoning	22	63
Symbol search	29	25
Standard scores, mean = 100, SD = 15		
Verbal Comprehension	105	68
Perceptual Organization	93	32
Working Memory	84	14
Processing Speed	84	14
Memory/Wechsler Memory Scale II		
List of subtests – raw scores		
Digit span – forward	5	7
Digit span – backward	3	41
Spatial span – forward	5	9
Spatial span – backward	4	36
Information and orientation	14	>94
Logical Memory I	11	.1
Face Recognition	36	25
Verbal Paired Associates I	4	1
Family Pictures I	8	0.1
Words List, 1st recall	9	23
Words List, Total recall	23	3
Letter Number Sequencing	8	9
Spatial Memory	12	9
Mental Control	35	95
Digit Span	13	9
Logical Memory II	1	.1
Logical Memory II, retention (%)	12.5	.1
Face Recognition II	39	50
Verbal Paired Associates II	0	.1
Family Pictures II	9	2
Words List II	9	.1
Standard scores, mean = 100, SD = 15		
Verbal Immediate Recall	58	.3
Verbal Delayed Recall	54	.1
Visual Immediate Recall	67	1
Visual Delayed Recall	75	5
Delayed Recognition	54	.3
Working Memory	77	6
Attention & Executive Functions		
2 & 7 Ruff Selective Attention Test		
Speed	267	45

(continued on next page)

Table 1 – (continued)

Cognitive domains/tests	Raw scores	Percentile Ranks
Efficiency	1.166	57
Verbal Fluency		
Letter F	20	46
Letter R	20	59
Fruits category	16	35
Ruff Figural Fluency Test		
Unique designs (raw score corrected for age & education)	74	21
Perservative errors ratio (raw score corrected for age & education)	.086	68
Trail Making Test		
Part A (seconds)	33	73
Part B (seconds)	72	80
Hayling Test		
Part A, total response time (seconds)	8427	31
Part B, total response time (seconds)	8530	–
Part B, raw score	0	80
Dual task interference paradigm		
Mo index	92.02	50

Altogether, clinical and neuroimaging data suggested that patient KA presented with a developmental amnesia syndrome (DA) as described in Vargha-Khadem et al. (1997) and Gadian, Alcaraz, Watkins, Porter, Mishkin, & Vargha-Khadem et al. (2003). With patient HC (Hurley, Maguire, & Vargha-Khadem, 2011; Rosenbaum et al., 2013), KA's level of memory impairment is amongst the most severe ever reported across prior cases with DA. Moreover, and as recently reported (Ducicol, Bachevalier, Saleem, Gadian, Sarnsten, King Chong et al., 2017), brain abnormalities in KA extended beyond the hippocampal formation, with the involvement of diencephalic structures and thalamus nuclei, suggesting that the whole hippocampal system has been compromised (for further details and a cortical thickness analysis, see Jonin et al., submitted).

5.2. Memory tasks

5.2.1. Hippocampal-dependent tasks

We selected a set of three memory tasks based on their robust accuracy in identifying early AD: a Paired Associates Learning task ("PAL") similar to that incorporated in the CANTAB (Saksian et al., 1988), the Free and Cued Selective Reminding Test (FCSRT) (Buschke & Grober, 1988; Grober & Buschke, 1987) and the 4 mountains test ("4 MT") (Dartley et al., 2007). We further describe each of these tasks and provide a brief overview of the evidence accumulated for (1) their relative specificity in identifying hippocampal damage and (2) their efficiency in identifying early AD.

The PAL is a visuo-spatial associative learning task requiring participants to encode series of object-location associations, then to recall the correct locations when cued with the object. We devised a PAL task similar to that reported by CANTAB, which was implemented with E-prime 2.0 software (Psychology Software Tools, 2013) as follows. In the study phase, participants were asked to carefully look at an array of 8 boxes, one of which would contain an abstract object, visible during 2 sec. Subjects were instructed to memorize the location of the object. Immediately after the presentation of the

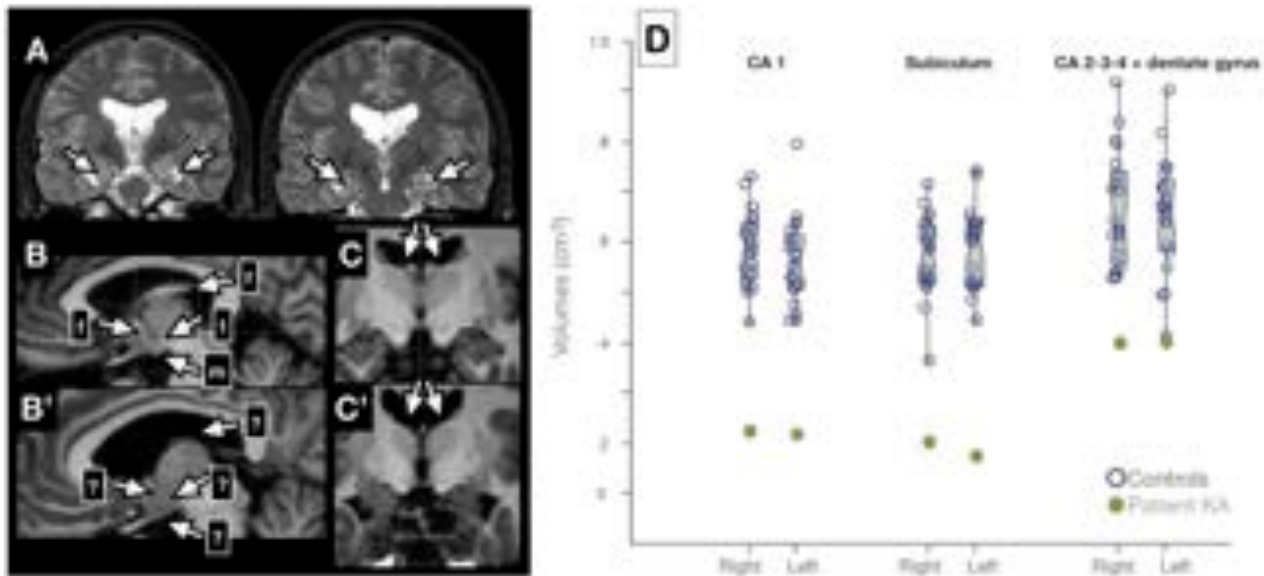


Fig. 1 – Structural MRI findings in the patient KA. (A) bi-hippocampal atrophy; (B) normal brain; (B') atrophy of the fornix, mammillary bodies and mammillo-thalamic tract in KA's brain; (C) normal brain; (C') atrophy of the anterior thalamic nuclei in KA's brain; (D) notched boxplots displaying normalized hippocampal volumes subfields in KA versus 20 matched control subjects. Notches represent 95% CI for the median; all comparisons being significant (Crawford's modified t-tests, all p -values $< .05$).

object-location association, the test phase started. The same array of 8 empty boxes remained on the screen, with the object displayed at the centre. The subject had to use the mouse to click on the location (box) where the object was presented during the study phase. After a practice trial instructing the subjects that the number of object-location associations would increase along the test, the first study phase started. A total of six different levels were used, each corresponding to a different number of object-location associations, from 1 to 6. To progress to the next level, subjects had to succeed in the current level, so that participants were allowed to repeat study and test phase until they had learned the associations, up to a maximum of 10 attempts, after which the task stopped. The locations of the objects were randomly chosen for each trial, and objects were randomly selected among a set of 8 different abstract coloured objects.

The PAL task assesses relational binding functions by requiring participants to bind together each target object with its correct spatial location. Arguably, such relational binding functions mainly rely on long-term memory. Several lines of research demonstrated that PAL performance is tightly linked to hippocampal functions. An fMRI study revealed a load-dependent hippocampal activation such as activation increased when the number of to-be-learned patterns increased (Jefferies, Finnell, McCabe, Acosta-Carboneiro, Ariani, Moreno-Zamir et al., 2011). Besides, animal lesion studies which inspired the task development (Parkinson, Murray, & Mishkin, 1980) confirmed the reliance of PAL performance upon hippocampal integrity (Olm, Heath, East, Bussey, & Sakaida, 2013). Moreover, PAL has been successfully used in identification of AD, at various stages of the disease, including very early stages (e.g., Sahakian et al., 1988; Swanson et al., 2001; see also Barnett, Blackwell, Sahakian, & Robbins, 2004) for a complete review about PAL findings). Finally, the number of errors across

all attempts during PAL has recently been shown to correlate with the available biomarkers of AD in a sample of patients with MCI, i.e., CSF levels of tau, P-tau, Aβ42, and hippocampal volumes (Nathan, Lim, Abbott, Galuzzi, Marisano, Sabbioni et al., 2017), strongly arguing for the use of that task to identify hippocampal abnormalities in the context of early AD.

The FCSRT is a multiple trials verbal learning task, involving successive free and cued recall of 16 target words (Grober & Buschke, 1987). We used the French version of the task, developed by Van der Linden et al. (2004), together with corresponding available normative data. Under explicit learning instructions, four written words are displayed on a sheet of paper. The subject is asked to point to and read out each word in response to its semantic category label (e.g., for the word kipper: "Can you point to the fish and tell me what its name is?"). This first stage of the task allows the experimenter to check that the words have been semantically processed. Immediately after the words have been correctly identified, a cued recall task is administered. Based on a semantic association between the cue and the target word (e.g., for the word kipper: "What was the name of the fish?"), this task measures the effectiveness of associative encoding processes. Once immediate cued-recall has been performed for the 16 words, and after a 20-sec verbal interference task, participants perform free recall trials, followed by selective cued recall trials (cues are only provided for items not recalled during the previous free recall trial). This procedure (free recall + cued recall) is repeated three times, with a 20-sec verbal interference task between each trial, to avoid subvocal rehearsal. This same procedure (delayed free + cued recall) is repeated after a 20-min interval. Finally, the selective reminding method is used, so that, in all the cued recall tasks except the third one, the correct answer is given only if the participant fails to recall the target word.

Since its initial development (Buschke, 1984; Buschke & Grober, 1986; Grober & Buschke, 1987; Grober, Sanders, Hall, Lipton, 2010), the FCSRT has been extensively studied in clinical settings. Prior research confirmed its accuracy in identifying mild dementia due to AD (Grober et al., 2010; Mars et al., 2017), but also showed that cue recall accurately predicts conversion to dementia due to AD in individuals with Mild Cognitive Impairment (Saraux, Ben, De Rotrou, Fabrigoule, Pasquier, Legrain, et al., 2007). This led some authors to propose that the FCSRT may detect the “Amnesic syndrome of the medial temporal type” as a core sign of prodromal AD (Saraux et al., 2007). The relationships between hippocampal integrity and index scores from the FCSRT have been highlighted in correlational imaging studies. For example, total recall score (i.e., free + cue recall) correlated with hippocampal volume in patients with AD at the dementia stage (Saraux, Charvillat, Genard, Collet, Einkingshaus, Cruz de Sousa et al., 2015). Conversely, hippocampal volume has recently been found to accurately predict cueing efficiency scores in a sample of controls subjects and patients with mild cognitive impairment (Quenou, Drirot, Woodard, Hanneuse, Gils, Lhomme et al., 2014). Moreover, the authors reported that MCI patients with supra-threshold amyloid- β load in the brain had impaired cue efficiency measures as well as total recall scores relative to MCI patients whose amyloid- β load did not reach the threshold. Finally, the FCSRT has recently been associated with very high sensitivity and specificity for prodromal AD, including in clinical samples with mixed aetiologies (Frischmann et al., 2017; Wagner, Wolf, Relachies, Doerr, Wolfgruber, Jensen et al., 2012). Available evidence therefore suggests that the FCSRT is very sensitive to the hippocampal dysfunction observed in early AD.

The “Four Mountains Test” (4 MT) is an immediate forced-choice visual recognition task requiring participants to encode pictures of artificial scenes (Hartley, Bird, Chan, Cipolletti, Husain, Vargha-Khadem, et al., 2007). Briefly, participants are instructed that they will be presented with a picture representing a landscape with mountains, which they must look at carefully to further recognize it among 4 pictures. Subjects attention is drawn to both the mountains shapes and their spatial layout at encoding, because at test, the target picture is presented from a different viewpoint than during encoding. Subjects are therefore instructed that they should encode both the individual components of the landscape (i.e., mountains) but also their spatial layout. After a series of 6 practice trials, 15 items are presented as follows: the target picture is presented for 8 sec, then a blank slide is shown for 2 sec, then the 4 pictures of the test phase are displayed on the screen during 20 sec. A 2-sec inter-stimulus interval precedes the next trial. Subjects respond by simply pointing to the picture they thought was shown during the study phase. Because all landscapes pictures included 4 mountains, and because the viewpoint of the target picture differed between study and test, this task requires binding processes to allow the integration of mountains shapes with their relative placement. Such a topographical memory task therefore involves object-location associations learning (i.e., relational binding). Consistently with the “cognitive map” theory (O’Keefe & Nadel, 1978), these spatial relational processes were shown to heavily rely on hippocampal functioning. Lesion studies for example have highlighted the sensitivity of that task to amnesia following

selective hippocampal damage (Hartley et al., 2007), and hippocampal volumes were found to correlate with task performance in healthy subjects as well (Hartley & Harlow, 2012). Accordingly, this task has been successfully used to identify early AD, among both healthy controls and other degenerative diseases (Bird et al., 2010; Chan et al., 2016; Peugas et al., 2010). Moreover, it has recently been found that the 4 MT score correlated with CSF tau-levels and further predicted conversion to dementia in a small sample of patients with Mild Cognitive Impairment (Wood, Moody, Lever, Minati, & Chan, 2014).

5.2.2. Conjunctive and relational memory binding tasks

A set of eight polygons and a set of eight non-primary colours were used (see Parra et al., 2010; Parra, Alcahama, Logie, Mendez, Lopez, & Della Sala, 2010) to create visual arrays presented during two Visual Memory Binding Tasks (VMBT), one tapping conjunctive and the other one relational binding functions. Fig. 2 illustrates the experimental procedure for one trial. A total of 6 trials were used for each condition (i.e., relational and conjunctive).

In the conjunctive task, 3 polygons randomly selected from the set of eight polygons (hereafter called “shapes”) were filled with 3 colours also randomly selected from the set of eight colours. These conjunctions were displayed for encoding for 6 sec on a white background. An empty white screen followed for 1 sec, preceding the test screen. At test, 4 shapes (3 targets + 1 distractor shape) were vertically presented on the left side of the screen, and 4 coloured blobs (3 targets + 1 distractor) were also vertically presented on the right side. Participants had to select using the mouse each target shape and its corresponding colour with reference to the study phase. After a minimum of three consecutive correct attempts (i.e., study + test phases with 100% accuracy), the task progressed to a delay period (15 sec), during which participants were asked to repeat out loud the letter “D” for 15 sec. If after 10 attempts participants failed to correctly learn the bindings between shapes and colours, the task progressed to the retention stage. After the filled retention interval, the test phase was administered once more (delayed component). Shapes and colours positions were randomly changed in the two recognition sets, so that position of test items could not be used as a memory cue. A series of 6 trials were administered, and instructions were summarized between trials for the amnesic patient. This resulted in a total of 18 shape-colour combinations to be learned. Shapes and colours were randomly chosen from the set of eight polygons and eight non-primary colours, thus resulting in different target and distractor sets for each participant.

In the relational task, the same procedures described above were used except that shapes and colours formed associations rather than conjunctions. A small black line joined the shape and its paired colour blob. The relational task was always administered before the conjunctive task for the entire sample.

For each memory binding task, several variables were considered regarding immediate (i.e., WM) and delayed (i.e., LTM) performance. Regarding WM, we first measured the recognition accuracy at the first immediate attempt, both for combinations (i.e., features conjunctions or relations) and individual features (i.e., shapes and colours). Maximum scores were 18 for each variable. We then computed the number of

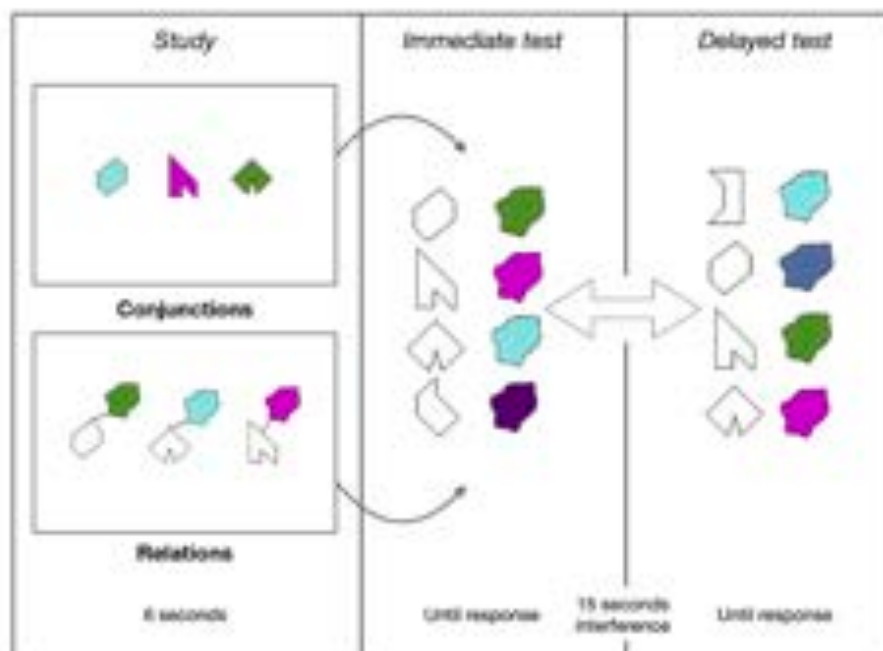


Fig. 2 – Illustration of the Visual Memory Binding Tasks (VMBT) for one trial. Subjects had up to 6 sec to encode either shape-colours relations or conjunctions, before being presented with an immediate forced-choice recognition test for individual features (shapes, colours), and the combinations. Study and immediate test phases were repeated until the participants reached 3 consecutive successful attempts. Then, after a 15 sec delay filled with verbal interference, the same test phase was repeated.

attempts required to reach the learning criterion, defined as the number of times the study - test phase had to be repeated to reach 100% accuracy (i.e., correctly selecting the 3 shapes and their corresponding colours). Finally, accuracy across all learning attempts was also computed, defined as the percentage of correct recognitions for either individual features (i.e., shapes and colours recognition accuracy) or combinations (recognition accuracy for conjunctions of features and for relations of features) across all trials. Regarding LTM, recognition accuracy scores for delayed task performance were also recorded, again for individual features and for combinations of features.

Our protocol therefore included of a set of three memory tasks that have proved sensitive to the early stages of AD as well as to be reliant on the hippocampal functioning. Of the three that assessed relational binding functions, two required to bind together an item with its location (i.e., PAL & 4 mountains test) and one required to associate words and semantic categories (i.e., semantic associative memory). Due to the selective damage to the hippocampal system sustained by patient KA, he should not succeed in any of these tasks. Regarding the contrast between conjunctive and relational memory binding procedures, patient KA's performance should be equally impaired after a delay in both conditions, because they will both rely on LTM processes to support retention of feature bindings. However, as stated in the Introduction, if hippocampal processing does not support conjunctive but only relational WM binding, KA performance on the first attempt of the relational task should be impaired but it should be normal on that of the conjunctive task.

5.3. Participants

A group of 15 male healthy participants (mean age = 36.1, SD = 3.31, range = 32–42; mean years of education = 12.5, SD = 2.33, range = 9–16) signed an informed consent to participate in the present study. Such a sample size and matching parameters are in line with prior case studies on that topic, which generally involved a smaller control group (Allen, Vaughn-Khadem, & Raddeley, 2014; Raddeley et al., 2010; Ercyrt & Olson, 2008; Jensen et al., 2010, 2011, 2012; Parris et al., 2008, 2015; Shrager et al., 2006). They were matched to patient KA for age and education (bilateral p values > .1). All participants signed an informed consent for the study, which was performed in accordance with the 1964 Declaration of Helsinki principles.

5.4. Procedure

All participants were assessed in a quiet room, free of any interference. The order of the tasks was fixed as follows: 1) PAL task; 2) VMBT-relational; 3) VMBT-conjunctive; 4) Four mountains test. The PCSKT was administered to patient KA as part of another testing session, and his scores were compared to available normative data, as stated above.

5.5. Statistics

Patient KA's performance was compared to that of healthy controls by means of Bayesian single-case statistical methods taken from (Crawford & Garthwaite, 2007). This approach

allows controlling for type I errors when comparing a single case to a typically small sample of matched controls subjects. It further provides a Bayesian p value together with a Point Estimate (PE) of the abnormality of a given score, associated with the 95% credible interval for the estimation. The Bayesian PE directly provides an estimation of the percentage of the control population susceptible to obtain a lower (or, in case of measures like RTs or total number of attempts to reach learning criterion, a higher) score, than the cases score. Besides, Bayesian Standardized Difference Tests (BSDT) were applied to compute the probability that differences observed in the patient KA between conjunctive and relational binding performances could be observed in the reference population. Again here, a Bayesian p value is provided together with a PE corresponding to the percentage of the reference population susceptible to obtain a larger discrepancy, associated with a 95% confidence interval for the PE. Unless otherwise specified, one-tailed tests were used given the expectation of patient KA being impaired. Note that for the Free and Cued Selective Reminding Test, we made use of available normative data. Non-parametric testing was used to examine whether control participants performance differed between the two binding tasks (Wilcoxon signed-rank test), or whether some correlation between relational and conjunctive binding tasks could be found (Spearman's rank correlation coefficient). Finally, for the sake of clarity we have run a Monte-Carlo simulation ($N = 10,000$) that allowed us plotting the chance levels for each relevant scores of the two experimental tasks (see Fig. 4), thus making it easier for the reader to interpret the controls' and the patient' scores.

6. Results

6.1. Hippocampus-dependent memory tasks

6.1.1. Paired Associates Learning task

Every control participant reached the last level of the task (i.e., 6 object-location associations to be remembered), meaning that they also successfully completed all the previous levels. Besides, each control subjects succeeded at the last level, with

a maximum number of attempts of 4, and a maximum number of errors of 6. By contrast, patient KA succeeded the 4th level on the first attempt, but he failed to complete the 5th level, despite 10 consecutive attempts, making a total of 35 errors (see Fig. 4). Because this task requires participants to succeed at the current level before moving on to the next level (i.e., increasing the number of object-location associations), and because patient KA failed to complete the 5th level that was accurately completed by all controls, patient KA's performance can be considered as severely impaired. We also compared the number of learning attempts necessary to succeed in KA and controls (see Fig. 3). Patient KA did not need more attempts than controls to correctly recall 1, 3 and 4 object-locations associations, however he needed 2 attempts to succeed at level 2 (2 object-location associations), whereas all control subjects succeeded on their first attempt.

6.1.2. Free and Cued Selective Reminding Test

Patient KA successfully performed the immediate cued recall phase, scoring 15/16, which did not differ from normative data [mean = 15.5, SD = .9; $p = .29$; PE = 29.65%, (17.48–43.41)]. Similarly, patient KA performed normally at the first total recall attempt (i.e., free + cued recall score) [controls' mean = 14.9, SD = 1.6; patient KA = 15; $p = .48$; PE = 52.63%, (32.82–71.52)]. However, we found KA to be impaired for all the other learning indexes. On average across the 3 immediate free recall trials, patient KA recalled 5.3 words [$p = .0025$; PE = .25%, (.00–1.34)]. The cueing procedure did not allow him to reach controls' level, KA recalling 12.7 words on average across the three immediate total recall trials (i.e., free + cued recall score, max. = 48) [$p = .0049$; PE = .49%, (.00–2.25)]. Finally, delayed recall scores were also impaired in KA, either considering free [5/16, $p < .001$; PE = .00%, (.00–.00)] or total recall scores [10/16, $p < .001$; PE = .00%, (.00–.00)] (for detailed scores, see Fig. 3).

6.1.3. Four mountains test

Patient KA scored 8/15 on the task, well below controls scores, with an estimate of less than .5% of the normal population expected to perform below KA's score [$p = .0044$; PE = .44%, (.00–3.04)] (see Fig. 3).

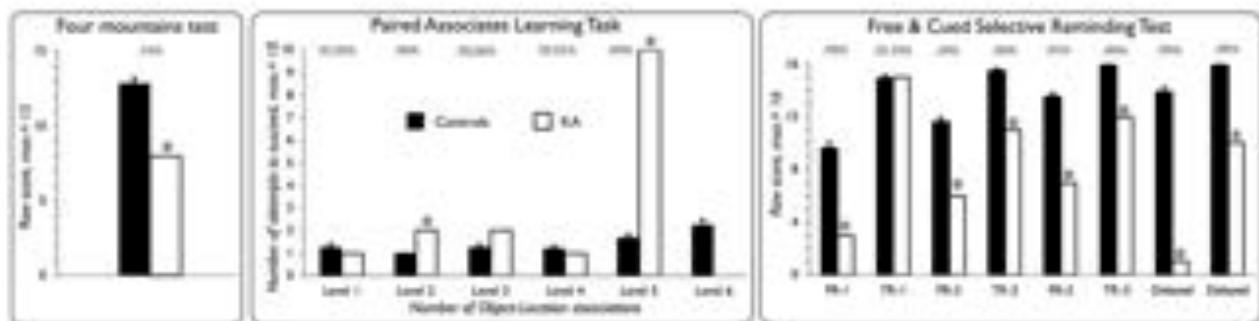


Fig. 3 – Patient KA's performance for the hippocampus-dependent memory tasks. Asterisks mark impaired scores (one-tailed Bayesian tests). Percentages correspond to the Bayesian Points Estimates of the proportion of the normal population susceptible to obtain either lower (Four mountains test & FCSRT) or higher (PAL task, total number of learning attempts required to succeed) scores. See text for detailed results. (TR-1 = Free Recall, first attempt; TR-1 = Total Recall (i.e., free + cued), first attempt).

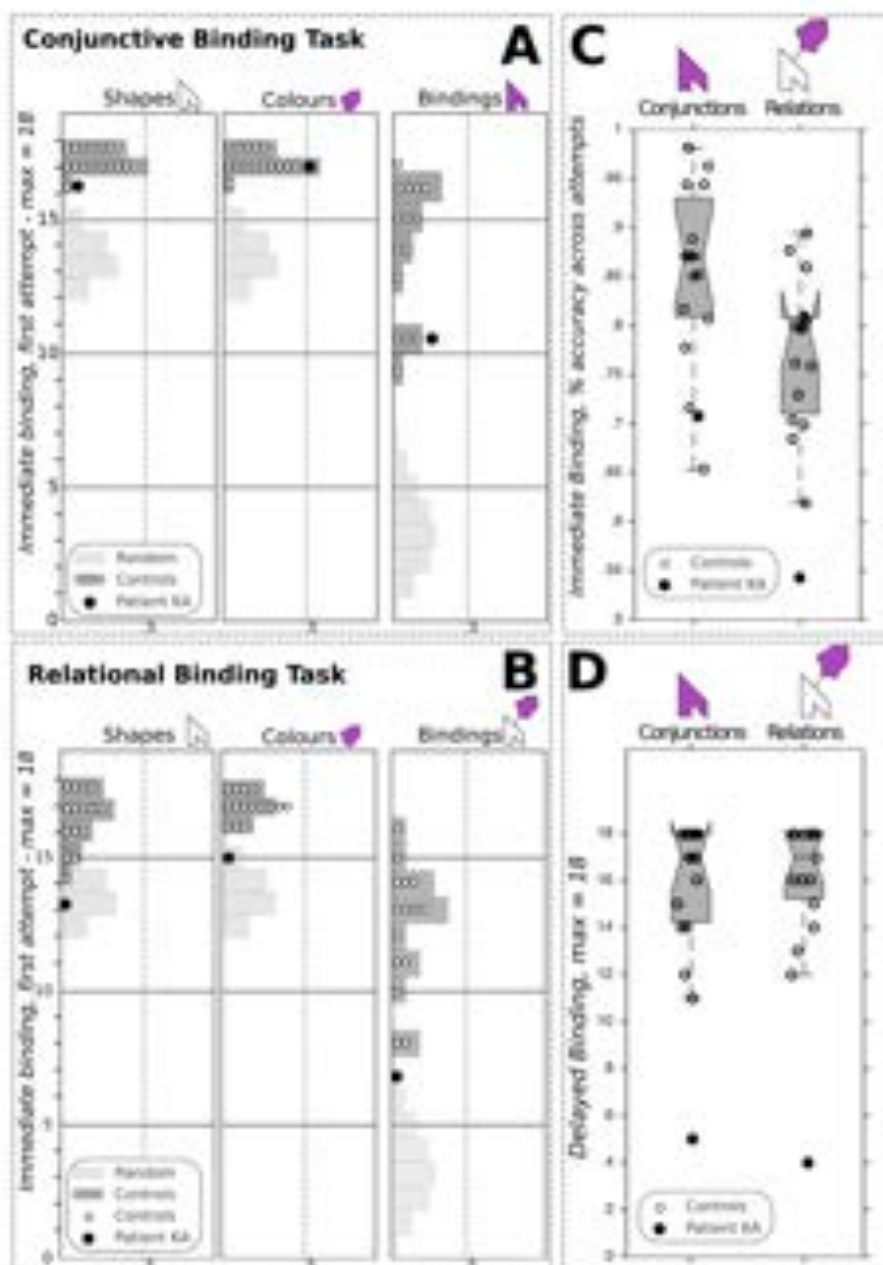


Fig. 4 – Visual memory binding performance of patient KA. Individual features and binding immediate recognition scores at first attempts for (A) the conjunctive and (B) the relational tasks. Random distribution in light grey corresponds to a Monte Carlo simulation run with 10,000 iterations; Controls's scores distribution is displayed in dark grey; individual observations are plotted. (C,D) Notched boxplots showing the immediate binding accuracy (% correct) across all immediate attempts (C) and the delayed binding raw scores (D); notches represent the 95% CI around the median.

6.2. Visual memory binding tasks

Fig. 4 illustrates patient KA's performance for the immediate & delayed recognition parts of the visual binding tasks. Regarding conjunctive binding, patient KA performed at the bottom of the range of controls at first attempt and his score did not differ from controls [patient KA = 11/18; controls mean = 13.93, SD = 2.40; $p = .128$; FE = 13, [3.0–29.7], and removing the lowest controls' score did not alter that result [$n = 1$, FE = 7.1%, [9–20.7]]. While patient KA needed

significantly more attempts than controls to succeed [patient KA = 24; controls mean = 18.93, SD = 1.87; $p = .010$; FE = 99%, [94.4–100.0]] – to make it clear, such FE means that only 1% of the normal population is susceptible to need more attempts than KA], he proved as accurate as controls across all attempts [patient KA = .71%; controls mean = .85, SD = .09; $p = .077$; FE = 7.7%, [1.1–21.8]]. Given that control participants presented with an overall high level of performance in the conjunctive binding task, a ceiling effect may have reduced the probability of detecting impairment in the patient KA. To

address this, we computed the skewness of the controls' scores distributions for both immediate binding score at first attempt and percent accuracy across immediate attempts. Skewness values are -0.7638 (SE = $.5801$) and -0.959 (SE = $.5801$), respectively, which confirms that while the distributions are indeed negatively skewed, they do not show ceiling effects and remain in the acceptable range for normal univariate distributions (Crawford & Wallace, 2014). Finally, when specifically testing the corresponding distributions for normality (Shapiro–Wilk test), we found p values well above the alpha level ($p > .37$). Overall, patient KA therefore seems to have preserved conjunctive binding scores, especially regarding the most relevant score, namely the accuracy at first attempt. Here, the patient performs in the low range of controls but remains unimpaired.

Turning to relational binding, patient KA was impaired at first relational binding attempt [patient KA = $7/18$; controls mean = 12.33 , SD = 2.35 ; $p = .023$; PE = 2.3% , $(1-9.5)$]. He again needed significantly more attempts than controls to succeed [patient KA = 35 ; controls mean = 20.07 , SD = 2.46 ; $p < .001$; PE = 100% , $(99.2-100.0)$], but remained well below controls' accuracy across all attempts [patient KA = 54% ; controls mean = 77% , SD = $.08$; $p = .007$; PE = 3% , $(0-4.7)$]. Interestingly, we found that patient KA's difference regarding the total number of immediate binding attempts between conditions fulfilled criteria for a strong dissociation, with a PE of 2.56% [$.81-5.08$]. In other words, these results suggest that the discrepancy observed in KA between conjunctive and relational learning attempts required for successful memory binding is likely to occur in less than 3% of the normal population. For that difference, the observed performance of KA was clearly out of the range of controls [KA = -11 ; controls' range = $(-3; 4)$], and a similar difference was found for the total number of immediate trials [KA = -33 ; controls' range = $(-9; 12)$]. Importantly, controls' performance did not differ between binding conditions, either for the first attempts scores ($W = 55$; $p = .063$) or the total number of attempts required ($W = 12$; $p > .121$), ruling out any significant difference in terms of task difficulty. Moreover, we failed to find any significant correlation between conjunctive and relational immediate binding scores (Spearman's r values ranging from $.273$ to $.359$, all p values $> .05$). To further emphasize our main finding, we estimated the uncertainty over the percentile rank of KA's scores at first attempts, for both conditions (Crawford, Garthwaite, & Slick, 2003). This led to a 95% Bayesian interval of $1.8-45.1$ around the estimated percentile rank of 17 for the conjunctive condition, whereas the estimated percentile rank was 0 in the relational condition, with an associated interval of $0-15.2$.

Considering delayed binding performance, patient KA proved severely impaired in both conditions to a similar extent (conjunctive: $5/18$; relational: $4/18$, p values $< .001$ in both cases, with PEs = $.0\%$).

Patient KA's memory for individual features was also assessed, and compared with controls by use of two-tailed testing procedures for immediate scores, given the uncertainty about the status of recognition memory for single items in patients with amnesia (Baldstock, Mayes, Gong, Roberts, & Kapur, 2005; Yonelinas, Aly, Wang, & Koen, 2010). Delayed scores were severely impaired in both

conditions, with PEs ranging from 0 to 3.43% , all p values being well below 5% .

Considering immediate performance, patient KA presented normal scores at first recognition attempt for individual features in the conjunctive binding task (Shapes: patient KA = 16 ; controls' mean = 17.33 , SD = $.62$; $p = .057$; Colours: patient KA = 17 ; controls' mean = 17.27 , SD = $.59$; $p = .665$), but he was impaired in the relational task (Shapes: patient KA = 13 ; controls' mean = 16.6 , SD = 1.24 ; $p = .014$; PE = $.69\%$, $(.00-4.32)$; Colours: patient KA = 15 ; controls' mean = 17.07 , SD = $.07$; $p = .013$; PE = $.63$, $(.00-3.99)$). Similarly, when considering overall accuracy across recognition trials for both shapes and colours as individual features, the relational binding task yielded impaired performance (Shapes: patient KA = $.80$; controls' mean = $.95$, SD = $.04$; $p = .003$; PE = 1.4% , $(.00-1.14)$; Colours: patient KA = $.90$; controls' mean = $.96$, SD = $.02$; $p = .018$; PE = $.91$, $(.00-5.27)$). However in the conjunctive task, only Shapes recognition accuracy across trials proved impaired [patient KA = $.90$; controls' mean = $.98$, SD = $.03$; $p = .022$; PE = 1.09% , $(.01-5.98)$], whereas Colours recognition remained in the fully normal range [patient KA = $.97$; controls' mean = $.97$, SD = $.02$; $p = .92$]. To sum up these findings about recognition accuracy for individual features, we found that in the conjunctive binding task, patient KA could normally hold individual colours and shapes in WM. By contrast, the patient failed to recognize individual features (either Shapes or Colours) in the relational binding task at first attempt, and he remained well below the controls' level across further learning attempts.

Altogether, we therefore found patient KA to be severely impaired for both binding conditions after a delay filled with verbal interference. However, STM binding performance differed according to the task condition, since the patient completed the conjunctive task in the low but normal range, but was clearly impaired in the relational task. Moreover, the observed difference between the numbers of attempts required for learning shape-colours associations in the relational versus conjunctive binding conditions fulfilled the criteria for a strong dissociation. In fact, KA needed 75% more trials than controls to successfully learn the relational bindings while 26% more attempts were enough for the conjunctive bindings.

Nonetheless, the low-range score of the patient at first attempt in the conjunctive binding condition may suggest that, rather than being impaired in the relational WM binding task only, KA is also unable to normally hold conjunctions of features in WM. We therefore ran an additional conjunctive binding experiment, with a larger sample of controls subjects, to independently assess whether the patient's ability for visual WM conjunctive binding is truly preserved.

6.3. Additional visual memory binding task

Patient KA underwent a last visual WM binding task including three conditions: STM for individual features (Colours or Objects) and STM for conjunctive binding (i.e., Colours–Objects combinations). The task has been described in details elsewhere (Goebel-Jones et al., 2017). Briefly, the procedure was very similar to the binding tasks described above. In the critical binding condition, participants were presented with a pair of

coloured objects (line drawings of living or manmade entities), with the same timing as in the other binding experiments (i.e., 1.5 sec per feature at study). An immediate recognition test involved the reconstruction of the object-colours bindings exactly as described in previous sections: participants had to select among a similar number of targets and lures, objects and their colours as they were presented during the study phase. For the individual features conditions (i.e., Objects or Colours), the study arrays included 4 items, while 2 items (i.e., two Object–Colours pairs) were used in the binding condition; the same number of lures was added at test. The number of features to be held in STM was kept constant across conditions, and 8 trials were performed for a total of 24 STM test trials. For the purpose of the present study, we will focus on the immediate test scores, namely those corresponding to the first attempt score described in the previous section (5.2).

The scores of patient KA were compared to those of 32 healthy controls matched for age and education (see [Hoozemans et al., 2017](#)), using the same statistical methods as the ones described in previous sections. One limitation that must be stressed here is that the control participants were Spanish-speaking Colombian subjects, while patient KA is a native French-speaker; note however that the set of objects was taken from the International Picture Naming Project (<https://oi.uci.edu/experiments/ipsn/>), thus limiting cultural biases. Patient KA performed very well for all conditions, with accuracy scores ranging from 93.75 to 100%. [Colours-only: patient KA = 93.75; controls' mean = 91.41, SD = 7.75; $p = .768$, PE = 61.6%, (47.8–74.4); Objects-only: patient KA = 100.00; controls' mean = 92.68, SD = 8.35; $p = .394$, PE = 80.3%, (67.8–90.0); Objects–Colours binding: patient KA = 100.00; controls' mean = 93.164, SD = 9.31; $p = .475$, PE = 76.3%, (63.2–86.9)].

These results provide additional evidence suggesting that patient KA is not impaired in the STM conjunctive binding of pairs of individual features (Object–Colours in that case). Moreover, STM for individual features also was preserved, consistently with the results of the conjunctive memory binding task described in the section 5.2.2.

7. Discussion

The present single case study was set out to investigate two questions. At a theoretical level, we investigated whether binding functions carried out in WM could dissociate after hippocampal damage. We sought evidence that could inform recent hypotheses regarding the anatomo-functional architecture of WM buffers. At the applied level, we investigated whether the forms of binding which have proved sensitive and specific to AD are equally relying upon the hippocampal system.

We presented the case of patient KA with a syndrome of developmental amnesia due to bilateral hippocampal atrophy as well as severe atrophy of the anterior thalamus and diencephalic structures. Such a pattern of extensive and selective damage to the whole extended hippocampal system, leaving anterior subhippocampal structures intact, represents a unique opportunity to deepen our understanding of how that system contributes to binding functions. Based on current

views and debates about (1) the role of the hippocampus and related MTL structures in WM binding functions, (2) tests devised to assess hippocampal functions in the early detection of AD, (3) and the vulnerability of these brain regions (MTL) to the neurodegenerative course of such a type of dementia, we thought KA's assessment would likely provide evidence to help address some of these outstanding issues. Three main findings resulted from KA's assessment. First, as predicted, patient KA proved severely impaired across three memory tasks selected for their known sensitivity to hippocampal damage, often performing below the 1st percentile relative to controls. Second, patient KA was unable to hold in WM (1-sec delay) three shape-colours associations (relational binding), whereas he could hold three integrated coloured shapes (conjunctive binding) remaining in the normal range of performance. Third, when tested after a 15-sec delay filled with a verbal task, performance dramatically dropped close-to-floor levels, both during conjunctive and relational binding conditions. In the discussion that follows, we map these findings to the outstanding issues abovementioned.

7.1. Binding in LTM and WM: what is unique and what is shared?

Evidence from the literature has consistently indicated that the relational or associative binding functions of the hippocampus support memory operations carried out both in WM and in LTM. [Olsson et al. \(2012\)](#) suggested that processing stimuli relations may follow a continuum from the very early stages of information processing (i.e., perception) to the stable representation in memory (i.e., LTM). Our data seem to support this view. We have reported that after early damage to the whole extended hippocampal system, patient KA is unable to perform three associative memory tasks. These tasks require the binding of features that share external relationships, which defines relational binding function (object – location (PAL), word – word (FCSRT), mountain – location (4 mountains test)). Similarly, patient KA was found unable to hold in mind for 1 sec three associations (or relations) between a shape and a colour blob. It is well acknowledged that relational representations are the core elements supporting declarative, long-term memories ([Olsson & Eichenbaum, 2015](#)). These findings suggest that STM tasks tapping relational binding function share a common reliance upon hippocampal function with tasks assessing associative LTM. KA's impairment in the delayed recall trials (i.e., free and cued recall) from the FCSRT strengthens this idea. The fact that patient KA was unable to recognize such relationships after 15 sec filled with verbal interference therefore opens the question of whether relational LTM deficits found in patients with amnesia result from poor consolidation of such memory traces or just impaired associative encoding. The fact that patient KA shows an impaired ability to hold three shape-colour relations after a 1-sec delay and then also failed to retrieve them after a longer filled interval is suggestive of the latter. Overall, our findings thus speak for a common binding function, namely, relational binding, as responsible for associative learning impairments across test delays (i.e., STM & LTM), and highly dependent upon the hippocampal system. That interpretation implies a role of the hippocampal system

for STM, which remains a matter of debate as we discuss in the next section.

7.2. The case for hippocampal involvement in relational WM binding

Prior neuropsychological evidence suggested that amnesic patients with damage thought to be limited to the hippocampal formation are perfectly able to hold relations between features at short delays (see Introduction section). For example, *Shrager et al. (2008)* found that 3 patients with damage limited to the hippocampal formation successfully maintained for 1 sec up to 6 relations between drawings and locations. Likewise, *Jenkinson et al. (2010)* found that, relative to 9 controls, 3 patients with damage limited to the hippocampal formation (also included in *Shrager et al., 2008*) displayed normal performance when asked to replace up to 4 objects onto their correct location after 1-sec delay. Such discrepancies across the current and these earlier studies may be accounted for by differences in the paradigms used.

Shrager et al. (2008) used a PAL task notably different from our PAL task. In the test phase, subjects were asked to make a Same/Different judgement on one single probe (i.e., either correct or recombined object – location association). By contrast, the PAL task used here requires participants to recall the location of each target object (i.e., location recall). Thus, the procedure used by *Shrager et al. (2008)* does not allow definitive conclusion about how many single associations have truly been held in WM, and may therefore have overestimated the actual WM binding performance. Moreover, *Shrager et al. (2008)* used a 3 × 3 grid whereas our PAL task involves a round-shaped array of eight boxes; finally, while concrete objects were used by *Shrager et al. (2008)*, we used abstract designs. These latter features could be of great importance because the associations between concrete objects and easily nameable locations (e.g., ‘there is a car in the bottom right case’, or ‘the car is in 3, 3’) may have supported a unitization strategy at encoding, which has been shown to boost recognition, even in amnesia (e.g., *Bonders, Aly, Parks, & Yonelinas, 2017; Parks & Yonelinas, 2015; Quamme, Yonelinas, & Norman, 2007; Ryan, Moses, Evarone, & Rosenbaum, 2013*). These differences may help explaining why by using an apparently similar PAL task to that reported here, *Shrager et al. (2008)* found their amnesic patients to perform far better (they all reached 6 object-location associations) than patients with early Alzheimer’s Disease (AD) in the PAL task, where these patients typically cannot reach the level 6 (e.g., *Swanson et al., 2010*). Accordingly, the fact that patient KA succeeded only up to 4 associations makes sense given that his amnesia is far more severe than people with early AD. Moreover, this apparent limit of 4 object-location associations in the case of KA fits well with the findings of *Jenkinson et al. (2010)* in 3 patients with hippocampal damage, who also seemed to systematically fail beyond this number of associations. Nonetheless, these authors report on the preserved STM of these patients for three object-location relations. What, then, could account for KA’s failure to hold only 3 relations of features within WM in our relational binding task?

One possibility is that in the *Jenkinson et al. (2010)* experiment, participants could again rely upon unitization strategies at encoding, because 1) real, nameable objects were used

and 2) rather than a Same/Different judgement at test, subjects had to replace the correct objects in their correct area on a table, defining errors as the deviations from exact locations measured in controls. In our relational binding task however, such unitization is far less likely because only abstract shapes and hardly nameable colours were used, and exact relations between shapes and colours was required at test. Furthermore, *Jenkinson et al. (2010)* asked participants to encode a set of real objects displayed on a table, and immediate test was performed on another table where subjects were instructed to physically replace the objects by reference to the study phase. This, again, may have overestimated their performance because in such a task not only visual but also kinaesthetic and, as stated above, verbal codes may have been involved. Contrary to such procedures, our binding task only probed visual WM, with no spatial, verbal, or kinaesthetic components. Patient KA’s impairment in relational WM for three relations also fits with the findings from *Olsen et al. (2008)*, who reported impaired ability to hold 3 object-location associations after a 1-sec delay in 4 patients with amnesia and damage thought to be limited to the hippocampus. Because the design was quite similar to the one used in *Shrager et al. (2008)*, the source of such divergent findings remains unclear. *Shrager et al. (2008)* pointed out that the patients from *Olsen et al. (2008)* lacked MRI quantitative arguments for the absence of extra-hippocampal damage, and suggested that the absence of self-paced pause between trials could have been confusing for amnesic patients (i.e., possible forgetfulness of the instructions). In the present case study, instructions were repeated to patient KA between trials, and whole-brain volumetry failed to find any abnormalities beyond the extended hippocampal system (*Jonin et al., 2018*).

An alternative interpretation for the WM binding deficits of amnesic patients that has consistently been proposed by some authors is that their failure is due to an impaired contribution of LTM. If the WM binding task requirements exceed STM capacity (see *Jenkinson & Squire, 2013*), that contribution would be necessary to perform the task at normal levels. Obviously, any WM task involving supra-span capacity at least partly relies on LTM. However, we think that this interpretation is very unlikely in the present report, for three reasons. First, estimates of spatial and verbal (digit) spans in the patient KA consistently reached 5 units of information (see *Table 1*), which, at first sight, seems to exceed the STM capacity required to hold in mind 3 shape-colour relationships for 1 sec. However, we do acknowledge that spatial and digit spans are insufficient proxies to estimate the visual span for abstract shapes and colours involved in our tasks. Future studies should design dedicated span tasks suitable to the working memory procedure used. Second, patient KA succeeded on the PAL task up to the level 4: he successfully recalled 4 different locations when probed with the corresponding objects. This, again, suggest that his STM capacity for single objects and, in that case, for object-location associations, is above the required size of 3 required in our WM binding tasks. Third, if patient KA’s STM capacity was to be exceeded in the relational binding task, it should also have been the case in the conjunctive binding condition. However KA remained unimpaired albeit in the bottom range of controls.

With respect to the possible contribution of LTM, *Olsson et al. (2012)* acknowledged that the hippocampus supports relational binding and comparison with or without conscious awareness for the relational representations that are formed, retrieved and/or compared. They suggest that for these binding and comparison functions the reach of the hippocampus may expand beyond LTM memory and underlies task performance in multiple cognitive domains. Considering this assumption, we cannot completely rule out some support from LTM to our WM relational binding task. Should that be the case, both individual features and their associations may have become vulnerable in KA, whose hippocampi were severely damaged.

Finally, an unexpected finding concerned patient KA's scores for individual features. We found that while colours and shapes were individually correctly recognized in the conjunctive binding condition (at first attempt), he failed to accurately recognize these very same features in the relational condition. A straightforward account for this result could be related to the fact that we did not counterbalance the order of the conditions across subjects, always starting with the relational task. This should be taken into account, e.g. in a replication study. Notwithstanding, this result is not in line with the idea that STM for single items should be preserved in patients with amnesia. Note however that KA's performance for shapes was indeed low, but well beyond chance levels (i.e., 80% and 90% correct, in the relational and conjunctive tasks, respectively). One way to account for this finding is to consider that the encoding of black outlined polygons may require relational processing. Analytical visual perceptual processing would be required to perceptually bind together the components of these meaningless shapes. Such additional perceptual processing at encoding may have interfered with the encoding of the individual features (i.e., the shape and the colour blob). Similarly, the need for binding features presented separately in space may on its own have interfered with the perceptual processing of the single features. However, when the features are presented bound together, or "unitized", these interference effects are no longer expected. We can only speculate that this could account for a relative weaker performance of KA for individual features in the relational binding task. If correct, that interpretation would imply that the use of meaningful, rather than meaningless, shapes should have little impact on STM for individual features, independently of the binding condition. Support for this view comes from the findings of *Buckley et al. (2010)* in another patient with developmental amnesia, patient Jon. The authors used meaningful shapes (diamond, cross, square, etc.) and found that Jon's STM for individual features was perfectly normal, in both relational and conjunctive binding conditions (see below for further discussion). Moreover, we think that our data are unlikely to be accounted for by some feature memory deficit in the patient KA because the shapes used in the Conjunctive and Relational binding tasks were the same. Had KA had a deficit in processing shapes in WM, this would have become apparent in both tasks not just in the relational task.

Finally, one has to consider that this task is not very suitable to assess memory for single features, which would ideally rely on recognition. By contrast, our procedure involves retrieval of the binding/relation, thus requiring a

reconstruction process. Recognition of individual features and reconstruction of features combinations are distinct processes. Previous studies relying on this task have only focused on the reconstruction element as this allows assessment of the core relational and conjunctive functions for which this paradigm was intended (*Parra et al., 2015; van Geldrop, Parra, & Kissler, 2015*). This is the first study that reports on memory for single features during this reconstruction paradigm. We acknowledge that although KA's performance across a wide range of tasks seems to confirm the presence of relational memory deficits across memory domains (WM and LTM), future studies with more specific designs are needed to investigate whether and to which extent processing in WM relations but not conjunctions also renders memory for constituent parts more vulnerable in patients with hippocampal damage.

7.3. Conjunctive WM binding following hippocampal amnesia

While patient KA failed to hold relational information at both short and long delays, he performed within the controls' range on the conjunctive binding task only when such bindings were held in memory for 1 sec. Several arguments reinforce our interpretation of impaired relational binding despite relatively preserved conjunctive binding in the patient KA.

First, the relational and conjunctive binding tasks we used are closely matched, but nonetheless failed to yield any significant statistical association in controls. This result adds to the past reports using similar procedure and generally speaking for the view of two distinct binding constructs (*Parra et al., 2009; Parra et al., 2010; Parra, Abraham, Loge & Mender, 2010; 2013*).

Second, several arguments do not support the intuition that the relational task may be more complex than the conjunctive task. The task was designed to allow an encoding time of 1 sec per feature in the two conditions (see Fig. 3). We believe this is sufficient amount of time to successfully encode the to be remembered items regardless of perceptual differences across task conditions. The two tasks presented the same type and number of features; the need to associate or integrate them being the only difference between task conditions. We did not find evidence for a significant difference between the two tasks in controls. When computing the difference between raw binding scores at first trial in controls (Relational minus Conjunctive), we found a median score of 1, with 2 controls presenting a negative score, and a majority of controls presenting a score at or below 2. Finally, it is worth noting that the order of the tasks was kept constant across participants, who started with the supposedly more complex condition. These facts all converge to rule out a complexity account for our findings of impaired relational but preserved conjunctive WM binding in the patient KA.

Third, our testing procedure required participants to make a forced-choice recognition task for each individual feature as well as for the associations between these features. That is, even in the conjunctive condition, participants must have successfully encoded both individual features and their associations to perform correctly, thus ruling out any strategy relying on single-feature encoding.

Fourth, study items were made of non-overlapped features (i.e., paired) in the relational binding condition and at test, recognition relied on two spatially separated sets of features which provided no cues to aid memory for relations or conjunctions (or even support from familiarity). Such design features make it very unlikely that a conjunctive strategy would aid performance on the relational condition of our paradigm. Moreover, the colours and the shapes were elaborated so that they both are very hardly nameable. Any encoding strategy based on encoding a single verbal token for a particular shape-colour association was therefore very unlikely. However, if some participants had to use such a strategy (resulting in some unitization of the features to be bound), one might expect this to facilitate the relational condition, but not the conjunctive condition where the features are presented already bound together. Altogether, we thus argue that our binding tasks do tap into non-overlapping working memory binding processes, which have been shown to dissociate in prior studies, and that the dissociation observed in KA is unlikely to be accounted for by different encoding strategies.

When shape-colour conjunctions were the memoranda, damage to the extended hippocampal system therefore left WM binding unimpaired. However, a longer retention interval of 15 sec filled with a simple verbal interfering task was sufficient to dramatically disrupt patient KA's ability to retain such conjunctions as indicated by performance far below controls level. These observations are suggestive of a WM function independent from LTM, allowing only temporary storage of features that share internal relationships (i.e., conjunctive binding), and that do not rely on the hippocampal system function. Thus, while relational binding function seems to support the formation of both short- and long-term memories, low-level conjunctive binding seems to operate only within WM. Earlier neuropsychological and neuroimaging studies have provided support for such a view (for an overview, see Olsen et al., 2012), albeit they rarely directly investigated the contrast between relational and conjunctive binding functions. For example, patient AE (Parrs et al., 2015) with unilateral right ischaemic lesions of the posterior thalamus, parahippocampal gyrus, and hippocampus presented with impaired WM relational binding leaving conjunctive binding unaffected. Importantly, this held even when using the same abstract shapes as we used in the present study, ruling out any subvocal rehearsal contribution to performance. It has been suggested that the neural underpinnings of LTM encoding may differ depending on the strategy used, either based on unitization or on relational binding, the former relying on perirhinal cortex activity (Davachi, Mitchell, & Wagner, 2003; Staresina & Davachi, 2006). Quite recently, event-related potentials at encoding brought evidence that these strategies might reflect two distinct and complementary learning systems, again relying upon distinct neural networks (Tu, Ahij, & Chan, 2017). The discrepancies between our findings in patient KA and prior findings in patient Jon (see below) suggest that when the design of STM binding tasks makes it possible to use a unitization strategy, sub-hippocampal structures like the perirhinal cortex, preserved in both patients, could be sufficient to perform at a fair level. However, in that case, performance would reflect preserved

unitization at encoding, rather than relational binding. An interesting possibility is that conjunctive binding and unitization share common properties, starting with a common neural substrate, but also a critical role in forming new representations for within-domain associations. Nevertheless, a question that remains is which cognitive system can support conjunctive binding and on which neural basis it relies, a question we address in the following section.

7.4. Which WM buffer supports conjunctive binding?

With respect to the cognitive substrates of conjunctive binding, Allen et al. (2006) demonstrated that feature binding in visual WM does not require executive resources above and beyond those needed to process single objects. This evidence already questioned whether the episodic buffer would be necessary for this form of binding. Besides, the hippocampus had been considered a binding device, which grants integrative abilities to the episodic buffer necessary for episodic memory formation (Prabhakaran, et al., 2003; Jeffries, et al., 2004; Baddeley, et al., 2011). Therefore, being independent of both executive resources and the hippocampus leaves conjunctive binding functions carried out in WM in need of an alternative buffer. An obvious candidate is the visuo-spatial sketchpad, since it was assumed to support low-level binding functions as the ones needed to form objects identity (Staresina & Davachi, 2006). This would also fit with the last revision of Baddeley's model of WM (Baddeley et al., 2011), suggesting that low-level features binding do not rely upon the episodic buffer.

Turning to the potential neural underpinnings of conjunctive binding, an obvious candidate is the ventral visual stream, and particularly the perirhinal cortex, acknowledged as being the core substrate of the conjunctions of features that support objects' recognition (e.g., Olsen et al., 2012; Staresina & Davachi, 2006), and being fully preserved in patient KA. The neuroimaging literature has also lent support to the idea that conjunctive binding within WM binding may be independent from the hippocampus. Parrs et al. (2014) for example have shown that the active maintenance of conjunctions of features (shapes – colours) at short delays mainly relied upon a temporo-parietal network, associated with left frontal areas (precentral gyrus and premotor cortex), without involvement of the hippocampus. Similarly, Piskerns et al. (2010) suggested that intra-item binding in WM (a kind of conjunctive binding) did not involve MTL activations. It could thus be speculated that different binding functions carried out in WM may rely on different networks subserving different buffers. While the episodic buffer would have a frontal-parietal-MTL network as a neural correlate (Baddeley, Jarrod, et al., 2011), the perirhinal cortex and a large frontal-temporal-parietal network could be the correlate of the visuo-spatial sketchpad (Parrs et al., 2014; Shallice et al., 2002; Todd & Marois, 2005; Xu & Chun, 2006), as the locus of conjunctive binding in WM.

7.5. Relational WM binding in developmental amnesia

We are aware of only one other study of WM binding in developmental amnesia. Baddeley et al. (2010) have extensively studied visual WM binding (i.e., shape-colour) in patient

Jon, who suffers from developmental amnesia like patient KA, thus making their study very relevant to our own findings. Participants had to encode four shape-colours associations that were displayed simultaneously for 250 msec, but presented separated in space (i.e., a colour blob on top of an un-filled shape) to further make an Old/New judgement on a coloured shape (i.e., target or lure) used as the test probe at a 900 msec delay. Jon's performance averaged across 24 trials was in the fully normal range, and he even tended to outperform controls. It is therefore surprising that, with a very similar procedure, we found patient KA to fail the active maintenance of only 3 shape-colours associations. However, a single probe was always used with patient Jon, always presented as a conjunction (i.e., a coloured shape), which might have allowed the patient to rely upon a unitization strategy (see also *Farrs et al., 2015*), which was not possible in our relational binding task where the reconstruction at test required KA to recognize the target single features and recall their bindings after 1-sec delay (see *Brockmole and Loge (2013)* and *Hawke (pers. et al. (2017)* for similar procedures). Moreover, *Buddley et al. (2003)* used meaningful shapes (a cross, a diamond, a square, etc.). We therefore consider the possibility that other STM processes like subvocal rehearsal, depending on extra-hippocampal structures (*Buchbaum, Olson, Koch, & Berman, 2005*), might at least partly have contributed to Jon's performance, thus overcoming a relational binding deficit. Early support for this interpretation comes from studies showing that abstract shapes maintenance rapidly decays in amnesic patients (e.g., *Tuller, Lewis, Cermak, & Goodglass, 1973*). By contrast, when testing patient KA with non-nameable polygons, such subvocal rehearsal is very unlikely, making our design possibly less contaminated by WM processes independent from binding itself.

7.6. Which memory binding function should we assess in AD and when?

The applied aim of the present study was to make the case of KA's assessment informative about the construct validity of tests devised for the early diagnosis of AD. We are not aware of prior studies systematically assessing the validity of hippocampus-dependent memory tasks used in the context of AD diagnosis by administering these tests to patients with amnesia (but see *Hartley et al., 2007* for an exception with the 4 mountains test). We reasoned that if tests failed very early in the course of AD could be successfully performed after damage to the hippocampi, this would suggest a need to move from hippocampal-dependent memory tasks towards new tests, better suited to their early cognitive markers properties for AD.

The recommended tests for the assessment of early AD are tapping relational (or associative) binding processes. It is the case for tasks such as the PAL test from the Cambridge Neuropsychological Test Automated Battery (CANTAB; *Sahakian, et al., 1988*); the Face Name Associative Memory Exam (FNAME; *Amariglio et al., 2012*; *Feritz, Amariglio, Becker, Frey, Olson, Frishe, et al. 2011*), Free and Cued Selective Reminding test (FCSRT; *Grober, Buschke, Crystal, Bang, & Dresner, 1988*), Memory Capacity Task (MCT); Memory Impairment Screen (MIS; *Buschke et al., 1995*). People with AD typically show difficulty in these specific tasks. Such an associative memory

deficit in AD is linked to the hippocampal stage which correspond to stage III or IV of Braak's scale (*Braak, Thal, Ghebremedhin, & Del Tredici, 2011*). This involves structures of the posterior MTL network (*Didic et al., 2011*), such as parahippocampal cortex, medial entorhinal cortex, posterior hippocampus and posterior cingulate cortex where neurofibrillary tangles develop later. These structures play a relevant role in context-rich memory tests (*Didic, et al., 2011*). The reason is that damage to the hippocampus and related structures at that stage of the disease prevents the formation and maintenance of new associations. These observations have been confirmed by a study conducted by *Sperling, Bates, Chua, Cocchiarella, Feritz & Rosen et al. (2003)*, who observed a significant reduction of hippocampal activation during encoding of new face-names associations in patients with mild AD. Importantly, they observed that healthy elderly also presented significantly reduced hippocampal activity, albeit to a lesser extent than mild AD patients. These findings may explain the difficulties of the elderly in performing associative memory tasks, in accordance with the influential associative deficit hypothesis (*Yevch-Benjamin, 2003*). Thus, the tests involving relational binding function, including WM relational binding tasks, would present a sub-optimal specificity for the early diagnosis of AD.

In the present study, the fact that patient KA is impaired in the three tasks currently used in the early detection of AD brings evidence reinforcing the sensitivity of these tasks to the hippocampal stage of AD. Interestingly, the score of patient KA at the "4 mountains test" (8/15) exactly replicated an earlier finding with that task in patient Jon, and also fits with the cut-off score of 8 or below for differentiating between Mild Cognitive Impairment patients with or without positive CSF biomarkers for AD pathology (i.e., levels of β -amyloid₄₂ and phosphorylated tau) (*Chan et al., 2016*). This confirms that WM relational binding function is very sensitive to hippocampal damage, either arising from early hypoxia as in patient KA, or from AD-related pathology at the hippocampal stage, or simply from ageing.

However, in the subhippocampal stages of AD, the early target of tau pathology is the entorhinal cortex (*van Hoesen, Hyman, & Damasio, 1991*; *Joutonen et al., 1998*). Several studies already demonstrated that the volume of the entorhinal cortex compared with the hippocampus volume is a more informative signal of conversion from MCI to AD (*Pickles et al., 2001*; *Shoghi-Jadid, Small, Agleppa, Kope, Dvok, Siddarth et al., 2002*; *deTolledo-Morrell et al., 2004*). It is also known that context-free tasks such as familiarity based-recognition memory (*Rabeau et al., 2004*; *Benson et al., 2015*; *Haskins, Yonelinas, Quamme, & Kanganath, 2008*) could be suitable cognitive markers to probe the early dysfunction of brain areas that appear affected in this stage, but it is not clear how the different MTL areas are related to memory deficits in AD (*Boefjeijers, Colla, & Farrs, 2015*). *Didic et al.'s* model (2011) suggested an account for how memory systems are affected in the AD continuum. Early damage to the subhippocampal structures may determine impairments in context-free memory tests, while the hippocampus seems to be related to context-rich memory tasks. Interestingly, there is consistent evidence that WM conjunctive binding accurately detects AD in its earliest, preclinical, stages (*Della Sala, Kozlowski, &*

Parra, 2017; Della Sala, Parra, Fabbis, Luzzo, & Alrahalma, 2012; Koppola et al., 2015; Parra et al., 2011; Parra, Alrahalma et al., 2010b; Reutz et al., 2013), while relational binding remains completely preserved. Furthermore, recent studies in cases of both familial and sporadic AD using electrophysiological techniques (EEG-ERP and brain connectivity), have reported both poor activation (Pietto, Parra, Trujillo, Flores, García, Bustin, et al., 2016) and connectivity (Parra, Mikulic, Trujillo, DellaSala, Lopez, Manes, et al., 2017) within the cortical network thought to underlie the visuo-spatial sketchpad. Considering that patient KA successfully performed the same WM conjunctive binding task as the one impaired in the pre-clinical stages of AD, while he was severely impaired on the WM relational binding task that is fully preserved at that stage of AD, we argue that conjunctive, not relational, binding function should be targeted for the early detection of AD. These observations in patient KA finally suggest that memory tests currently recommended for the diagnosis of AD (e.g., Costa et al., 2017) may actually lack specificity for the disease and, perhaps more importantly, miss their target as they may be sensitive to memory dysfunctions associated with late hippocampal stages, rather than early, subhippocampal stages.

8. Conclusion

We have reported on the case of patient KA, with a syndrome of developmental amnesia associated with selective damage to the whole extended hippocampal system. While the patient proved severely impaired in all tasks involving relational binding function, including WM tasks, he remained in the low to normal range in WM conjunctive binding tasks. Our findings therefore speak for a dissociation between STM binding functions after hippocampal damage, and inform the clinical assessment of early AD. Future studies will be needed to test the independence of conjunctive binding from the episodic buffer as well as its neural underpinnings, and to investigate whether, within WM, tasks tapping into the visuo-spatial sketchpad rather than the episodic buffer might offer better opportunities for the early detection of AD.

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