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Unraveling the neural circuitry of sequence-based navigation using a combined fos imaging and computational approach

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THESE DE DOCTORAT
DE L'UNIVERSITE PARIS DESCARTES

Spécialité Neurosciences

Ecole doctorale 474 Frontières du vivant

*Laboratoire Neurosciences Paris Seine, Equipe Cervelet, Navigation et Mémoire,
Université Pierre et Marie Curie*

**UNRAVELING THE NEURAL CIRCUITRY OF SEQUENCE-
BASED NAVIGATION USING A COMBINED FOS
IMAGING AND COMPUTATIONAL APPROACH**

présentée par

Bénédicte BABAYAN

pour obtenir le grade de

DOCTEUR DE L'UNIVERSITÉ PARIS DESCARTES

soutenue le 27 juin 2014, devant le jury composé de :

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Prof Alessandro TREVES	Professeur, Trieste	Examineur

To my grand-parents, Vlasta and Hamilton Mills

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Caractérisation des circuits neuronaux sous-tendant la navigation de type séquence: imagerie Fos, connectivité fonctionnelle et approche computationnelle

La navigation spatiale est une fonction complexe qui nécessite de combiner des informations sur l'environnement et notre mouvement propre pour construire une représentation du monde et trouver le chemin le plus direct vers notre but. Cette intégration multimodale suggère qu'un large réseau de structures corticales et sous-corticales interagit avec l'hippocampe, structure clé de la navigation. Je me suis concentrée chez la souris sur la navigation de type séquence (ou stratégie égocentrique séquentielle) qui repose sur l'organisation temporelle de mouvements associés à des points de choix spatialement distincts. Après avoir montré que l'apprentissage de cette navigation de type séquence nécessitait l'hippocampe et le striatum dorso-médian, nous avons caractérisé le réseau fonctionnel la sous-tendant en combinant de l'imagerie Fos, de l'analyse de connectivité fonctionnelle et une approche computationnelle.

Les réseaux fonctionnels changent au cours de l'apprentissage. Lors de la phase précoce, le réseau impliqué comprend un ensemble de régions cortico-striatales fortement corrélées. L'hippocampe était activé ainsi que des structures impliquées dans le traitement d'informations de mouvement propre (cervelet), dans la manipulation de représentations mentales de l'espace (cortex rétrosplénial, pariétal, entorhinal) et dans la planification de trajectoires dirigées vers un but (boucle cortex préfrontal-ganglions de la base). Le réseau de la phase tardive est caractérisé par l'apparition d'activations coordonnées de l'hippocampe et du cervelet avec le reste du réseau.

Parallèlement, nous avons testé si l'intégration de chemin, de l'apprentissage par renforcement basé modèle ou non-basé modèle pouvaient reproduire le comportement des souris. Seul un apprentissage par renforcement non-basé modèle auquel une mémoire rétrospective était ajoutée pouvait reproduire les dynamiques d'apprentissage à l'échelle du groupe ainsi que la variabilité individuelle.

Ces résultats suggèrent qu'un modèle d'apprentissage par renforcement suffit à l'apprentissage de la navigation de type séquence et que l'ensemble des structures que cet apprentissage requiert adaptent leurs interactions fonctionnelles au cours de l'apprentissage.

Mots clés: Navigation; Apprentissage de séquence; Comportement; Imagerie Fos; Analyse de réseau; Apprentissage computationnel; Apprentissage par renforcement

Unraveling the neural circuitry of sequence-based navigation using a combined Fos imaging and computational approach

Spatial navigation is a complex function requiring the combination of external and self-motion cues to build a coherent representation of the external world and drive optimal behaviour directed towards a goal. This multimodal integration suggests that a large network of cortical and subcortical structures interacts with the hippocampus, a key structure in navigation. I have studied navigation in mice through this global approach and have focused on one particular type of navigation, which consists in remembering a sequence of turns, named sequence-based navigation or sequential egocentric strategy. This navigation specifically relies on the temporal organization of movements at spatially distinct choice points. We first showed that sequence-based navigation learning required the hippocampus and the dorsomedial striatum. Our aim was to identify the functional network underlying sequence-based navigation using Fos imaging and computational approaches.

The functional networks dynamically changed across early and late learning stages. The early stage network was dominated by a highly inter-connected cortico-striatal cluster. The hippocampus was activated alongside structures known to be involved in self-motion processing (cerebellar cortices), in mental representation of space manipulations (retrosplenial, parietal, entorhinal cortices) and in goal-directed path planning (prefrontal-basal ganglia loop). The late stage was characterized by the emergence of correlated activity between the hippocampus, the cerebellum and the cortico-striatal structures.

Conjointly, we explored whether path integration, model-based or model-free reinforcement learning algorithms could explain mice's learning dynamics. Only the model-free system, as long as a retrospective memory component was added to it, was able to reproduce both the group learning dynamics and the individual variability observed in the mice.

These results suggest that a unique model-free reinforcement learning algorithm was sufficient to learn sequence-based navigation and that the multiple structures this learning required adapted their functional interactions across learning.

Keywords: Navigation; Sequence learning; Behaviour; Fos imaging; Network analysis; Computational learning; Reinforcement learning

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FOREWORD

The ability to maintain a sense of direction and location while moving in one's environment is a fundamental cognitive function. Humans and more generally animals rely on spatial cognitive processes in complex environments for obtaining food, avoiding prey and finding mates.

Navigation has been the subject of extensive research in the domains of sensory integration, information processing and decision making amongst others. It indeed involves multiple processes. A detailed breakdown of how navigation processes when one is driving to a destination in a well-known city has been proposed by Spiers and Maguire (2006): we initially plan our route to a destination. Sometimes we may also see an opportunity to adjust our plan whilst driving. We set up expectations, waiting to see a certain landmark to check if we are on the right route, occasionally inspecting the city around us as we travel through it. We monitor the surrounding traffic to achieve safe passage to our destination, and plan our own actions (stay in a traffic lane, change lanes). And often, within a familiar environment, we are driving without having any thoughts at all, "coasting" along the planned route. These processes do not necessarily occur as linearly as presented and each of them involves different brain regions (Spiers & Maguire, 2006). Furthermore, when the city is unknown, another set of processes is required to discover its organization. All these processes also involve memory functions as the mental representations of space are maintained and manipulated in short- and long-term memory to guide navigational behaviour.

Thus navigation is a highly complex behaviour, involving many subprocesses, which can vary in time depending on the amount of knowledge one has of our environment. During my PhD, I have studied navigation in mice through this global approach. I have focused on one particular type of navigation, which consists in remembering a sequence of turns, named sequence-based navigation or sequential egocentric strategy (Rondi-Reig *et al.*, 2006). The two main questions I have wanted to answer are:

- 1) What are the brain regions involved in sequence-based learning? What are their dynamics across learning? What is their network organization?
- 2) What are the learning mechanisms underlying sequence-based navigation? What information is taken into account (place? distance?) and how is it manipulated?

The first question was answered using Fos imaging, a technique that allows quantifying a regions' level of activation, combined to functional connectivity analysis to identify the network organization of the regions. The second question was dealt with

computational learning models by testing which learning process replicates best the behaviour. This work was done under the supervision of Dr Benoît Girard (ISIR, UPMC). The results are presented in the second article in this thesis, which is under preparation.

The first article presented in this manuscript concerns a project I participated in when arriving in the lab to do a master internship. I took part in Céline Fouquet's project that characterized the neural basis of the sequence-based navigation and a map-based (or allocentric) navigation. Contrary to sequence-based navigation that involves learning a given route (e.g.. *"first left, then right,..."*) to a destination, map-based navigation relies on a map-like representation of the environment to identify one's destination in a viewpoint-independent manner (*"my destination is between the post-office and the pharmacy"*). This study involved Fos imaging and a lesion study to decipher the role of the hippocampus and the dorsomedial striatum, two structures identified as being activated in each type of navigation. I was involved in the lesion study.

In the introduction of this manuscript, I shall first present the different processes involved in navigation and their known neural substrates. These will be grouped in two main processes: building a mental representation of space and using it.

As mentioned earlier, the processes involved in navigation differ if we are discovering one's environment and the route to take or if both are very well-known. These two phases are actually common to most learning situations. They have been the subject of intense research in motor task learning mostly which I will present in the second part of the introduction.

Most of the structures presented in these two parts have been analyzed in Fos imaging and this first part of the introduction will help identify the neural processes involved in the different learning phases of sequence-based navigation and the nature of their interactions, if any.

Memory is essential for all processes subserving navigation. Indeed going to one's destination can be done using different type of information that are stored for future use. The organization of memory will be briefly presented.

Finally the last section will focus on the different ways of navigating towards a goal in terms of the way information is manipulated. These are called "strategies" and they will be presented both from a computational and an experimental point of view. In this section, we will introduce sequence-based navigation and will see what is special about it and why we believe it is an interesting model to study.

As I was willing to have a global approach to navigation, my thesis encompasses several areas of neurosciences. In my work I have focused more on some particular aspects. These are described in details in the introduction. The other aspects on which I have less concentrated on are described in lesser details but it seemed however essential for me to present them even if briefly in order to give you a picture as full as possible of navigation.

INTRODUCTION

PART I Navigation and Mental representation of space

Before going into the processes involved in building and using a mental representation of space, I shall present pioneering work which have introduced the notion of mental representation of space and have first defined them. The following section will focus on the sensory processing involved in building the mental representation of space and the neural substrates known to represent spatial information. In the third section we will go through potential neural substrates which allow representing a goal, planning a trajectory to it and performing the motor command to carry out the trajectory. I have separated for clarity the processes involved in building and using a mental representation of space but processes involved in building a representation are continuously used when using the mental representation of space.

1. Mental representation of space

1.1. Tolman's "Cognitive maps"

When analysing the choice a rat makes at an intersection in a maze to obtain some food, the dominant view at the beginning of the 20th century was that animals learned the motor response which was automatically triggered off by the identification of the intersection (Hull, 1943). Such associations, termed **stimulus-response**, resulted from repeated exposure to the maze during which the representation of the stimulus (here the intersection) became, with increasing experience, more strongly connected to the mechanism generating the behavioural response (here a turn). The creation of such associations was thought to be driven by the presence of reinforcements (positive or negative), in this case the food reward. Stimulus-response associations were described as being habitual and not flexible.

In 1948, Edward Tolman sought to demonstrate that animals could also learn facts about the world that they could use in a flexible manner by creating what he termed a "**cognitive map**" representation (Tolman, 1948).

His hypothesis was first based on "latent learning" experiments performed by Blodgett in 1929 in which he showed that rats could learn the configuration of a maze without reinforcement (Blodgett, 1929). To do so, he ran three groups of food-restricted rats through a six-unit alley T-maze (Figure 1a). Only the control group (group I) found food in the food box,

the other two groups were fed in their home cages after each trial. On the third day for group II rats and seventh day for group III rats, the rats started finding food at the end of the maze for the first time. As long as the group II and III rats did not find food at the end of the maze, they did many errors, visiting dead-ends between the start and the food boxes. But as soon as they started finding food in the food box, their error curves dropped suddenly (Figure 1b). It appeared that during the non-rewarded trials the rats had been learning the configuration of the maze and this learning, termed “latent learning”, manifested itself after the food had been introduced. Tolman suggested that “*they [the rats] had been building up a ‘map’ and could utilize the latter as soon as they were motivated to do so*”. This “map” contained information about the configuration of the maze such as the relationships between its different sections, corridors, dead-ends and start and food boxes.

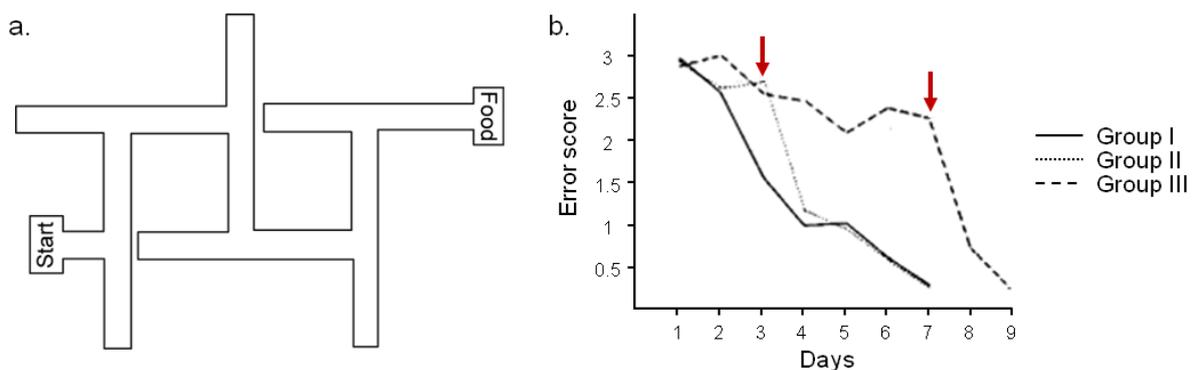


Figure 1: Latent learning experiments. (a) 6-unit alley T-maze where rats had to go from the start box to the food box, doing one trial a day. (b) Group I (control rats) diminished their number of errors across training days. Group II and III maintained a high level of errors, i.e. visited many dead-ends, when no food was in the food box. When food was added on day 3 for group II and day 7 for group III (red arrows), the rats performed similarly to the control group as from the following trial. *From* (Blodgett, 1929).

Tolman then sought to show that the maps could be used flexibly, in adaptation to the context, which contrasted to the non-adaptable performance of stimulus-response associations. To do so Tolman and Honzik used a maze in which three paths of different lengths all lead from the start box to the food box (Figure 2) (Tolman & Honzik, 1930).

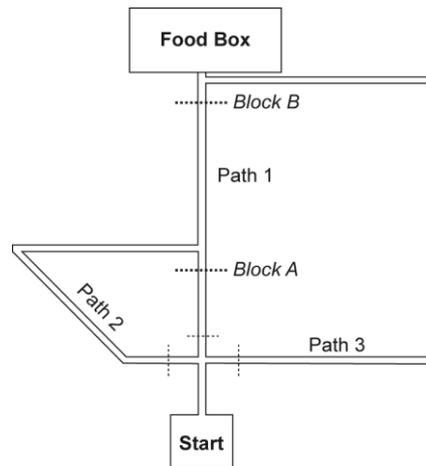


Figure 2: Tolman and Honzik maze. Dashed lines represent blocks that can be inserted. *Adapted from* (Tolman & Honzik, 1930)

Rats were first free to explore the maze during 13 days but the experimenters made sure that the rats went through the three different by different combinations of blocked alleys. As from the first training day, a preference for the shortest path, path 1, developed. Then when path 1 was blocked in A, rats developed a preference for path 2, the second shortest path. The authors then put a block at position B to interrupt the common section of path 1 and 2. The rats first went up path 1 but were blocked and had then to decide between path 2 (which also ultimately led to the block) and path 3. Rats chose path 3, the only effective trajectory. The rats had gained sufficient knowledge (called “insight”) about the configuration maze to determine that two paths had a common section (path 1 and 2) and to adapt their behaviour when this common section was closed to select the third alternative path.

This series of experiment led Tolman to postulate that rats could learn facts about the world that they could manipulate and use in a flexible manner by creating a cognitive map-like representation of their environment (Tolman, 1948).

1.2. The discovery of hippocampal place cells, substrate for Tolman’s cognitive map

In 1971, O’Keefe and Dostrovsky’s discovery of **place cells** in the hippocampus gave a new impetus to Tolman’s cognitive theory (O’Keefe & Dostrovsky, 1971).

In the 1970’s, the development of implanted microelectrodes to monitor single-neuron activity of behaving animals allowed describing the relationships between cellular activity and

a variety of sensory and behavioural parameters (Hirano *et al.*, 1970; Vinogradova *et al.*, 1970; Ranck, 1973). Using this technique, O'Keefe and Dostrovsky discovered “place cells” in the hippocampus of freely moving rats (O'Keefe & Dostrovsky, 1971). These cells were characterized by firing patterns that increased from a generally low level to higher rates as a freely moving animal moved through a particular region of space. As different place cells were responsive in different locations, it was proposed that the collective firing of different place-cell ensembles in different environments could be the neural substrate of “maps” of space (Wilson & McNaughton, 1993). These cells' properties will be described in more details in chapter 0.

Place cell recordings were followed by testing the effect of lesions of the fimbria/fornix, a major fiber tract of inputs into the hippocampal formation, on spatial learning (O'Keefe *et al.*, 1975). The authors trained water-restricted rats in a circular maze task to locate a water-filled cup which was always in the same place. Lesions in the fornix resulted in a deficit of the spatial learning by rats.

Further evidence that the integrity of the hippocampal formation was essential for spatial learning came with the introduction of the watermaze (Morris, 1981). Morris *et al.* (1982) trained rats to find a hidden escape platform in a circular pool of opaque water. Some had been subjected to hippocampal aspiration lesioning (damaging the hippocampus, dentate gyrus, and subiculum), others cortical control lesioning (damaging the same small amount of cortical tissue in the region of the parietal cortex as was necessarily damaged when making the hippocampal lesion), or no surgery (unoperated control). In the watermaze, both the operated and cortical tissue-lesioned groups quickly learned to swim toward the hidden platform from any starting location; only the hippocampal region lesioned group was impaired in executing directed swim-paths. Performance during a post-training probe test, where the platform had been withdrawn, showed that both control groups swam persistently across the exact spot where the platform had been located during training. In contrast, the hippocampus-lesioned group swam all over the pool. The deficit in escape latency disappeared when the platform was made visible, indicating that the impaired place navigation was unlikely to be secondary to any change in motivation to escape from the water and reappeared when it was subsequently hidden again. Similar results were obtained with hippocampal neurotoxic lesions in the watermaze by (Sutherland *et al.*, 1983).

The hippocampus and its place cells thus appeared as the substrate of Tolman's cognitive map, a theory which was developed by O'Keefe and Nadel in their book "The hippocampus as a cognitive map" (O'Keefe & Nadel, 1978).

1.3. From cognitive maps to mental representations of space

Tolman had introduced the concept of cognitive map and O'Keefe and Nadel used it explicitly in relation to the ability of the hippocampus to represent the environment in a viewer-independent (allocentric) manner (O'Keefe & Nadel, 1978). However rodents with nearly complete cell loss in the hippocampal formation can, with certain training procedures, learn allocentric spatial tasks despite a slower learning rate (Morris *et al.*, 1986). This suggests that extrahippocampal structures can support spatial learning. Moreover, as mentioned earlier, other forms of learning can underlie navigation, such as stimulus-responses associations (Hull, 1943), path integration by insects (Wehner *et al.*, 1996) and rodents (Etienne & Jeffery, 2004) or the "snapshot" processing of landmarks by bees (Collett, 1992).

These different processes however all involve manipulating information about one's environment (whether it is a place defined by its geographical coordinates or a place defined by its configuration of walls forming an intersection) and one's movements in it, and using both to build a general spatial framework which will enable navigating to a place. This spatial framework is what I will refer to as a "**mental representation of space**".

I will describe the processes involved in building and using mental representations of space in the two following sections.

2. Building a mental representation of space – processes and neural substrates

Building a mental representation of space involves collecting information about it and about our movements in it, as will be presented in this chapter. Most of the gathering of such information occurs during the **exploration** of a given environment, when an animal first discovers it.

2.1. Multi-modal information integration

To perceive our environment and navigate in it, sensory inputs are essential to detect information concerning the external world and concerning our own movements within this world. I will go briefly through the different modalities and the neural substrates which are essential to navigating.

Space can be detected through two types of **sensory information** (Arleo & Rondi-Reig, 2007):

- **allothetic** information which comes from the environment and is transmitted through visual, auditory, tactile and olfactory sensors;
- **idiothetic** information generated by our own movements (or self-motion) and conveyed by vestibular, proprioceptive, motoric (through the efferent copy of the motor command) and optic flow signals.

2.1.1. Allothetic information

Visual input is a major sense used in navigation. Whenever vision is altered or experiments are performed in the dark, spatial navigation is impaired (Zoladek & Roberts, 1978; Goodale & Dale, 1981). Most of the spatial experiments I will be citing in this manuscript will depend on visual cues to be performed accurately.

Audition, olfaction and touch seem to deliver information used in building a mental representation of space but do not seem sufficient independently to allow optimal navigation.

Indeed a series of experiments performed by Lavenex and Schenk on olfactory cues have shown that adding **olfactory** cues in spatial tasks does not increase the rats' performances except if the visual cues are not sufficiently prominent (Lavenex & Schenk,

1995; Lavenex & Schenk, 1996; Lavenex & Schenk, 1997). But in the absence of light, they can be used to find a goal (Figure 3) (Lavenex & Schenk, 1998). It is however noteworthy that the rodent entorhinal cortex, main input to the hippocampus, receives a massive direct projection from the olfactory bulb and secondary olfactory cortices (Shipley & Adamek, 1984). None of the other sensory inputs connect directly the entorhinal cortex but rather come from polysensory associative cortices. Thus the olfactory system retains a privileged position in relation to the hippocampal formation.

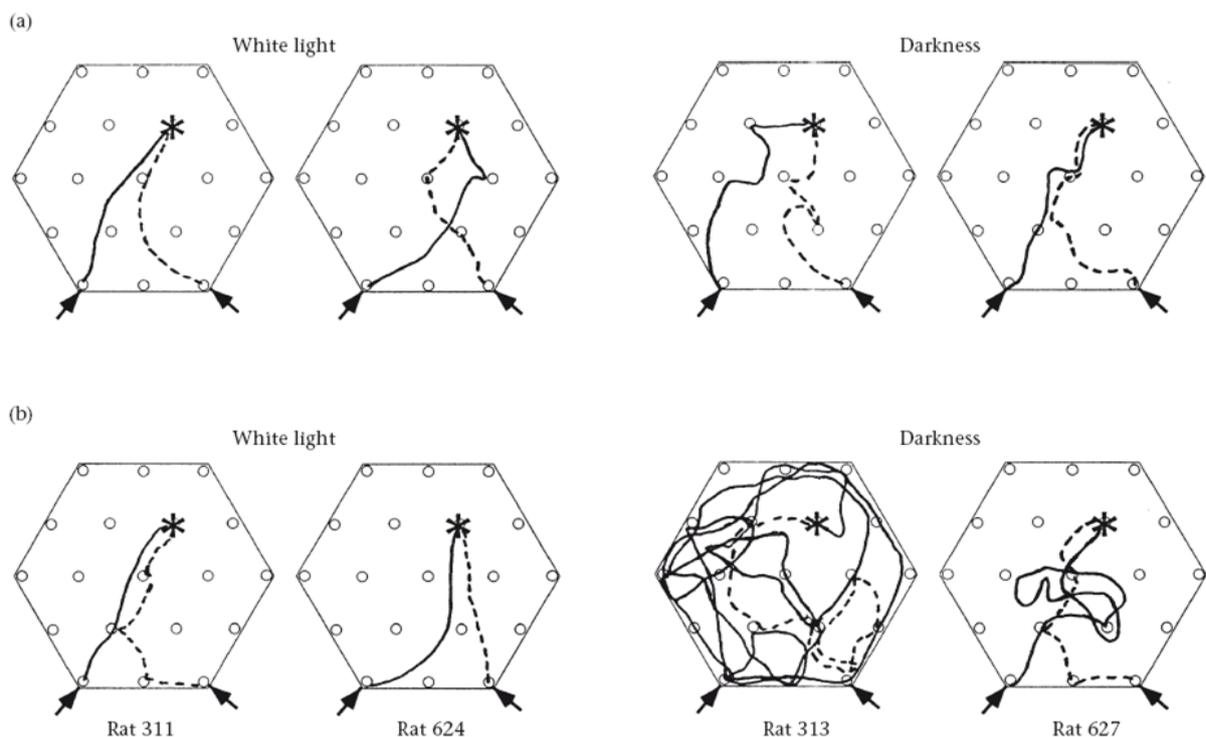


Figure 3: Role of olfactory cues in spatial navigation. Typical paths of rats in white light and in darkness, from two different starting points (indicated by arrows). Continuous and dashed lines are used to distinguish the two paths. (a) Training session with a fixed table and relevant olfactory traces. Rats can find their goal in the light using visual cues in the room and also in the dark. (b) Olfactory traces are made irrelevant: in the light rats still find the platform but not in the dark. *From* (Lavenex & Schenk, 1998).

Despite the excellent **auditory** capacities of rodents due to their crepuscular nature (Heffner *et al.*, 1994), rats cannot use only auditory cues to locate a goal. However, similarly to olfactory cues if combined with insufficiently informative visual cues, they will allow correct place navigation (Rossier *et al.*, 2000).

Few studies have actually tested the influence of **tactile** stimuli on navigation. It has however been recently shown that tactile stimuli detected through the whiskers modulated place cells activity in rat (Gener *et al.*, 2013). In an enriched tactile environment and in the

absence of other sensory information, a majority place cells altered their firing properties when removing the whisker input, suggesting that tactile information may also participate to creating mental representations of space.

The different allothetic inputs are handled by their corresponding primary cortices (visual, auditory, olfactory, somato-sensory) which all have projections to the parietal cortex (or the entorhinal for the olfactory cortex) (Calton & Taube, 2009).

2.1.2. Idiothetic information

Mittelstaedt and Mittelstaedt (1980) performed an experiment to test if rodents could go back to a given place without allothetic information. They tested the ability of gerbils to return to their nest at the arena border after exploring the circular arena to retrieve their pups. The authors observed that after sometimes convoluted paths to find their pups, the gerbil returned to their nests using direct paths, even in darkness. This was called path integration (Mittelstaedt & Mittelstaedt, 1980). It suggested that gerbils could integrate their movements to calculate a direct vector towards their departure. These **self-motion cues** derive from several sensory sources including **vestibular** (translational and rotational accelerations), **proprioceptive** (feedback information from muscles, tendons and joints) and, in the presence of light, visual information (linear and radial **optic flow**) (Etienne & Jeffery, 2004).

To test the role of the **vestibular** system, in this behaviour, the authors slowly rotated the arena while the gerbils were picking up a pup. The rotation's angular acceleration was below the vestibular threshold (thus not detected by the animals) and the gerbils returned "home" in a direction that deviated from the nest by the amount they had been rotated themselves. In other words, they homed using an internal (and in this case disrupted) sense of direction rather than external references. If the angular acceleration was over the vestibular threshold, they returned to the original nest indicating that they had detected the rotation. The role of the vestibular system in spatial navigation has since been confirmed by lesion experiments in rats (Stackman & Herbert, 2002; Zheng *et al.*, 2007). The vestibular system's captors are in the internal ear which detects linear acceleration through the otoliths and rotational movements through the semicircular canals.

The **proprioceptive** system provides information about the relative position of the

different parts of one's body using information from proprioceptors (i.e., stretch receptors located in the muscles, tendons, and joints). **Optic flow** corresponds to the displacement of images on the retina due to the relative motion between the observer and the scene. The displacement speed can be used to estimate one's own acceleration.

It has been suggested that during an active movement, while the motor cortex sends a command to the periphery, a copy of the motor command is also generated and is sent to the cerebellum where it could be used to generate a prediction of the sensory consequences of the intended movement. This prediction can then be compared to the proprioceptive input to, for example, adjust the movement.

Mittelstaedt and Mittelstaedt (1980) had shown that shifting sideways the gerbil when it had just found its pups resulted in a parallel run to the line connecting the nest and the point where the mouse had been before the shift, thus missing home by the amount of the sideways displacement. However gerbils or hamsters update their position much more accurately if the translation is active, showing the contribution of the proprioceptive system to accurate path integration (Etienne *et al.*, 1988).

A recent study in our team has revealed that the cerebellum is involved in self-motion information manipulation for shaping the hippocampal place cell representation (Rocheffort *et al.*, 2011). Indeed, mice lacking PKC dependent LTD at the parallel fiber – purkinje cell synapses (L7-PKCI mice) (De Zeeuw *et al.*, 1998) presented impaired hippocampal place cell firing properties when mice had to rely on self-motion information. These mice were then tested in a path integration task, in which they had to find a platform in a constant location and from a fixed departure point with an alley guiding the initial orientation of the body (Figure 4a). They first learned the path in the light and then had to reproduce it in the dark. Consistently with their hippocampal place cell alteration, L7-PKCI mice were unable to navigate efficiently toward a goal in the absence of external information (Figure 4b). According to these findings, cerebellar LTD participates in the mental construction of the representation of space in the hippocampus, suggesting that the cerebellum takes part in the representation of the body in space (Rocheffort *et al.*, 2013).

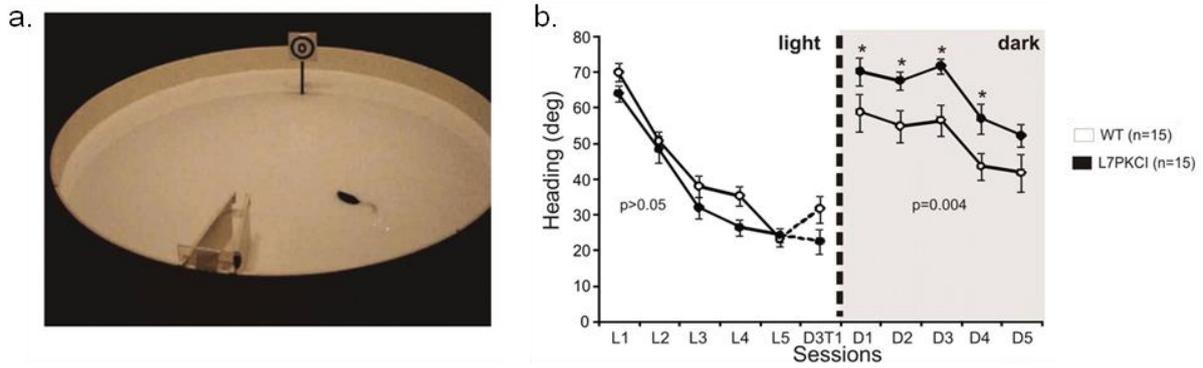


Figure 4: Role of cerebellar LTD in path integration. (a) Design of the experimental task developed to evaluate navigation abilities using self-motion cues. (b) Quantification of the heading in wild-type (WT) and L7PKCI mice during light and dark conditions. Heading measures for each point of the trajectory the angle between the direction of the animal and the ideal direction toward the target. In the light condition, WT and L7PKCI mice improved their performances significantly over sessions without genotype effect. In the dark condition, both groups improved their performance over time, but the performance of LKPCI mice was significantly poorer than that of their control littermates. *Adapted from* (Rocheffort *et al.*, 2011).

Interestingly, path integration occurs independently of the modality of locomotion, as shown by walking bees (Chittka *et al.*, 1995) and swimming rats (Benhamou, 1997) or mice (Rocheffort *et al.*, 2011).

2.2. Reference frame manipulations

Spatial navigation is an active process that requires the accurate and dynamic representation of our location, which is given by the combination of both external (allothetic) and self-motion (idiothetic) cues. Allothetic or idiothetic labelling characterizes the *type of information* it conveyed. On the other hand, **reference frames** characterize *the way this information is represented* by the navigator. A reference frame defines the framework in which spatial information (e.g., the position of an object) can be represented relative to an origin point. Depending on the anchorage of the origin of the reference coordinate system, the same information can be encoded egocentrically or allocentrically. If the reference frame is centered on the subject (e.g., on a body part such as the head) the representation is said **egocentric**. If the origin of the framework is a fixed point of the environment (e.g., a corner of the room), the representation is called **allocentric**. As shown in Figure 5a, the same allothetic spatial information (e.g., the position of a visual cue in the environment) can be represented either egocentrically (e.g., relative to the body of the navigator) or allocentrically (e.g., relative to the room corner). Likewise, as shown in Figure 5b, idiothetic signals (e.g., vestibular information) can be employed to describe self-motion information either

egocentrically or relative to an allocentric reference frame. Egocentric to allocentric reference frame bidirectional transitions are necessary to representation of space or to produce body movements egocentrically coded in an allocentric reference frame (e.g. “*I have to turn right when I get to the post office*”).

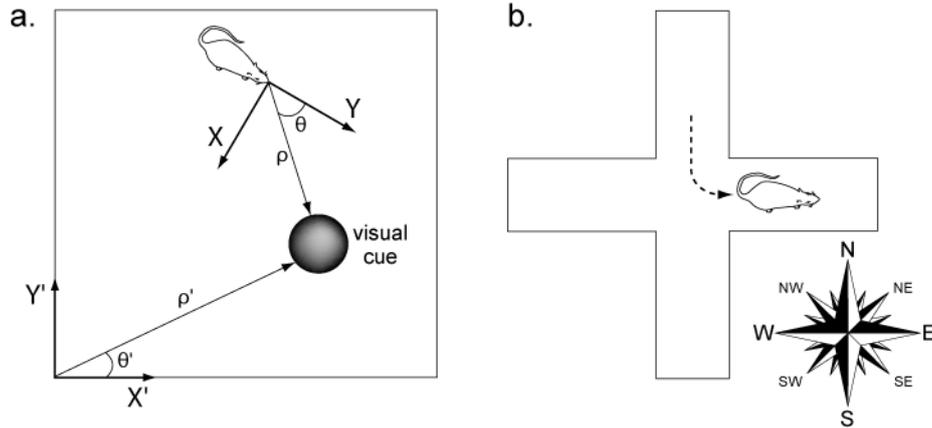


Figure 5: Encoding spatial information within a reference coordinate system. (a) The circular object provides an allothetic (visual) spatial cue to the navigator (rat). The latter can represent the spatial position of the external cue within the egocentric reference frame X-Y (centered on its head), that is estimate the distance ρ between its head and the object, as well as the angle θ between its heading and the direction to the object. Alternatively, the rat can encode the same spatial information within the allocentric coordinate system X'-Y' (centered on the bottom-left corner of the experimental environment), that is estimate the distance ρ' and the angle θ' . (b) In this example, the navigator can employ idiothetic information (e.g., vestibular signals) to represent the change of its motion direction within an egocentric reference frame, that is “I turned to my left”. Alternatively, it can refer to the allocentric directional system based on the geomagnetic north, that is “I turned eastward”. *From* (Arleo & Rondi-Reig, 2007).

Building mental representations of space in either reference frame first requires idiothetic and allothetic information to be expressed in both reference frames. However as vestibular organs are located in the head, vestibular signal is detected in head coordinates. This implies several transformations of the vestibular signal to correctly compute body motion in a body-centred reference frame or in a world-centred reference frame (reviewed by (Rochefort *et al.*, 2013)).

2.2.1. Head-to-body and head-to-world transformations

Vestibular information is first detected in the inner ear by the otoliths organs for the linear component and by the semi-circular canals for the rotational component. As receptor cells are fixed to the cranial bone, vestibular signals are detected in a head reference frame. This means for example that based on semicircular signals only, a rotation of the head upright relative to the vertical axis cannot be distinguished from a rotation of the head horizontal

relative to the horizontal axis (Figure 6). In other words, semicircular canal information alone does not discriminate vertical or horizontal body position. To compute the movement of the body in space, vestibular information needs to be integrated relative both to the body (taking into account the relative position of the head and the body, given by the neck curvature) and to the world, converting the signal initially in head-fixed coordinates into a signal in world-frame coordinates (taking into account gravity) (Rocheftort *et al.*, 2013). These computations are not necessarily successive and result from the integration of different types of signals. Several recent studies showed that these two reference frame transformations occur in different cerebellar subregions.

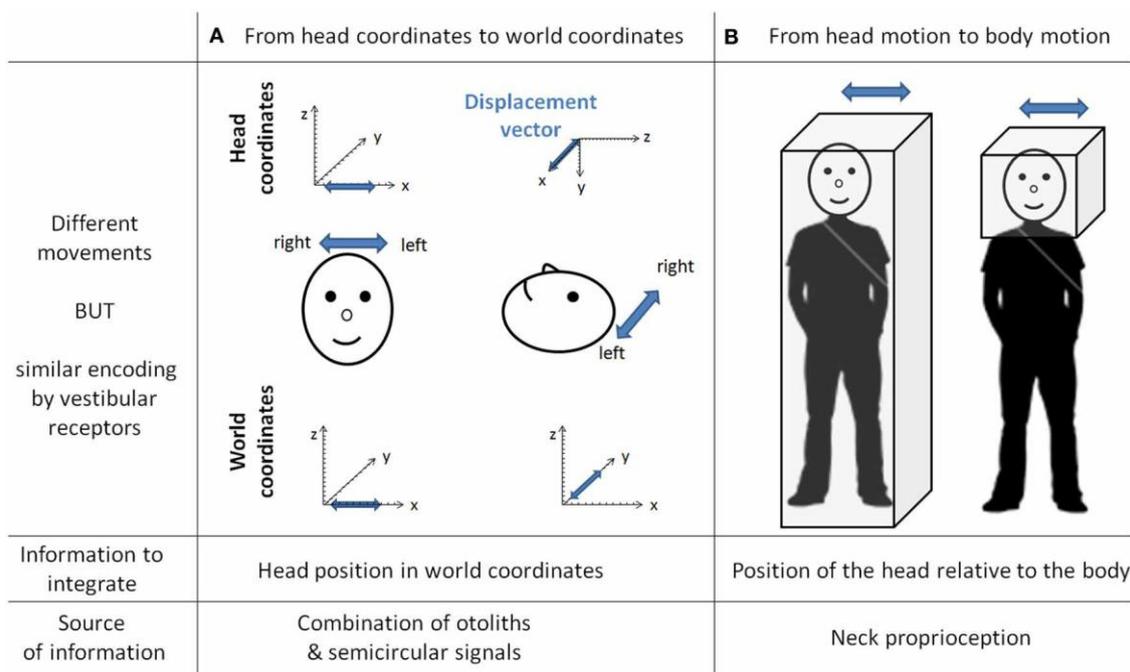


Figure 6: The need for transformation of the vestibular signals. This figure gives two examples of different movements similarly encoded by vestibular receptors. In column (A) is a linear displacement from left to right, with the head either vertical or horizontal. Indeed both movements are identical in the head reference frame [displacement vectors (in blue) project onto the x-axis] whereas they are different in the world coordinates (displacement vectors project either onto the x-axis or onto the y-axis). These two movements can be distinguished by taking into account the head position in space, which can be extracted from the combination of semicircular and otolith organs signals (Yakusheva *et al.*, 2007). Column (B) illustrates two movements corresponding to the same head motion in space, but different body motions in space (i.e., on the right the body is stationary). These two movements can be distinguished by integrating information about the position of the head relative to the body (that is, the neck curvature, given by neck proprioceptors). From (Rocheftort *et al.*, 2013).

Head-to-body frame transformation seems to occur in the cerebellar fastigial nucleus. This region contains a subpopulation of neurons (50%) that has been shown to encode motion in body coordinates (Kleine *et al.*, 2004; Shaikh *et al.*, 2004). This idea has been further

supported by the demonstration that fastigial neurons respond to both vestibular and neck proprioception, and specifically encode body movement in space (Brooks & Cullen, 2009). Head to body position has also been shown to modulate Purkinje cell activity in the cerebellar anterior lobules IV and V in decerebrate cats (Manzoni *et al.*, 1999) thus the head to body frame transformation might also take place in the cerebellar cortex.

The **head-to-world** reference frame conversion has been proposed to take place in the cerebellar cortex by combining semicircular and otolith organs inputs (Yakusheva *et al.*, 2007). This computation takes place in the lobules IX and X of the cerebellum and involves GABA transmission (Angelaki *et al.*, 2010).

It has been proposed that the information, adequately transformed, is subsequently conveyed to the hippocampus to provide self-motion information (Figure 7) (Rocheffort *et al.*, 2013). This could be through a polysynaptic pathway involving the thalamus, the parietal and the entorhinal cortices as relays (Giannetti & Molinari, 2002).

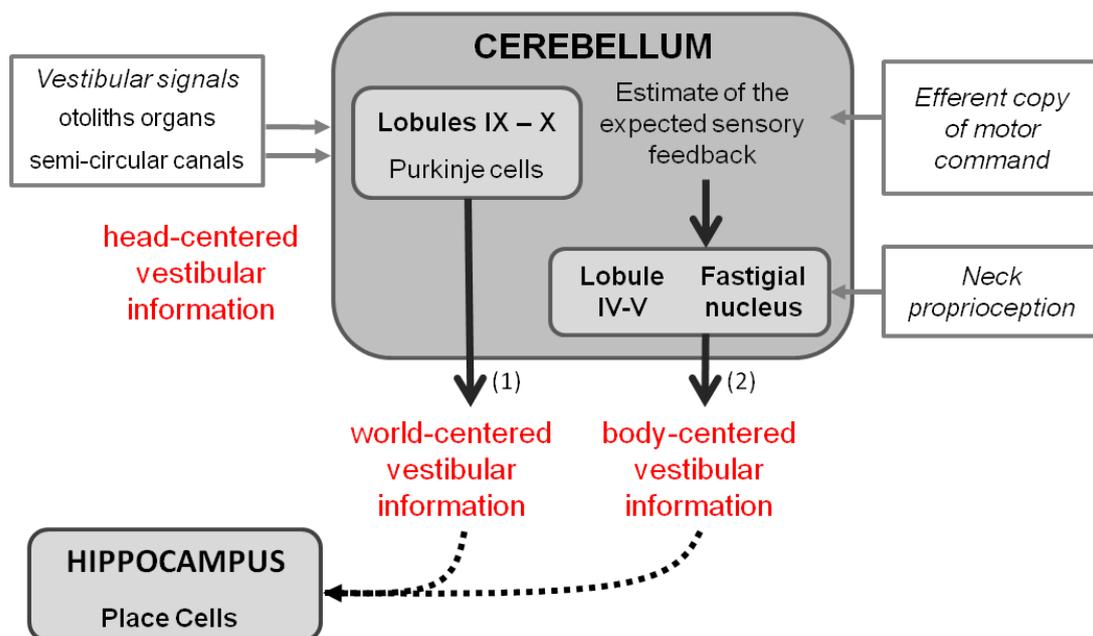


Figure 7: Cerebellar processing of self-motion information that can be used for building a mental representation of space. Based on the existing literature, cerebellar processing of self-motion information could involve two computations: (1) The combination of otolith and semi-circular signals to convert head centred vestibular information into world centred vestibular information (Angelaki *et al.*, 2010). (2) The integration of neck proprioceptive information with head motion vestibular information to compute an estimate of body motion in space (Kleine *et al.*, 2004; Shaikh *et al.*, 2004; Brooks & Cullen, 2009). These transformations are required to provide the hippocampus with the appropriate self-motion information (dotted lines). *Adapted from* (Rocheffort *et al.*, 2013).

2.2.2. *Translation between whole-body egocentric and allocentric reference frames*

Egocentric to allocentric reference frames manipulation consists in transforming information coded in egocentric coordinates into an observer-independent representation.

The **retrosplenial cortex** is thought to be involved in the allocentric-to-egocentric and egocentric-to-allocentric transformation processes (Burgess *et al.*, 2001a; Byrne *et al.*, 2007; Vann *et al.*, 2009). Retrosplenial inactivation has been shown to impair spatial memory in rodents (for review see (Troy Harker & Whishaw, 2004)) but the magnitude of spatial deficits are smaller than the magnitude of the deficits associated with hippocampal damage. The full impact of retrosplenial cortex lesions appears when animals are forced to shift modes of spatial learning, for example from dark to light (Cooper & Mizumori, 1999) or from local to distal cues (Vann & Aggleton, 2004; Pothuizen *et al.*, 2008).

In humans, a functional imaging study specifically identified the retrosplenial as being involved in acquiring allocentric knowledge of an environment from ground-level observations (Wolbers & Buchel, 2005). Subjects repeatedly encountered a virtual environment composed of intersections and shops and were then tested on their knowledge of the topographical organization of the environment. The retrosplenial cortex was the only structure to parallel behavioural measures of map expertise of the subjects. In another study, Spiers and Maguire (2006) scanned participants navigating through a realistic virtual-reality simulation of central London to determine when during navigation different brain areas are engaged. Activity in the retrosplenial increased specifically when new topographical information was acquired or when topographical representations needed to be updated, integrated or manipulated for route planning (Spiers & Maguire, 2006). This could relate to the proposal that the retrosplenial acts as a short-term buffer for translating between egocentric and allocentric representations (Burgess *et al.*, 2001a; Byrne *et al.*, 2007).

The retrosplenial cortex has reciprocal projections with the hippocampal formation and thalamic nuclei (van Groen & Wyss, 1990; 1992; 2003). In rodents and primate it can be separated into dysgranular and granular region. The granular regions is distinguished by reciprocal connections with sites that contain head-direction cells (the lateral dorsal and anterior dorsal thalamic nuclei and the post-subiculum), whereas the dysgranular cortex region is more interconnected with visual areas through reciprocal connections (Vogt & Miller,

1983). It has been estimated that 10% of retrosplenial cortex cells are head-direction cells, equally distributed across the dysgranular and granular cortex; but interestingly, in the granular region only, the spatial tuning of some of these cells is modulated by velocity of locomotion (Chen *et al.*, 1994). Immediate-early gene and lesion studies suggest that, in accord with the anatomical connections, the dysgranular retrosplenial cortex seems more important for visually guided spatial memory and navigation, whereas the granular retrosplenial cortex has a greater involvement in internally directed navigation (Vann & Aggleton, 2005; Pothuizen *et al.*, 2009).

2.3. Place information: element of the mental representation of space

This section will describe the properties of three types of cells: head direction cells, grid cells and place cells. These cells were all discovered in rats but two of them have since been identified in humans. In 2003, Ekstrom *et al.* recorded from electrodes implanted in several regions as participants, epileptic patients, navigated in a virtual town. The authors found cells that could be confidently classified as place cells, amongst which the majority was found in the hippocampal region (Ekstrom *et al.*, 2003). Grid cells have also been found in the entorhinal cortex and in the cingulate cortex using functional imaging (Doeller *et al.*, 2010) and electrophysiological recordings (Jacobs *et al.*, 2013).

2.3.1. Head-direction cells

Head direction (HD) cells fire when a rat's head is facing a specific direction relative to the environment, irrespective of its location or whether it is moving or still (Taube *et al.*, 1990a; Taube *et al.*, 1990b). These cells were first discovered in the dorsal portion of the rat presubiculum (often referred to as the postsubiculum (PoS)) (Ranck, 1984) but have since been found in several regions belonging to the Papez circuit: the anterior dorsal thalamic nucleus (Taube, 1995a), the lateral mammillary nucleus (Stackman & Taube, 1998), the retrosplenial cortex (both granular and agranular regions) (Chen *et al.*, 1994), the parasubiculum (Boccaro *et al.*, 2010) and entorhinal cortex (Sargolini *et al.*, 2006). HD cells have also been identified in other non-Papez circuit areas, including the lateral dorsal thalamic nuclei (Mizumori & Williams, 1993), the dorsal striatum (Wiener, 1993) and the medial precentral cortex (also known as FR2 or AGm cortex) (Mizumori *et al.*, 2005). Other areas in which they have been reported in smaller numbers include the medial prefrontal cortex

cortex (Chen *et al.*, 1994), CA1 hippocampus (Leutgeb *et al.*, 2000), and the dorsal tegmental nucleus (DTN) (Sharp *et al.*, 2001).

These cells are thus found in multiple structures which are anatomically interconnected. Lesion and electrophysiological studies have shown that the head-direction signal travels from the dorsal tegmental nucleus, which receives input from vestibular nuclei, to the hippocampus, through the hypothalamus (mammillary nucleus), the thalamus and the retrosplenial, subicular and entorhinal cortices (Taube, 2007). It is however important to keep in mind that most of the connections between these structures are bidirectional and that the transfer of head direction information is not necessarily unidirectional.

The primary correlate of head-direction cells is the orientation of the head in the horizontal plan. Pitch and roll appear to be relatively unimportant, as is the orientation of the rest of the body. Figure 8a shows the firing rate for one HD cell plotted as a function of the direction of heading. It has a single preferred direction, and firing falls off rapidly as the head direction rotates away from the preferred direction. The distribution of peak firing directions across the population of cells is uniform, with no direction preferred over any other. There does not appear to be any topography to the directions represented by neighbouring neurons. Importantly, unlike hippocampal place cells which can be active in only one environment, HD cells fire in all environments tested.

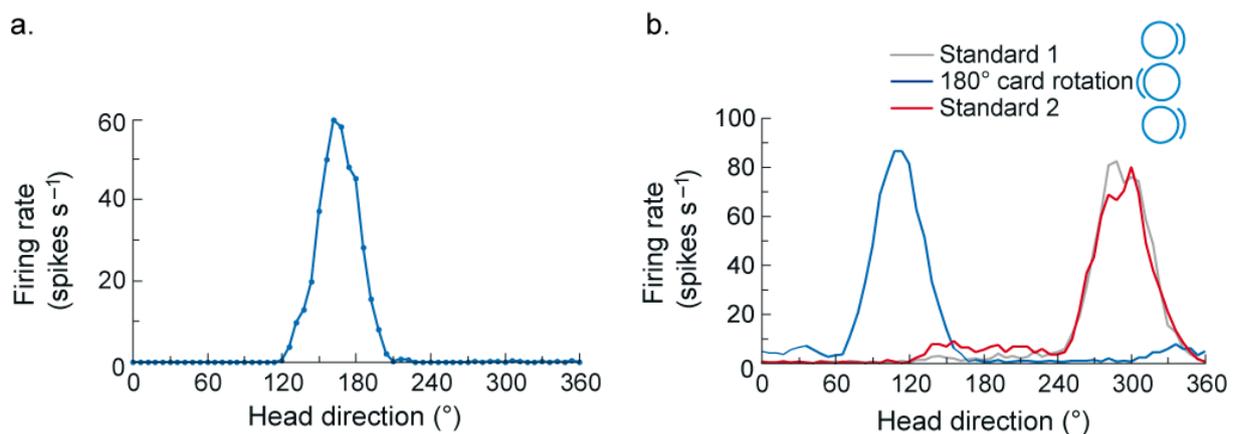


Figure 8: Head direction cell firing. (a) Example of one HD cell. (b) HD cell under cue card rotation: the preferred direction is always maintained relative to the cue card. *From* (Taube, 2007).

The animal's orientation is given partly by allothetic cues and partly by idiothetic cues.

Indeed Taube *et al.* (Taube *et al.*, 1990b) found that rotations of a cue card fixed to the apparatus wall produced rotations of the directional firing field (Figure 8b). In addition to cue

card shifts, Taube and colleagues (Taube *et al.*, 1990b) found that changing the shape of the testing enclosure from a cylinder to a square or rectangle also caused changes in the preferred direction, showing the influence of distal visual cues on HD cells. Further experiments also showed that once head-direction cells had established a directional preference, removing the visual cues or turning off the lights does not lead to a change in cell activity (Taube *et al.*, 1990b; Mizumori & Williams, 1993). Knierim *et al.* (1998) tested the relative contribution of visual and idiothetic cues on directional information by creating a conflict between both type of information. HD cells of the anterior thalamic nuclei were recorded as rats foraged for food in a high-walled apparatus. In the middle of the session, the apparatus and the rat were rotated abruptly, thereby introducing an explicit conflict in directional information from idiothetic and visual landmark cues: vestibular and other idiothetic sources informed the rat it had been rotated and was facing a new direction; however the cue card which was rotated by the same amount as the rat, informed the rat it was facing the same direction as before. When the mismatch between the two sources of information was small (45 degrees), the visual landmarks had robust control over the firing properties of HD cells; but the idiothetic input usually predominated over the visual landmarks when the mismatch was larger (Knierim *et al.*, 1998).

A lesion of the dorsal presubiculum did not stop head direction cells firing in the anterior dorsal thalamic nucleus but abolished the control of a cue card over the preferred heading direction. On the other hand lesioning the anterior dorsal thalamic nucleus abolished head-direction cell signal in the postsubiculum (Goodridge & Taube, 1997). It is thus suggested that, through inputs from the vestibular nuclei, idiothetic cues serve as the primary drive to head direction cells, and then visual information mediates influence through the subiculum and retrosplenial cortices (Taube, 2007). However, as mentioned earlier, the connections within the Papez circuit are bidirectional explaining the influence of visual cues on HD cells in the anterior thalamic nuclei.

In addition to directly controlling behaviour based on environmental directions, these cells may provide directional information to the place cells (Yoganarasimha & Knierim, 2005).

2.3.2. Grid cells

Another type of cells which has been identified as processing spatial information is **grid cells**. Grid cells were first discovered in the dorsal medial entorhinal cortex (Fyhn *et al.*, 2004; Hafting *et al.*, 2005), but have also been found in the pre- and parasubiculum (Boccaro *et al.*, 2010). They are most abundant in layer II and III of the medial entorhinal cortex (Sargolini *et al.*, 2006), which sends major projections to the hippocampus, but are also found in the layers V/VI, which receive inputs from the hippocampus.

Each grid cell fires in several locations in an environment, with the locations forming a regular pattern as though they were nodes on a triangular grid (Figure 9). The grid field can be characterized in terms of three properties: scale (determined by the distance between adjacent firing rate peaks), orientation (of grid axe relative to a reference direction) and spatial phase (i.e. the two-dimensional offset of the grid relative to an external reference point).

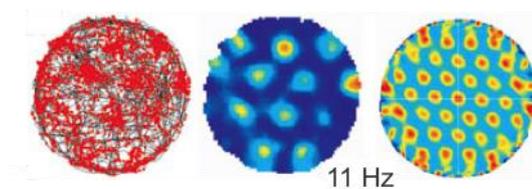


Figure 9: Firing fields of a grid cell. Left, trajectory of the rat (black) with superimposed spike locations (red). Middle, colour-coded rate map with the peak rate indicated. Red is maximum, dark blue is zero. Right, spatial autocorrelation for each rate map. The colour scale is from blue ($r=-1$) through green ($r=0$) to red ($r=1$). From (Hafting *et al.*, 2005)

Different cells recorded at the same location have the same grid spacing and orientation relative to the environment. They differ, however, in the location of the nodes such that the firing peaks of one cell are slightly shifted from those of its neighbour. The multiple fields of several such cells together cover the environment. The grid cells probably do not form a map of a given environment by themselves but provide the Euclidean distance and direction (Fyhn *et al.*, 2004; Hafting *et al.*, 2005).

Similarly to the head-direction cells, each grid cell fires in every environment the animal encounters. For each cell, the size of the grid appears to be independent of the size or shape of the environment. There is a gradient of spacing distance along the dorsal-ventral axis of MEC, with larger separations found at more ventral loci (Hafting *et al.*, 2005). Recent work indicates that field separation distances do not change smoothly but rather fall into groups of

nearly the same separation, with intermediate distances not found (Stensola *et al.*, 2012). As the field spacing of individual grid cells is independent of the identity of the current environment, it has been inferred that this metric-like quantity is derived from processing of self-motion information (Etienne & Jeffery, 2004; Jeffery & Burgess, 2006; Jeffery, 2007). This notion is supported by the finding that grid cell firing patterns do not change drastically in the dark (Hafting *et al.*, 2005). The orientation of the grid relative to the environment, however, is dependent on the location of a visual cue on the wall of the enclosure (Figure 10) (Taube *et al.*, 1990b). Interestingly, muscimol inactivation of the hippocampus greatly reduces or eliminates the hexagonal array of grid cell fields (Bonnievie *et al.*, 2013). This treatment does not, however, silence grid cells; instead they show directional tuning. Overall, the average firing rate decreases, as if a net excitatory drive had been removed. It seems likely that the orientation of each grid cell is controlled by the head direction signals. Thus grid cell firing is controlled by both self-motion and extrinsic sensory input.

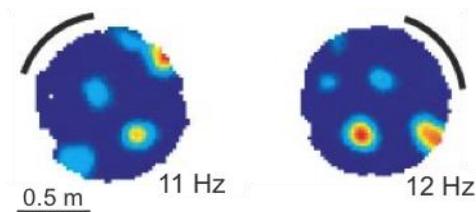


Figure 10: Rate maps for a representative cell after rotation of the cue card. From (Hafting *et al.*, 2005).

The grid cell discharge is omnidirectional but directional grid cells are found in layers III and V/VI and are called ‘conjunctive cells’. Their activity depends on head direction as well as location and is modulated by the rat's running speed (Sargolini *et al.*, 2006).

2.3.3. Boundary cells

An additional class of spatially selective cells is the **boundary cells**. The existence of these cell types was initially predicted based on theoretical models that proposed that place cells’ fields are generated from band-like activity patterns that intersect at a particular place (Burgess & O’Keefe, 1996) (Barry *et al.*, 2006). These putative cells were called “boundary vector cells”.

Cells with “boundary vector cells” properties were subsequently discovered in various regions, with various names:

- *boundary vector cells* were found in the subiculum (Lever *et al.*, 2009);
- *boundary cells* were found in the medial entorhinal cortex (Savelli *et al.*, 2008);
- *border cells* were found in the medial entorhinal, presubiculum and parasubiculum (Solstad *et al.*, 2008) (Figure 11).

The spatial properties of these cells appear to show some overlap and may be regarded as belonging to a common functional category, which can be labelled “boundary cells” (Hartley *et al.*, 2014). Indeed they either fire directly at the border or wall of an environment or form a firing band at a fixed distance from a prominent environmental boundary, such as a wall or a table edge. For these cells, the addition of a new wall within an environment will result in the emergence of additional firing fields at the characteristic distance from the new boundary (Figure 11) (Solstad *et al.*, 2008; Lever *et al.*, 2009) The boundary vector cell response therefore differs from that of grid cells, because grid cells continue to fire in a hexagonal lattice rather than directly aligning to multiple wall positions (Hafting *et al.*, 2005).

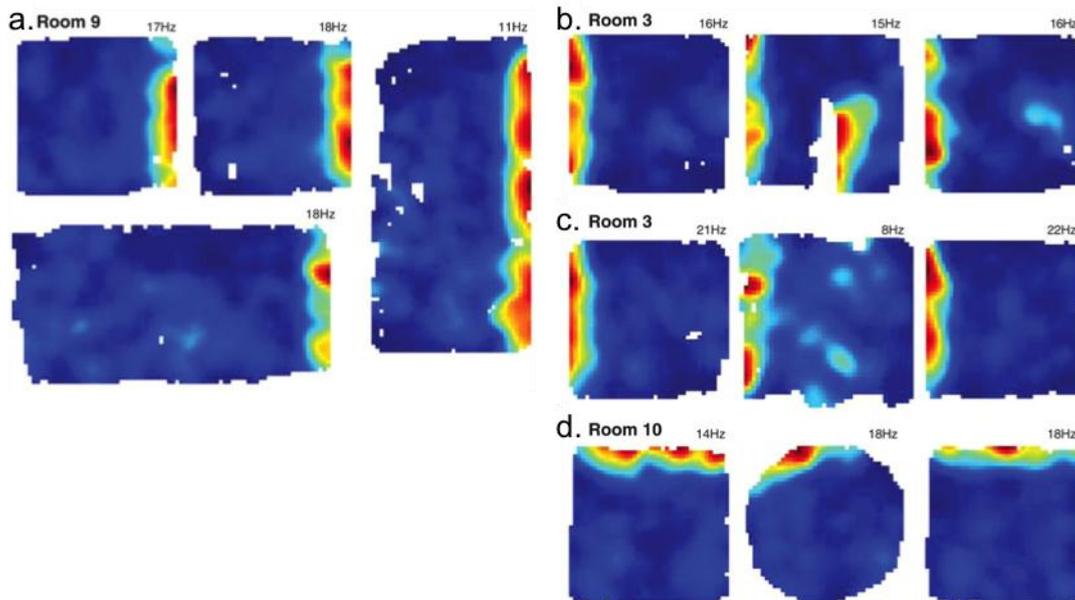


Figure 11: Border cells. Color-coded rate maps for a representative border cell in boxes with different geometric configurations. Red is maximum, dark blue is zero. Pixels not covered are white. Peak firing rates are indicated above each panel. Each panel shows one trial. (a) The border field follows the walls when the square enclosure is stretched to a rectangle. (b) Introducing a discrete wall (white pixels) inside the square causes a new border field to appear (middle panel). The new field has the same orientation relative to distal cues as the original field on the peripheral wall. (c) Border fields persist after removal of the box walls (middle panel). Without walls, the drop along the edges was 60 cm. (d) Preserved firing along borders across rooms and geometrical shapes. Trials in (d) were recorded in a different room than those in (a) to (c). *From (Solstad et al., 2008).*

In addition to their role in signalling borders, it is thought that the boundary cells may help in establishing place cells field, at least for those on the border (Hartley & Lever, 2014), and may help scaling the grid size to accommodate to the size of the environment (Buzsáki & Moser, 2013).

2.3.4. Identifying a place: hippocampal place cells

Since their discovery in 1971 (O'Keefe & Dostrovsky, 1971), there have been many technical and conceptual development in hippocampal single-unit recording which have shed light on different properties of place cells.

Their major behavioural correlate is the animal's location. O'Keefe and Dostrovsky reported that these place cells were silent as the rat moved around the environment until it entered a small area of the environment, the place field, where the cell began to fire (O'Keefe & Dostrovsky, 1971). When a rat is first exposed to an environment, place cells acquire their place fields within a few minutes (Hill, 1978) and once their firing fields are established, their locations may be stationary for weeks or months (Muller *et al.*, 1987; Thompson & Best, 1990). The activity of an ensemble of place cells covers a whole environment (Wilson & McNaughton, 1993). The same cells often fire in different environments, but the preferred locations are unrelated if the environments are sufficiently dissimilar from each other (Leutgeb *et al.*, 2005). One notable feature of these place cells is that in unconstrained open fields - environments in which the animal is free to move in all directions - the cells fire in the place field irrespective of the direction in which the animal is facing (Muller *et al.*, 1994). In environments that constrain the animal's behaviour, for example a linear track or a radial maze, the cells become directionally sensitive and may be said to represent the successive locations along a path (McNaughton *et al.*, 1983; O'Keefe & Recce, 1993; Muller *et al.*, 1994). Whereas in the first situation each cell may be said to represent a location, in the second it might more properly be described as representing a serial position along a path.

Place fields can be controlled by allothetic and idiothetic information (Jeffery *et al.*, 1997).

Information from the environment comprises visual cues, such as distal cues (Cressant *et al.*, 1997) or wall configuration of the maze (considered as intra-maze cues) (O'Keefe & Burgess, 1996). Indeed rotation of the box or rotation of a "cue-card" suspended prominently

on the interior wall of the box, generally causes equal rotation of the place fields (Figure 12) (Kubie & Ranck Jr, 1983; Muller & Kubie, 1987). On multi-arm mazes with high walls, the fields sometimes take their reference from specific arms and not from the entire maze (Shapiro *et al.*, 1997).

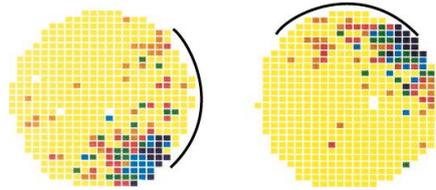


Figure 12: Place cell rotation. Each firing rate map was generated using data from the entire recording session. In the maps yellow indicates no firing and purple indicates maximum firing (orange, red, green, and blue indicate intermediate firing rates from low to high). The cell fired when the rat was in a specific location (*left*). When the visual cue was rotated by 90 °, the place field followed the same rotation (*right*). *From* (Muller & Kubie, 1987)

Place fields can also be located on the basis of idiothetic cues generated by an animal's own movements, which consist of interoceptive stimuli such as head, neck and limb proprioceptors, vestibular signals, and motor reafference signals from intended movements together with exteroceptive stimuli derived from optic flow and whisker-detected airflow. In an experiment performed by Jeffery and collaborators (1997), place cells were recorded while rats foraged in a rectangular box. Rotations of the box, the rat or both made in a dark condition resulted in shifts of the place field relative to the rat's internal direction sense (Figure 13a). When the lights were on and the room cues visible, the distal visual cues predominated on the orientation of the place fields (Figure 13b).

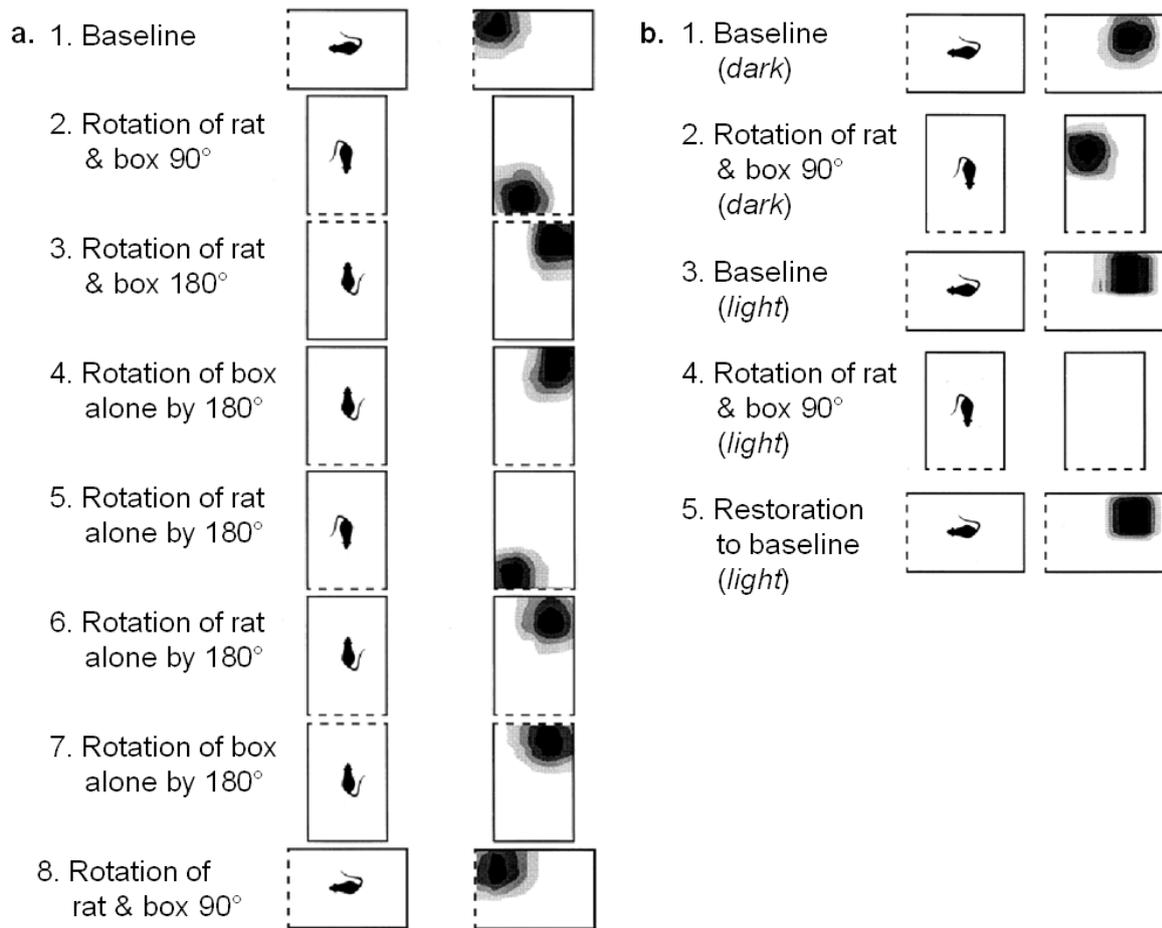


Figure 13: Behaviour of a typical place field following rotations according in the dark or on in the light. Note that, in each trial, the place field's orientation was aligned with the rat's interoceptive direction sense rather than with the physical, non-geometric cues of the box: that is, it failed to rotate when the box alone was rotated (steps 4 and 7) but rotated 180° when the rat was so rotated. (b). Comparison of rotations in the dark and light conditions for a place cell. When the box and rat were rotated together in the dark (step 2) the field rotated accordingly. However, when the procedure was repeated during the light protocol, with the room cues visible (step 4), the field broke down (peak rate <0.5 Hz). *Adapted from (Jeffery et al., 1997).*

Hippocampal cells in the rat have been shown to respond preferentially to the boundary geometry of an enclosure (e.g. Figure 13)(O'Keefe & Burgess, 1996). Doeller, King, and Burgess (2008) proposed that learning related to environmental boundaries in humans would be associated with higher activation in the hippocampus, consistent with place learning. They had participants navigate to the learned locations of target objects in desktop virtual reality (VR), while the locations of the objects were held constant either relative to boundaries and distal orientation cues or relative to a local landmark. The results showed that boundary learning did in fact promote global activation in the hippocampus. The parahippocampal gyrus also appeared to be activated during learning relative to boundaries; this region seemed to be involved in learning specific views or the spatial context required to orient to the distal cues. Further research has shown that the left hippocampus is active when imagining scenes

with walls or boundaries, as compared with equally complex scenes consisting of towers (Bird *et al.*, 2010), suggesting that the hippocampus is important for relating location to environmental boundaries.

Place cells outside the hippocampus

Place cells are typically recorded from the hippocampus proper but have also been recorded from other parts of the hippocampal formation, namely the subiculum (Sharp & Green, 1994), presubiculum (Sharp, 1996), parasubiculum (Taube, 1995b) and entorhinal cortex (Quirk *et al.*, 1992). The properties of cells in these various regions vary, and it is still not clear how this diverse population of place cells is organized into a functional network or which functions are performed by each region. The firing of extrahippocampal cells tends to be more environment-invariant than hippocampal place cell firing, generalizing across the various environments explored and routes taken. Thus, cells in the subiculum and entorhinal cortex may signal broadly equivalent locations, or similar points along a route, in different environments. Relative to hippocampal place cells, cells in some neighbouring extrahippocampal regions tend to have larger fields and are less sensitive to environmental changes such as alterations in the shape of the enclosure.

Ventral hippocampus

Place cells have mostly been studied in the dorsal hippocampus. However place cells are found along the rostro-caudal axis but as the recording electrode is moved to more ventral portions of the hippocampus, the size of place fields expands. Fields in the middle region of the hippocampus are almost twice as large as those in the septal hippocampus (Jung *et al.*, 1994) and in the most ventral regions cells appear to have fields at least twice the size of those in the middle region (Maurer *et al.*, 2005; Kjelstrup *et al.*, 2008). Some very large fields in the most ventral hippocampus could be large enough to cover areas the size of the usual laboratory testing enclosures or even larger. This wide range of field sizes has important implications for analysis of the differences in behavioural functions of the dorsal versus ventral hippocampus. Indeed fields that cover an entire testing enclosure could rather convey information about the spatial context rather than the position and in conditioning paradigms,

for example, their primary function might be to distinguish between two testing boxes rather than identifying different locations within the same testing box (Andersen *et al.*, 2006).

Ventral place cells receive considerable amounts of non spatial inputs from sources such as the amygdala and the hypothalamus (Witter *et al.*, 1989; Risold & Swanson, 1996; Petrovich *et al.*, 2001) or from neuromodulatory centres such as the ventral tegmental area (Gasbarri *et al.*, 1997), which may also be important in determining place cell firing properties and could play a role in producing dorsoventral place field differences.

Whereas the dorsal hippocampus is involved in spatial memory processes, current views suggest the ventral hippocampus is involved in modulating stress, emotions and affects (Bannerman *et al.*, 2004), for review (Moser & Moser, 1998b). Studies using the watermaze, T-maze alternation and contextual fear conditioning are consistent with this dorsal-ventral gradation of function (Bannerman *et al.*, 1999; Richmond *et al.*, 1999). For example, Kjelstrup *et al.* found that rats with selective lesions located in the ventral pole of the hippocampus were less fearful on an elevated cross maze and showed decreased neuroendocrine stress responses (Kjelstrup *et al.*, 2002). Bannerman *et al.* have also implicated the ventral hippocampus in anxiety as ventrally lesioned animals freeze less to unsigned foot-shock in a test chamber and showed less neophobia (the fear of novel foods) (Bannerman *et al.*, 2002).

It is also proposed that the connectivity between the hippocampus and the prefrontal cortex and subcortical sites would be important for the translation of hippocampus-dependent memories into adapted behaviours (Bast, 2011).

In support of a participation of the ventral hippocampus in spatial memory processes, immediate early gene (Fos, Zif268, Arc) or 2-deoxyglucose imaging studies in mice (Bontempi *et al.*, 1999; Maviel *et al.*, 2004) and rats (Gusev *et al.*, 2005) showed activations in both the dorsal hippocampus and ventral hippocampus during the retrieval of a recently acquired spatial memory (tested one to a few days after the end of acquisition).

Ventral hippocampus lesions were occasionally found to disrupt the acquisition of a spatial memory (de Hoz *et al.*, 2003; Broadbent *et al.*, 2004). Ruediger *et al.* (2012) showed that the ventral hippocampus is specifically involved in the early stages of water maze learning: indeed its lesion impaired performance during the first trials but did not prevent learning the location of the platform. They propose that the ventral hippocampus is involved

in learning consistent task-specific goal-context relationships, suggesting that it has a crucial function in relating reinforcers (here the platform) to context in learning.

It had also been shown that the retrieval and/or the expression of the representation of a spatial memory required the ventral hippocampus (Moser & Moser, 1998a). Recently, Loureiro et al. confirmed this lesion experiment using reversible inactivation with lidocaine infusions (Loureiro *et al.*, 2012). Reversible inactivation of the dorsal hippocampus or ventral hippocampus performed before a probe trial in a water-maze task impaired retrieval performance, whereas pre-training blockade of the ventral hippocampus did not prevent task acquisition and retrieval, contrary to pre-training blockade of the dorsal hippocampus. These results were supported by complementary experiments which excluded possible locomotor, sensorimotor, motivational or anxiety-related biases from data interpretation.

These results suggested that the ventral hippocampus is spatial memory retrieval (as long as the spatial task has been learned with an entire hippocampus).

2.3.5. Recognizing a place: pattern completion, pattern separation

The different areas of the hippocampus, dentate gyrus (DG), CA3, CA2 and CA1, all contain place cells (even though in the DG these cells are granule cells and not pyramidal cells) (Muller *et al.*, 1987; Jung & McNaughton, 1993; Mankin *et al.*, 2013). Regarding place recognition, the CA3 and DG have been attributed two specific roles: “pattern completion” and “pattern separation”, respectively.

Pattern completion is a phenomenon through which initial association between multiple stimuli allows the subsequent retrieval of the whole encoded event when the subject is presented with just a subset of the original stimuli. It is hypothesised to be an important role for CA3 due to its intrinsic network of recurrent collaterals.

Experimental evidence supporting the role of CA3 in pattern completion comes from studies involving mice with a deletion of the NR1 gene specific to the CA3 region (resulting in no NMDA receptor mediated plasticity) which were unable to navigate in a water maze task when a subset of their previously learned cues were removed (Nakazawa *et al.*, 2002). This corresponds to the early hippocampal model of David Marr in which he proposed that the area CA3 was ideally suited as a site for memory storage and retrieval because of this region's recurrent connections which could allow storing patterns of activity and later retrieving these same patterns if all or part of the original pattern re-occurred (Marr, 1971).

Nakazawa et al. (Nakazawa *et al.*, 2002) have proposed a model of pattern completion in the CA3 of control and mutant mice (Figure 14).

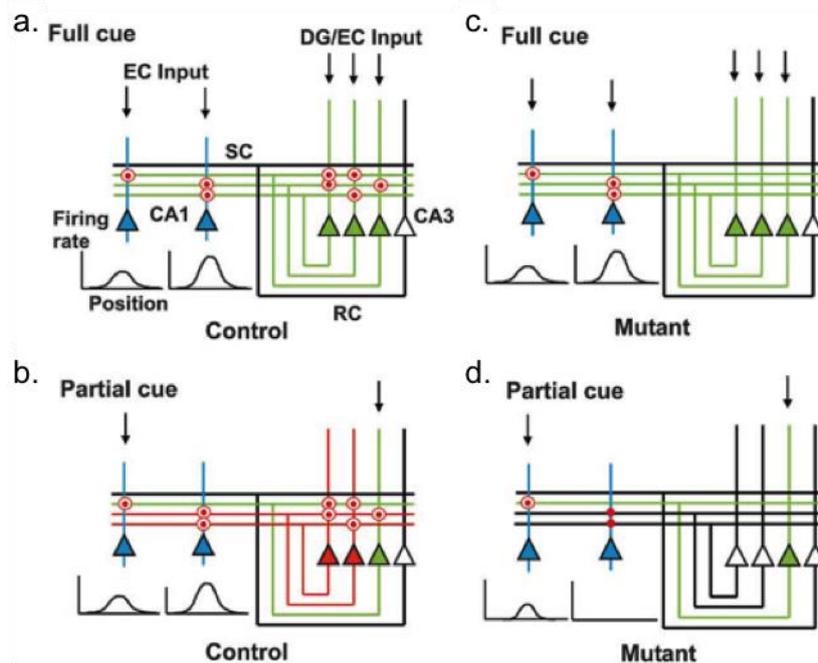


Figure 14: Pattern completion in CA3 region. Model for a distinct role of areas CA3 and CA1 in memory storage and recall. Basic wiring of CA3 and CA1, illustrating the proposed mechanisms for pattern completion. In control (a) and mutant (c), full cue input (downward arrows) is provided to CA3 from DG or entorhinal cortex (EC) and to CA1 from EC. In control (b) and mutant (d), a fraction of the original input is provided to activate the memory trace during recall. Red dots, CA3 synapses participating in memory trace formation; red circles, memory traces that are activated during recall; red dots without red circles, memory trace not activated during recall; red triangles and lines, CA3 pyramidal cell activity resulting from pattern completion through recurrent collateral firing; green triangles and lines, CA3 pyramidal cell response to external cue information; open triangles and black lines, silent CA3 pyramidal cells and inactive outputs; blue triangles, CA1 pyramidal cells. From (Nakazawa *et al.*, 2002).

Vazdarjanova and Guzowski (2004) compared the IEG activation patterns of two immediate early genes in CA3 and CA1 in an exploration task. The two immediate early genes, *Homer1a* and *Arc* are components of the postsynaptic density which participate in enabling lasting synaptic modification. They are thus used as neuronal activity markers. The expression time course is different: *Homer1a* is detected approximately 30 minutes after neuronal activation, whereas *Arc* is detected in the nuclei 2 to 15 minutes after. This technique, called cat-FISH (for *Cellular compartment Analysis of Temporal activity by Fluorescence In Situ Hybridization*), allows comparing in the same animal the neuronal activity triggered by two different behavioural conditions if they occurred at a 20 minutes interval. The study revealed that when confronted to two object arrangements successively (A then B), cells in area CA3 showed discontinuous activation patterns. However, when confronted with either

identical or very similar boxes (A then A or A'), the patterns overlapped very well, suggestive of pattern completion. The patterns in CA1 were more continuous across these environmental manipulations. The observations of Leutgeb et al. (2004) on the firing properties of CA3 and CA1 cells in various boxes and contexts are consistent with this conclusion.

Pattern separation on the contrary corresponds to the ability to distinguish environments or events which seem similar to known ones. McHugh et al. found that mice lacking the NR1 gene specifically in the DG were unable to discriminate between two similar contexts which were not spatially disparate (McHugh *et al.*, 2007). The DG is anatomically suited to pattern separation, regardless of the modality of the information to be encoded, due to its huge numbers of projection cells relative to CA3 or entorhinal cortex, giving it a large capacity for encoding new stimuli in novel network patterns (Amaral *et al.*, 1990). Leutgeb et al. provided single unit data supporting this idea (Leutgeb *et al.*, 2007). Granule cells were recorded from rats traversing several environments which shape gradually changed from a square to a circle. Granule cells were extremely sensitive to changes in the shape of the environment. Granule cells exhibited global remapping between the square and circle environments and gradual changes in firing rates with the incremental changes in the environment. This remapping occurred in granule cells of the DG even when grid cells in the medial EC (upstream to the DG) did not change their firing patterns.

The subregions of the hippocampus, dentate gyrus (DG), CA3, CA2 and CA1, are organized according to a trisynaptic circuit through which information primarily from layer II of the entorhinal cortex is projected to the DG, then to the CA3 via the mossy fiber pathway and finally to the CA1 via the Schaffer collateral connections. Another pathway of information transfer is directly between entorhinal cortex layer III and CA1 (Lorente de Nó, 1934; Witter *et al.*, 1989), called the direct pathway through a monosynaptic connection. Information flow through the hippocampus is primarily unidirectional, although CA3 also has a prominent network of recurrent collaterals (see Figure 15).

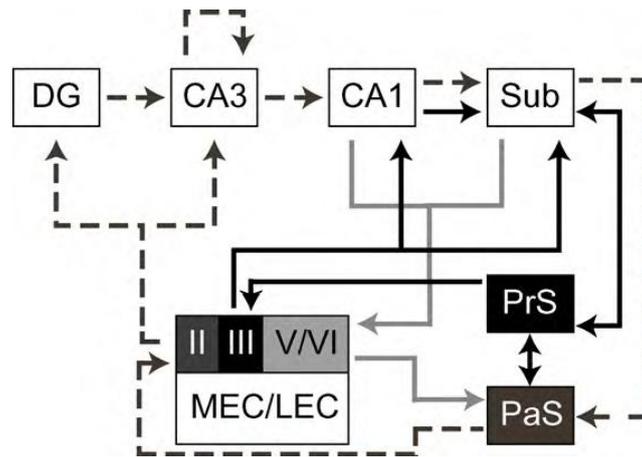


Figure 15: Simplified schematic of hippocampal and parahippocampal connectivity. Arrows indicate direction of information flow. Solid black lines indicate interactions predominantly with layer III of entorhinal cortex (medial and lateral), dashed lines indicate interactions predominantly with layer II and light grey lines indicate interaction predominantly with layer V/VI. Abbreviations: Sub, subiculum; PrS, Presubiculum; PaS, Parasubiculum; MEC, Medial entorhinal cortex ; LEC, Lateral entorhinal cortex. *From (Langston et al., 2010).*

The CA3 and DG areas may therefore be characterised as having two contrasting roles in memory processing, with the CA3 autoassociative pattern completion network matching incoming stimuli from the entorhinal cortex with previous familiar experiences and the DG pattern separator orthogonalizing the entorhinal cortex input and encoding stimuli as novel (Langston *et al.*, 2010).

The CA1 is the output of the hippocampus and therefore the “end-point” of its processing sequence. Two distinct roles have been assigned to it: mismatch detector and temporal tagging. Its role as a mismatch detector has been proposed theoretically as it receives both direct input about current events from the entorhinal cortex and stored information (putative “memories”) from CA3 (Lisman & Otmakhova, 2001). It could thus detect whether the current input from the direct the entorhinal cortex pathway matches previously stored representations arriving from the indirect CA3 pathway. An alternative view is that the CA1 adds a temporal context to events, to form associations between temporally discontinuous stimuli (Wallenstein *et al.*, 1998; Rolls & Kesner, 2006b). These proposed roles for CA1 could be equally valid, perhaps in terms of an encoding vs. retrieval distinction. Indeed during encoding the DG could be responsible for detecting novelty while CA1 would add temporal information to a situation. In contrast, during retrieval (in which DG is not thought to play a role), CA1 could act as a mismatch or novelty detector (Langston *et al.*, 2010).

The CA2 region, between the CA3 and CA1, has recently started being examined. An anatomical study using cell-type specific genetic and optogenetic tools has revealed that the CA2 pyramidal cells received direct input from the dentate gyrus and projected preferentially to CA1 pyramidal cells in the deep sublayer, whereas CA3 cell project preferentially in superficial sublayer (Kohara *et al.*, 2013). This suggests the existence of a second trisynaptic circuit in the hippocampus: Dentate Gyrus → CA2 → CA1. The functional role of the CA2 has been tested in an inactivation study which did not reveal any impairment in spatial and contextual memory, but did in social memory (in the ability of an animal to remember a conspecific), without any change in sociability (Hitti & Siegelbaum, 2014). The role of CA2 in non-spatial memory was suggested by its synaptic input from lateral entorhinal cortex, which conveys non-spatial information (Hargreaves *et al.*, 2005), with subcortical input from the serotonergic median raphe nucleus (Hensler, 2006) and the hypothalamic supramammillary nucleus (Pan & McNaughton, 2004). Another paper was simultaneously published on the CA2 using the cat-FISH method to track ensembles activated during contextual learning across CA3, CA2 and CA1 (Wintzer *et al.*, 2014). They found that exposure of mice to a novel context had a similar effect on neuronal ensemble activity across all CA fields, similarly to (Vazdarjanova & Guzowski, 2004). However CA2 ensemble is more sensitive than CA1 and CA3 to small changes in overall context, suggesting that CA2 may be tuned to remap in response to any conflict between stored and current experience and also playing a role as a comparator between stored information and external information (Wintzer *et al.*, 2014).

The two studies on the CA2 are difficult to conceal and supplementary studies will help dissecting its role. In a general effort to understand CA2's contribution to memory, I included this region in my Fos analysis (page 134).

3. Using the mental representation of space – processes and neural substrates

We have seen some of the brain mechanisms allowing the construction of a spatial representation. However, one often uses such representation with the aim to go somewhere. In the first section we will go through potential neural substrates which allowing representing a goal, and then we will see how one can plan a trajectory to the goal and how motivation to join the goal is up kept.

3.1. Goal information

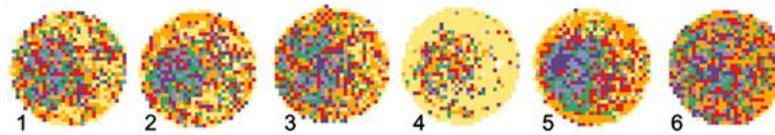
Different studies were interested in testing if as well as coding the current position of an animal in an environment, hippocampal place cells could convey information about goal position in a goal-directed navigation task.

Two studies employed experimental paradigms in which the goal was not marked by any physical stimulus. Hollup *et al.* (2001) observed that a high proportion of place cells had place fields at the position of a hidden platform when rats were trained in an annular watermaze: twice as many cells represented the unmarked goal than would be expected by chance. Similarly, Kobayashi *et al.* recorded place cells from rats trained to take fixed trajectories to obtain intracranial stimulation rewards at two specific locations in an open-field and found that some cells changed their firing patterns as rats learned the task and displayed excess firing at the two rewarded locations (Kobayashi *et al.*, 2003). However many studies did not find any goal representation in place cells (Speakman & O'Keefe, 1990; Trullier *et al.*, 1999; Lenck-Santini *et al.*, 2001).

A study has shown that the **prelimbic and infralimbic** areas situated in the rat's medial prefrontal cortex contained cells called "goal cells" (Hok *et al.*, 2005). Rats were trained in a cylinder to spend a short period of time in a localized but unmarked region (the goal zone) to receive a pellet of food elsewhere. The pellets dropped from an overhead dispenser into a localized zone but then bounced elsewhere, ending up all over the enclosure. There were thus two localized but unmarked zones, a goal zone, which upon entry triggered the reward, and a landing zone, where the pellets initially dropped. One-fourth of the cells in the prelimbic/infralimbic areas had place fields and these were about three to four times larger than those found in the dorsal hippocampus. The centres of a large percentage of these fields

were concentrated in the trigger (36%) and landing (42%) zones (see Figure 16). Rotating the cue card on the wall of the enclosure rotated the animal's representation of the trigger zone location, as judged by its behaviour, but had no effect on the landing zone place fields. Conversely, changing the location of the pellet dispenser and thus the location of the landing zone caused a shift in the landing zone fields to the new area but had no effect on the behavioural approach to the trigger zone. These goal cells also bear some resemblance to the goal cells postulated in the models of spatial navigation of Burgess and colleagues (Burgess *et al.*, 1994).

a. Firing rate maps of cells with fields in the trigger zone



b. Firing rate maps of ensembles with fields in the trigger zone (n=19)

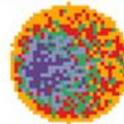


Figure 16: Goal cell in the prelimbic-infralimbic regions of a rat. (a) Firing rate maps of representative cells with fields in the trigger zone, where rats had to 2 sec to receive a food pellet which landed in another area of the arena. Each firing rate map was generated using data from the entire recording session. In all maps, yellow indicates no firing and purple indicates maximum firing (orange, red, green, and blue indicate intermediate firing rates from low to high). (b) Ensemble firing rate maps calculated from all fields in the trigger zone (n = 19). From (Hok *et al.*, 2005).

In a follow up study, Hok *et al.* (2007) showed that **place cells** in the same task also developed a weaker secondary firing field at the goal location (Figure 17). They then tested the effect of lesioning the mPFC on this goal-related firing of place cells but showed no impact of the lesion (Hok *et al.*, 2013). However, the rats were over-trained (over 2 months) before being lesioned. If the mPFC is necessary for establishing this goal-related activity in the hippocampal cells, its time window would thus be restricted to earlier stages of learning.

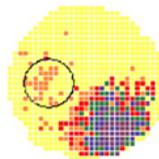


Figure 17: Goal-related activity in hippocampal place cell. Firing rate map for a place cells with putative excess discharge in the goal zone. From (Hok *et al.*, 2007).

Cells in the rat **orbitofrontal cortex** were also shown to code for spatial goals (Feierstein *et al.*, 2006). In an odor-cued two-alternative choice task requiring orientation and approach to spatial goal ports, over half orbitofrontal cortex cells recorded represented the location of the goal or the actions required to obtain it, indicating a spatiomotor coding of goal information. The orbitofrontal cortex is anatomically connected to the mPFC (Reep *et al.*, 1996) so it is possible that goal representation is spread amongst these regions known to be involved in general goal-directed decision-making processes (which will be further developed in section 3.1) (Euston *et al.*, 2012).

Ekstrom *et al.*'s study also reported goal cells in human patients while they played a taxi game in which they searched for passengers in a small virtual reality town and took them to their destinations in the form of specific storefronts (Ekstrom *et al.*, 2003). The electrodes were implanted in the hippocampal region, parahippocampal gyrus, amygdala, and several frontal sites. About one-fifth of the cells recorded were sensitive to the goal being sought, almost three-fourths of which responded while searching for a specific location. A small number of cells showed a place by goal interaction, firing in a particular location if the subject crossed it en route to a particular goal. These goal cells were located throughout the temporal and frontal lobes and not concentrated in the hippocampus as were the place cells recorded in the same study.

Functional neuroimaging studies have also linked prefrontal activity to goal processing (Spiers & Maguire, 2007). This study analyzed brain activity whilst taxi drivers dropped passengers off in a virtual simulation of the city of London. Brain activity was analyzed in combination with metric measures of proximity and direction to goal destinations which were derived from each individual subject's coordinates at every second of navigation. They found that activity in the medial prefrontal cortex was positively correlated with goal proximity. The medial prefrontal cortex activation was thus goal-selective and modulated by spatial proximity to the goal (Spiers & Maguire, 2007). A study by Paul Rodriguez using a virtual version of the Morris water maze showed that goal location could be predicted from the activity of the medial prefrontal cortex, but also from the hippocampus and the inferior parietal cortex. Combining all three improved the prediction performance, suggesting that goal-location information is disseminated across several areas (Rodriguez, 2010).

The prefrontal cortex integrates highly processed information important for guiding goal-directed behaviour (Pandya & Barnes, 1987). The prelimbic and infralimbic areas of the prefrontal cortex receive input directly from the ventral hippocampus (Jay *et al.*, 1989). The hippocampal input may provide positional information to the prelimbic and infralimbic cortex. Prelimbic and infralimbic also receive input from the amygdala (Kita & Kitai, 1990) and the ventral tegmental area (Thierry *et al.*, 1973) and indirect connections from the basal ganglia through the basal ganglia - thalamocortical loops (Uylings *et al.*, 2003). These projections convey multidimensional information onto the prefrontal cortex, including (but not limited to) emotional and motivational inputs (Aggleton, 1993), reward-dependent modulation (Schultz, 1998), and action-related signals (Uylings *et al.*, 2003). The prefrontal cortex seems then well suited to process manifold spatial information (Jung *et al.*, 1998) and encode the motivational values associated to spatiotemporal events (Poucet *et al.*, 2004).

3.2. Planning & Decision-making

Going to a given place (a goal location) implies that a decision has been taken. We have just seen that **the medial prefrontal cortex** is a structure that plays an important role in identifying the goal, through goal cells. It has also been implicated in decision-making in various tasks including conflict monitoring, error detection, executive control, reward-guided learning (Rushworth *et al.*, 2011) and decision-making about risk and reward (Bechara & Damasio, 2005). Rats with inactivated medial prefrontal are unable to make correct choices between rewarded or unrewarded locations based on memory ((Floresco *et al.*, 1997; Ragozzino *et al.*, 1998; Seamans *et al.*, 2008).

The **nucleus accumbens** has also been suggested as an important actor in route planning. It has been theorised to support translation of the hippocampal information it receives via direct connections (Thierry *et al.*, 2000) into a sequence of sensori-motor actions necessary to reach the destination (Redish & Touretzky, 1997; Poucet *et al.*, 2004). A support for this role has been provided in Spiers & Maguire's study (Spiers & Maguire, 2006) where the nucleus accumbens activated in initial goal-directed route planning, along with the hippocampus. Both dorsal and ventral **striatum** have been proposed to underlie decision-making by learning the correct actions to reach a goal in a given situation (Penner & Mizumori, 2012; van der Meer *et al.*, 2012). This has been classically associated with the reinforcement learning field. The striatum's role in decision-making and in reinforcement

learning will be further detailed in section 1.5 (page 77).

The **cingulate cortex** has been identified as maintaining a course of action in the face of countervailing forces rather than deciding which course of action to pursue (Cowen *et al.*, 2012; Holec *et al.*, 2014). Rats with cingulate cortex lesions are less willing to climb a wire mesh barrier to reach a high reward, opting instead to pursue a smaller but easier path to reach the reward (Walton *et al.*, 2002; Walton *et al.*, 2003; Rudebeck *et al.*, 2006) (Figure 18).

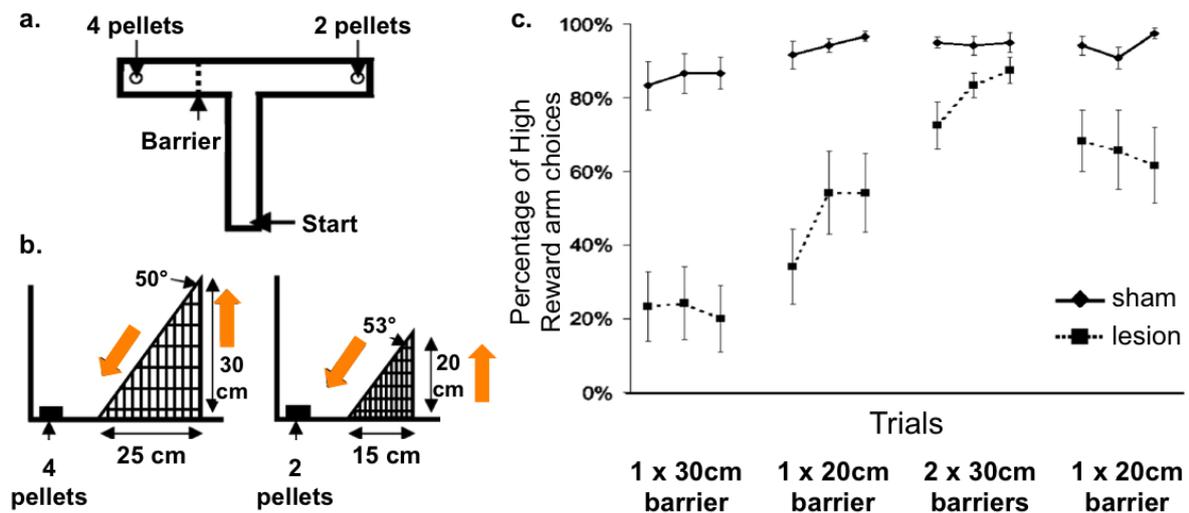


Figure 18: Cingulate cortex lesion in effort-based T-maze. (a) Schematic top view of the T-maze apparatus. On each choice trial, the animals could either choose the low reward arm with two pellets or could climb over a wire mesh barrier to obtain four pellets in the high reward arm. (b) The barriers were constructed out of thick wire mesh in the shape of a right-angled triangle. The rats climbed up the vertical side and descended down the slope to obtain the high reward (orange arrow). Two different size barriers were used. (c) Mean \pm SE percentage of trials in which sham and lesion group rats chose the high reward arm. Control rats always choose the high reward arm. When the size of barrier was of 30 cm, the lesion rats chose the low reward arm. When the barrier was lowered to 20 cm, lesioned rats started going to the high reward arm. When both arms had high barriers, lesioned rats performed like controls, choosing the high reward arms. *From* (Walton *et al.*, 2002).

Cowen *et al.* (2012) recorded cingulate neurons in rats which had to do trajectories with various level of effort (having an obstacle to climb or not) or reward. 52% of recorded cingulate neurons responded to the specific route taken to the reward while 21% responded prospectively to effort and 12% responded prospectively to reward. Effort- and reward-selective neurons also responded to the route, suggesting that these cells integrated motor-related activity with expectations of future outcomes. Action, effort, and reward responses occurred after animals initiated movements toward the left or right path, suggesting a more prominent role for cingulate cortex involvement in maintaining ongoing goal-directed actions.

These rodent studies have been followed by fMRI studies in humans, which have

shown that the dorsal anterior cingulate cortex encodes the value of an offered reward discounted by the effort needed to achieve it (Croxson *et al.*, 2009; Prévost *et al.*, 2010).

3.3. Organization of action sequences

Once a trajectory has been planned, different structures are then involved in organizing the actual sequence of movements to the goal.

The **parietal cortex** has been associated with movement planning (Andersen & Cui, 2009), egocentric spatial processing (Burgess *et al.*, 2002) and spatial working memory (Rowe *et al.*, 2000). But its role in navigation has recently been refined to organizing actions to guide trajectories.

Early studies had shown that it coded for route progression during navigation (McNaughton *et al.*, 1994; Nitz, 2006), which led to the proposal that the posterior parietal cortex translated coordinate information from spatial maps (in the hippocampus and medial entorhinal cortex) into body-centred representations and integrated this information with prefrontal goal information in the planning of a route to direct locomotion (Whitlock *et al.*, 2008; Calton & Taube, 2009).

Whitlock *et al.* (2012) recorded simultaneously cells in the posterior parietal cortex and the medial entorhinal cortex while rats were navigating in several foraging or navigation tasks. During foraging for food in an open arena, posterior parietal cortex cells encoded particular states of motion and acceleration. Indeed they showed increased firing for movement performed in a given direction and at a given speed (see Figure 19a). This activity preceded the movement to up to 500 ms. The tuning of these cells was sensitive to the animals' behaviour rather than the physical structure of the environment. Indeed their firing changed completely between the open field and a hairpin maze (the same size as the open field but with corridors forcing the rat to go up and down corridors to go from one end of the open field to another). Making the rat perform similar movement in the open-field as in the hairpin maze resulted in similar tuning to the hairpin maze (see Figure 19b). In addition, representations in the posterior parietal cortex were insensitive to changes in spatial inputs when an animal performed the same task in different rooms, as opposed to grid cells that expressed distinct spatial codes in different recording environments.

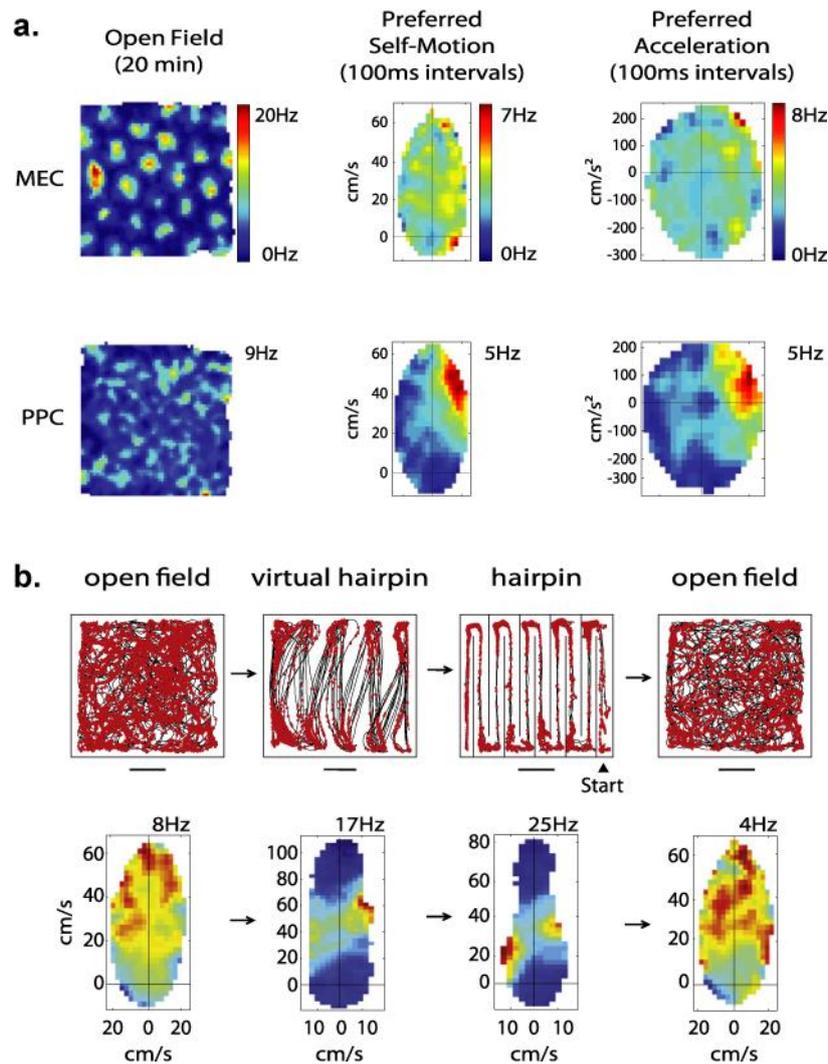


Figure 19: Self-motion and acceleration tuned posterior parietal cortex cells in the rat. (a) Rate maps are shown for representative cells in medial entorhinal cortex (MEC; top) and posterior parietal cortex (PPC; below) recorded over 20 min in a 1.5×1.5 m square arena. Rate maps in the left column are expressed in an allocentric reference frame, whereas maps in the right two columns are in egocentric reference frames. First column: spatial maps are shown in the open field, the color code is from blue (silent) to red (peak rate), with maximum firing rates written right of the rate map. Grid cells in MEC expressed a triangular firing pattern in the open field, whereas PPC cells showed poor spatial tuning. Second column: self-motion-based rate maps. The grid cell did not show movement-related firing fields, whereas many PPC cells did. The PPC examples typify the modes of movement to which the cells responded, such as forward motion to the left or right. Third column: acceleration based rate maps. The grid cell did not show tuning to acceleration status, but many cells in PPC did. Acceleration preferences of PPC cells often matched self-motion preferences. (b) PPC cells in the hairpin mazes. Top: path and spikes are shown for a PPC cell in the open field, virtual hairpin, the hairpin maze, and again in the open field. Below: Self-motion rate maps show the cell's tuning in each task. The cell's firing preferences in the virtual hairpin were similar to that seen in the hairpin maze (i.e., during left-right head swings). *Adapted from* (Whitlock *et al.*, 2012).

In another study, Harvey *et al.* (2012) showed that activity in the parietal coded for the mice's movement but specifically in memory-guided choices to a reward. They performed optical imaging of the posterior parietal cortex in mice which performed a T-maze decision

task in virtual reality where they had to select the correct turn based on a visual cue shown at the trial onset (Figure 20a). The authors recorded neurons in the layer 2/3 which expressed a genetically encoded calcium indicator, GCaMP3, which increases in fluorescence intensity in response to action potential firing (Tian *et al.*, 2009). They could record between 37 to 94 cells simultaneously and 73% of the cells they recorded had transient increases in fluorescence, of which the majority had significantly different levels of activity on correct left or right trials. When the activity patterns of all these choice-specific cells were ordered according to the time profile of their Ca^{2+} transients, the active periods across cells were staggered relative to one another in time, forming a sequence of neuronal activation covering the entire trial length (Figure 20b). Different sequences of neurons were activated on left and right trials (Figure 20b). Similarly to head direction cells or place cells, no spatial organization was found amongst the cells that were active at distinct time points in the task or that participated in different choice-specific sequences.

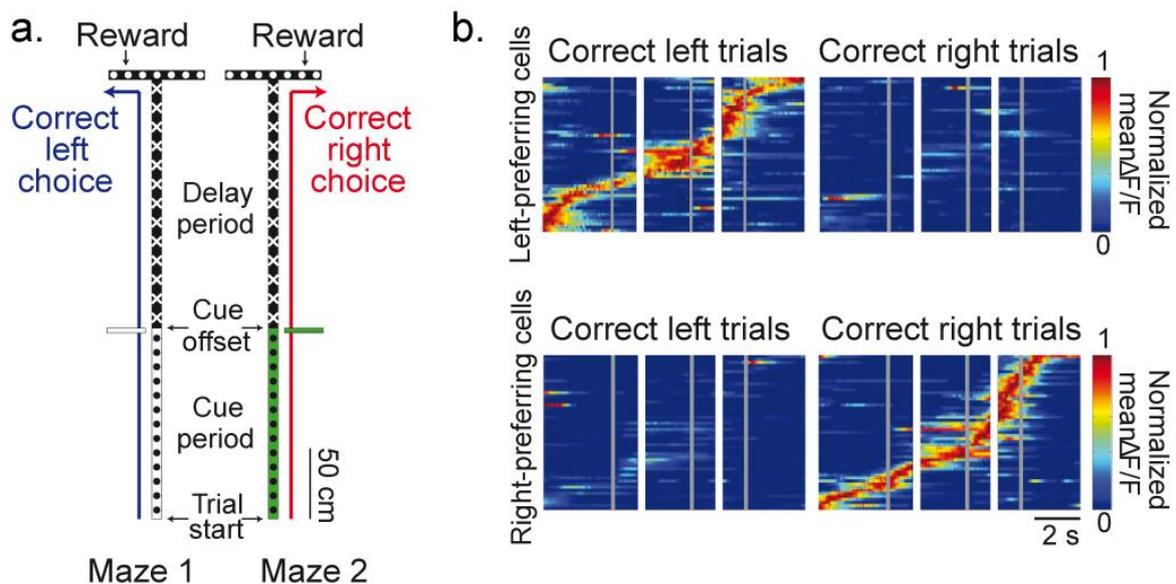


Figure 20: Choice-specific sequences in the parietal cortex during a virtual-navigation decision task. (a) Diagram of the two versions of the virtual T-maze that differed only in the cue period and the reward location. Patterns in the diagram reflect the patterns present on the virtual maze walls. (b) Normalized mean density ($\Delta F/F$) traces for all the choice-specific cells (one cell per row) imaged in a single mouse and divided by left preferring ($n=51$) and right-preferring ($n=54$) cells. Traces were normalized to the peak of each cell's mean $\Delta F/F$ trace on preferred trials and sorted by the peak time. Some cells were imaged on different days and in different fields-of-view. Adapted from (Harvey *et al.*, 2012).

This neuronal activity tracking the behaviour of the mouse could be the expression of egocentric motion information coding. However when mice passively viewed the visual scenes of left or right turn runs or if they ran up and down a virtual linear track with reward at each end, overall levels of activity were much lower than when mice actively performed the T-maze task. These results suggest that the sequential activation of the posterior parietal neurons was only activated for the memory-guided turn choice and not solely by the visual information or by the running patterns of the mouse. Moreover this activity seemed necessary to performing accurately the task as a local injection of muscimol in the parietal cortex, a GABA_A receptor agonist blocking neuronal activity, impaired the mice's performance but not in a version where a visual cue was present at the reward site and visible throughout the trial, thus not requiring to memorize the cue (Harvey *et al.*, 2012).

Whithlock *et al.*'s study proposes an involvement of posterior parietal cortex cells in the processing of cues related to the animal's locomotor space whatever the task whereas the second study rather points towards a specific role only when the memory of a cue must be kept in mind to join a reward. The discrepancies could be due to the different species (rat in the first study, mice in the second), activity recording technique (Spike recording vs calcium imaging) or to the layers which are recorded (deep layers vs layer 2/3). However both studies converge on the processing of egocentric movement. The fact that this activity precedes movement in Whitlock *et al.*'s study or that is not elicited by only movement or visual flow in Harvey *et al.*'s study suggest that the parietal cortex is involved in organizing actions towards a goal.

The posterior parietal cortex has extensive connections with sensory and motor cortices as well as cortical and subcortical limbic areas linked to spatial processing. It indeed receives inputs from most sensory cortices (see (Calton & Taube, 2009; Save & Poucet, 2009) for reviews) as well as from the cerebellum (Amino *et al.*, 2001; Clower *et al.*, 2001; Giannetti & Molinari, 2002; Prevosto *et al.*, 2010) and it has reciprocal connections with the retrosplenial cortex (connected to the hippocampus and entorhinal cortex and shown to manipulate egocentric-to-allothetic representations), the orbitofrontal and cingulate cortices (Kolb & Walkey, 1987), and the secondary motor cortex (Harvey *et al.*, 2012). The parietal cortex is thus ideally situated to receive a combination of allothetic, idiothetic and goal information to organize a goal-directed trajectory, which can then be sent to the secondary motor cortex to be performed. Indeed it has been recently that the secondary motor cortex is

essential to performing goal-directed behaviour (Gremel & Costa, 2013).

Studies in our team have also shown a role of the **cerebellum** in optimizing a trajectory. Indeed L7PKCI mice, which lack LTD at parallel fibre – purkinje cell synapses, could learn to locate the platform in the Morris water maze but they executed non-optimal trajectories, revealed by slower latencies despite spending more time in the quadrant of the maze containing the platform. The specific deficit in goal trajectory was corroborated by training the mice in the allocentric starmaze task, similar to the Morris water maze by requiring to locate an immersed platform using environmental cues but with lower procedural demands as it is composed of alleys which help guiding the mice's movements. In this task, mice also learned to locate the platform and showed no other learning deficit (Burguière *et al.*, 2005). The results of this study were further confirmed in a study using the same mice in a stimulus-dependent water Y-maze: here the L7-PKCI mice learned the association between a cue and a turn response, but exhibited a reduced optimization of their motor response regarding their trajectory (Burguière *et al.*, 2010). Together with the results presented earlier, our team has proposed that the cerebellum could have a role in building the mental representation of space through self-motion information processing (Rochefort *et al.*, 2011) and in using this representation through path optimization (Burguière *et al.*, 2005; Burguière *et al.*, 2010; Rochefort *et al.*, 2011). In support of such a role, the secondary motor cortex and the retrosplenial cortex, both receiving input from the parietal cortex, have been shown to provide input to the cerebellum, through the inferior olive (Suzuki *et al.*, 2012).

I have detailed processes involved in navigation through a linear process. However these do not necessarily happen always in this order, e.g. a mental representation of space can be updated whilst performing a trajectory towards a goal. Similarly, the flow of information in the structures is not linear. Indeed, lesions of some elements do not necessarily impair the whole system, suggesting that there are multiple pathways through which allothetic, idiothetic and goal information arrive to the hippocampal formation and there are probably multiple output pathways.

PART II Neural Dynamics across Task Learning

Studying navigation in rodent relies often on task learning. Indeed the way we probe building and correct use of mental representation of space is through maze learning. I am now going to present studies which have shown that task learning could be dissociated in different phases and that these phases involve different brain networks.

1. Learning stages

Navigating by performing a trajectory to a place involves motor skills. Many activities in our daily life actually depend on motor skills: writing, playing a musical instrument, riding a bicycle... Tasks involving motor skills are usually learned through trial-and-error and repeated practice, and psychophysical studies have demonstrated that the incremental acquisition of motor skills follows several phases.

Skill acquisition develops initially relatively fast and considerable improvement in performance can be seen even within learning sessions. Then performance increase slows down and further gains appear over longer periods of practice (Doyon & Ungerleider, 2002; Doyon & Benali, 2005) (Figure 21a). The relative duration of the **fast and slow learning stages** is highly task specific. For example, the fast stage learning of a simple four component key-press sequence could last minutes (e.g. (Karni *et al.*, 1995)), whereas the fast stage learning of a complex musical piece may last months (Figure 21b).

These skill changes occur during training, online, but they can also occur after training sessions, offline (Walker *et al.*, 2002; Fischer *et al.*, 2005; Albouy *et al.*, 2008) (Figure 21c). Offline processes reflect motor memory consolidation (Muellbacher *et al.*, 2002; Robertson *et al.*, 2004; Doyon & Benali, 2005). Once consolidated, the motor memory trace is believed to be resistant to interference (Balas *et al.*, 2007) and to become readily retrievable despite long periods of time without additional training. Online and offline skill gains can be maintained over time, resulting in long-term retention (Romano *et al.*, 2010).

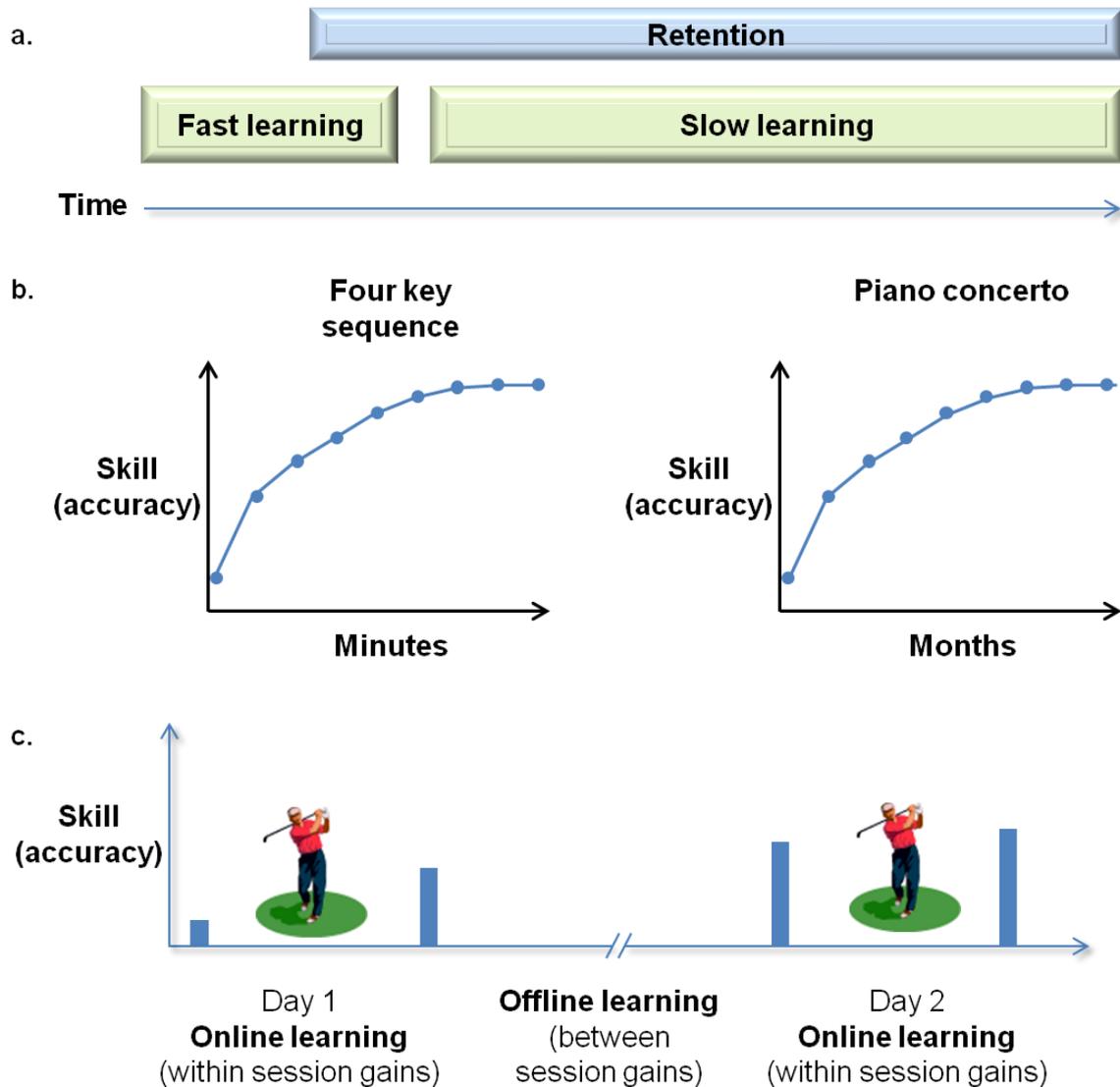


Figure 21: The different stages of motor skill learning. (a) Motor skill learning can be divided into a fast stage, in which typically significant improvements can be seen within a single training session, and a later, slow stage, in which further gains are achieved across multiple sessions of practice. Skill can be retained after a single or multiple training sessions. (b) The relative duration of fast and slow learning is highly task specific. For example, the fast stage of learning a four key sequence of keypress movements could last minutes, whereas the fast stage of learning to play a complex musical piece may last months. Although the shape of the learning curves for these two different tasks could theoretically be the same, the time bases of the fast stages of learning can be different. (c) Performance improvements during skill acquisition can occur not only during training (online learning), but also between sessions, with no further practice (offline learning). *Adapted from* (Dayan & Cohen, 2011).

Finally, motor skilled behaviours are regarded as fully **automatized** when actions are carried out effortlessly with little attentional resources needed for their successful completion (Doyon *et al.*, 2009). This resistance to interference is often tested by having a subject perform a secondary task at the same time as the studied task.

2. Network dynamics across learning

2.1. Imaging results

The neural basis and components underlying the different stages of task learning have been mainly studied in humans doing motor **sequence learning** tasks, using tasks designed to measure the incremental acquisition of sequential movements into a well-articulated behaviour.

The most common paradigm for studying motor sequence learning is the serial reaction time task (SRT) in which participants learn a sequence of key-press movements in response to a visual cue (Nissen & Bullemer, 1987). A variant of this task is the finger-tapping task in which subjects have to learn a sequence of finger movements that they are given (Lehéricy *et al.*, 2005). Improvements in performance on these tasks are measured by decreases in the number of errors and shortening of reaction time, as when the presentation of stimuli follows a sequential order the response time decreases compared to non-sequence (random) trials. Other tasks have been developed to test learning of a sequence of reaching movements (Seidler *et al.*, 2004; Ghilardi *et al.*, 2009), and eye movements (Albouy *et al.*, 2006; Albouy *et al.*, 2008) and force-pulses (where subjects track a continuously changing, visually presented target by varying the force exerted on a pressure sensor held in the hand) (Floyer-Lea & Matthews, 2004; Floyer-Lea & Matthews, 2005).

Lehéricy *et al.* (2005) studied the brain activity in subjects learning and practicing a sequence of finger movements over 4 weeks to identify the neural substrates of early and late learning phases. Different territories were engaged in early and advanced motor sequence learning. During early training, learning-dependent, blood oxygenated level dependent (BOLD) signal changes revealed a signal increase in the associative region of the striatum, as well as in the pre-supplementary motor area, supplementary motor area proper, premotor and anterior cingulate, superior parietal cortices and in the cerebellum (lobules V and VI, right Crus I, left dentate nucleus). This increase of activity during initial learning on the first day was then accompanied by a general decrease of activity in these areas 2 weeks or 4 weeks later. However late learning was accompanied by an increased activity in the sensorimotor region of the striatum 2 or 4 weeks after initial learning. Similar brain region dynamics across learning have also been observed in a force-pulse sequence learning task, with an additional activation of the somatosensory cortex in the late stage (Floyer-Lea & Matthews, 2005).

In Lehericy et al.'s study the dentate nucleus (one of the cerebellar output nuclei) was only engaged in the early stage of the task. However this aspect is controversial. Other studies have also shown strong activation during the early phase, followed by a progressive reduction of activation during the last phase of the dentate nucleus (Friston *et al.*, 1992; Jenkins *et al.*, 1994; Jueptner *et al.*, 1997) but some have noted an increase in dentate nucleus activity with learning (Nezafat *et al.*, 2001; Doyon *et al.*, 2002). These last studies have fostered the hypothesis that in motor learning there is a functional transfer of activity from the cerebellar cortex to the dentate nucleus during gain in performance, suggesting a transfer of plasticity in the neural representation of the motor sequence from the cerebellar cortex to the deep cerebellar nuclei.

Although imaging studies clearly established that the fast and late stages of motor skill learning are each sustained by activity across a distributed set of brain regions, univariate fMRI analysis, in which brain activity is analysed in a voxel-wise manner as if each anatomically distinguishable region is independent (Marrelec *et al.*, 2006), does not provide information on interregional interactions. The most used approach for assessing interregional interactions in neuroimaging data is based on analysis of **functional connectivity** (Friston, 1994), which refers to the statistical dependence defined in terms of correlation or covariance between the activation of various regions. Using this approach, Coynel et al. (2010) reanalyzed the data from Lehericy et al.'s study (2005) and showed that **early learning** was associated with increased integration, a metric reflecting functional interactions among several brain regions, between the **associative premotor-striato-cerebellar structures**. This premotor-associative striatum-cerebellar network was composed of the pre-supplementary motor area, premotor and parietal cortices, cerebellar lobule VI (belonging to the associative region of the cerebellum), associative regions of the thalamus and striatum (caudate nucleus). During **slow learning**, on the other hand, the authors reported decreased integration in this premotor-associative striatum-cerebellar network but stable connectivity within the **sensorimotor M1-striato-cerebellar network**, composed of the supplementary motor area, sensorimotor cortex and sensorimotor regions of the cerebellum (lobules IV-V), motor regions of the thalamus and striatum (putamen).

The results obtained for the early stage were consistent with those from another study which showed during early sequence learning that the primary motor cortex M1, the premotor cortex and the supplementary motor area had greater inter- and intrahemispheric coupling

compared to a later learning stage and increased functional connectivity between the dorso-lateral prefrontal cortex and premotor cortex (Sun *et al.*, 2007).

The **hippocampus** has also been implicated in motor sequence learning. Using serial reaction time task, Schendan *et al.* (2003) have demonstrated that the hippocampus was significantly activated, irrespective of whether sequential knowledge was acquired implicitly (unbeknownst to the subjects, the targets appear in a determined repeating sequence of locations) or explicitly (the participants are informed that the purpose of the task is to learn a sequence). This was the first study to have shown an activation of the hippocampus in an implicit version of the sequential finger tapping task but its implication seems to depend on the **complexity of the sequence**. Indeed Schendan *et al.* used a second-order sequence, where predicting the next event requires knowledge of the two immediately preceding events compared to first-order sequences which were most often used and which only require knowledge of the preceding event. However they did not look at the dynamics of hippocampal involvement.

2.2. Theoretical models

Based on the general pattern of behavioural and imaging finding that motor skill learning involves several changes supported by different networks, different theoretical models have been proposed, the main ones being **Doyon *et al.*'s model “stage” model** (Doyon & Ungerleider, 2002) and **Hikosaka *et al.*'s model “component” model** (Hikosaka *et al.*, 2002).

Doyon has developed an influential model where changes in performance across stages of learning are framed in terms of the differential contributions of cortical–cerebellar and cortical–striatal loops (Figure 22) (Doyon & Ungerleider, 2002; Doyon *et al.*, 2003; Doyon & Benali, 2005; Doyon *et al.*, 2009). In this model, early rapid changes in performance are attributed to both cortico-cerebellar and cortico-striatal mechanisms. Learning during the early stage also includes possible contributions from frontal and hippocampal executive control in tasks where learning is under explicit control or complex. Following early learning, striatal mechanisms are proposed to contribute specifically to consolidation of learned sequences. Finally, sequence retention is hypothesized to be supported by a network including the striatum, motor and parietal cortices.

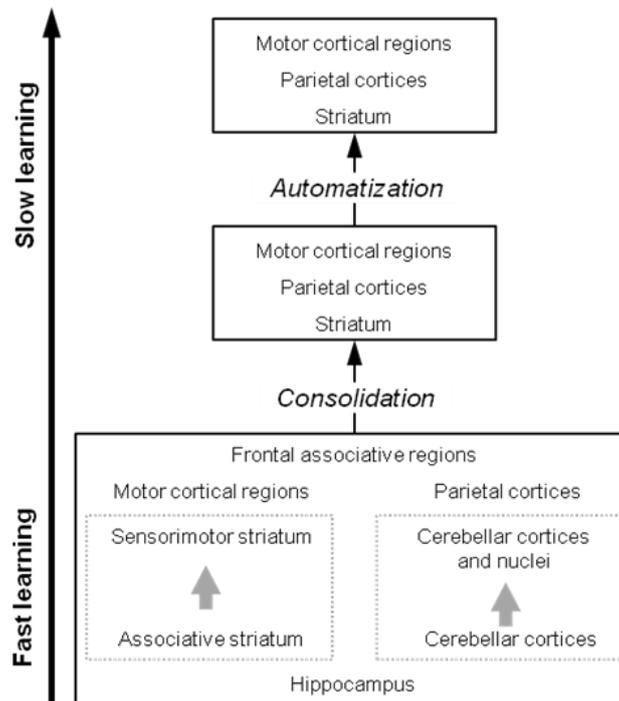


Figure 22: Doyon and et al.'s “stage” model of motor skill learning describing the cerebral plasticity within the cortico-striatal and cortico-cerebellar systems during the course of learning a new sequence of movements. *Adapted from* (Doyon *et al.*, 2009).

In contrast, Hikosaka *et al.*'s theory has focused on the different task components of motor skill learning rather than on learning stages. According to this model, two parallel loop circuits operate simultaneously in learning the spatial features (corresponding to the actual order of the movements) and the motor features (corresponding to the movement dynamics: speed, timing and sensorimotor integration) of sequences (Figure 23) (Hikosaka *et al.*, 2002). Hikosaka and colleagues have proposed that learning these components proceeds in parallel, but that they have different time courses and are controlled by different cortico-striatal and cortico-cerebellar loops. Whereas learning spatial coordinates, expressed in terms of accuracy, is supported by circuits linking frontal, parietal and premotor regions with association areas of the striatum and lateral cerebellum, learning motor coordinates is supported by circuits linking motor cortical regions with the putamen and midline cerebellar regions. Transformations between the two coordinate systems rely, according to this model, on the contribution of the supplementary motor area, pre-supplementary motor area and premotor cortices. This model predicts that performance improvements during early learning are dominated by circuits mediating spatial/sequential learning (based on more explicit reward-based learning through the associative striatum) while those of later learning are predominantly influenced by

mechanisms more relevant for motor optimization (based on error-based learning through the cerebellum). Importantly, it was argued that learning spatial coordinates is faster, yet requires additional attentional and executive resources (Dayan & Cohen, 2011), putatively provided by prefrontal cortical regions (Miller & Cohen, 2001).

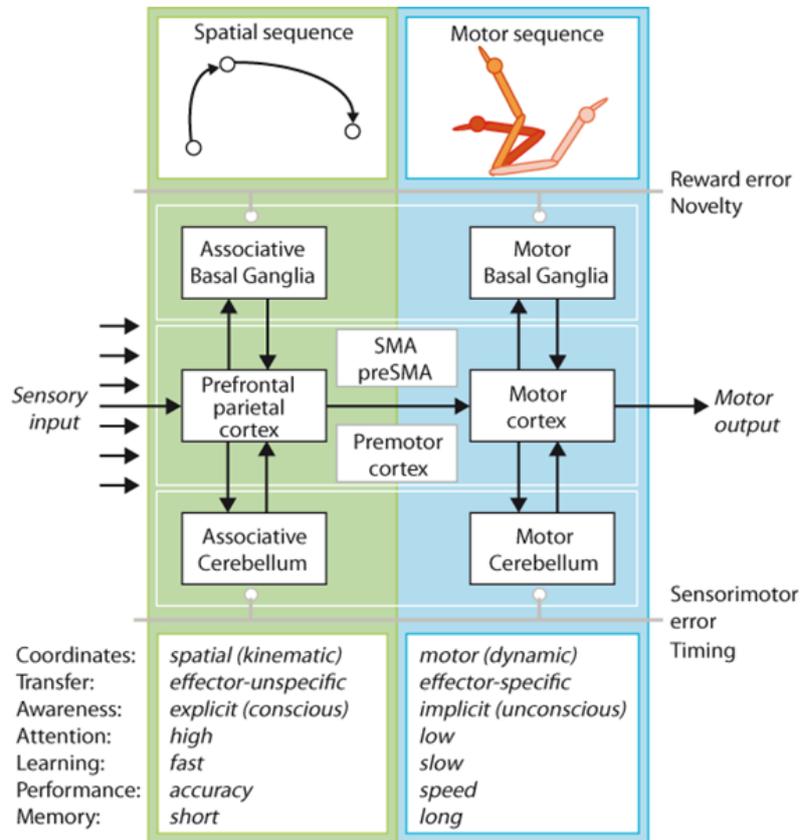


Figure 23: Hikosaka et al.’s “components” model of motor skill learning. They propose that motor skill learning operates as the interaction of two orthogonal connections: intracortical serial connections (horizontal arrows) and cortico–basal ganglia/cortico–cerebellar loop circuits (vertical arrows). The left side of the figure represent the spatial sequence learning component, the right side represents the motor sequence learning component. At the beginning of learning, movements are executed individually through the spatiomotor conversion process (horizontal connections). After learning, the movement sequence is represented by at least two networks in different coordinates: a spatial sequence supported by the parietal–prefrontal cortical loops and a motor sequence supported by the motor cortical loops (vertical connections). Signals from the frontoparietal cortices and the motor cortices are sent to different functional divisions of the basal ganglia and cerebellum (vertical arrows). In the basal ganglia, the signals are evaluated for their reward or likelihood values; in the cerebellum, they are evaluated for their sensorimotor or timing errors (gray lines). Hence, the performance of the spatial and motor sequence mechanisms can be optimized independently. *Adapted from* (Hikosaka *et al.*, 2002).

Both models share the view that motor skill learning involves interactions between distinct cortical and subcortical circuits, crucial for the unique cognitive and control demands associated with this stage of skill acquisition, but they differ in presenting either a serial or parallel involvement of the different networks.

Penhune and Steele recently proposed a **model combining** several aspects of the

“stage” (from Doyon and colleagues) and “component” (from Hikosaka and colleagues) models by assigning more specific task components to the structures involved in the different learning phases (Figure 24). This model also proposes that the cerebellum, striatum and motor cortical regions are always involved in motor skill learning and that depending on the learning stage and the component being learned (e.g. sequence ordering, error correction...), the structures may either work in parallel or interact (Penhune & Steele, 2012).

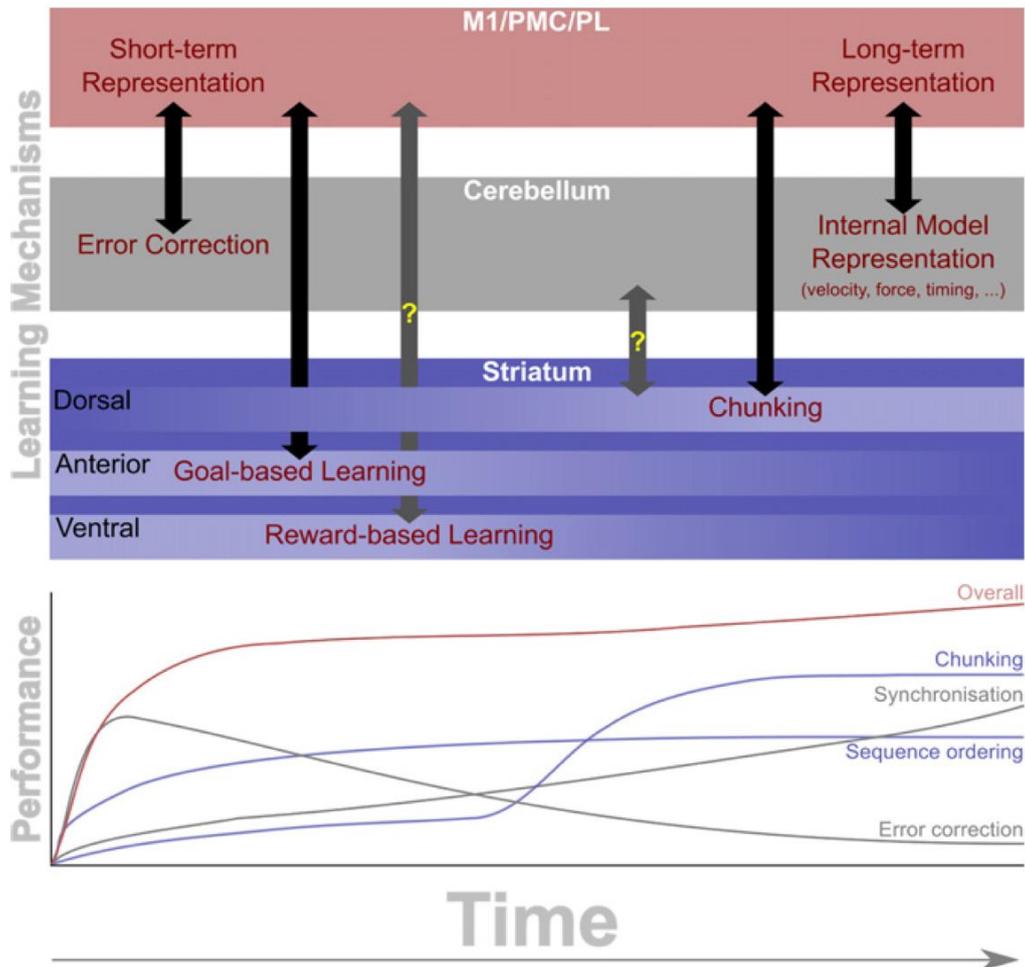


Figure 24: Penhune and Steele’s “integrated” model of motor skill learning. The top panel of the figure illustrates the brain regions and associated mechanisms involved in motor sequence learning, and highlights their connectivity. Interactions between regions/mechanisms are depicted by vertical arrows, with lesser known interactions depicted by light arrows. The colour gradient within the striatum represents the relative contribution of each learning mechanism (light = greater contribution; dark = lesser contribution). The bottom panel depicts the idealized learning curve for different components of performance over time. Each component is colour-coded to its associated brain region. Abbreviations: M1, Primary motor cortex; PMC, Premotor cortex; PL, Parietal lobe. *Adapted from* (Penhune & Steele, 2012).

Based on a review of human, non-human primate and rodent studies as well as their own results, the authors have assigned the several learning components to the different

structures involved in motor sequence learning (Penhune & Steele, 2012).

During **early learning**, the associative (or anterior) and ventral striatum would allow goal-directed learning of the sequence which would be stored in a distributed network involving the motor, premotor and parietal cortices. The cerebellum's contribution would be through error correction.

Indeed a current hypothesis about of the role of the **cerebellum** in motor control is that it instantiates **internal models** that facilitate optimal performance and learning (for reviews, see (Wolpert *et al.*, 1998; Ito, 2005a; Ramnani, 2006)). An internal model can be defined as a set of input-output relations between motor commands and their sensory consequences. Input to the model is the efference copy of a motor command and output is the predicted sensory consequences of that action. Internal models are hypothesized to be critical for motor learning because they allow for a comparison between the predicted and actual consequences of a movement, and thus for the assessment of movement error that is used to guide learning. Two brain stimulation experiments have demonstrated the role of the cerebellum in state estimation – a function closely related to internal models. In the first study, Miall *et al.* showed that transcranial magnetic stimulation (TMS) over the cerebellar cortex impaired the accuracy of reaching movements that depended on state estimation for accuracy (Miall *et al.*, 2007). In the second study, Galea *et al.* showed that transcranial direct stimulation (tDCS) over the lateral cerebellum enhanced learning of a visuomotor rotation task by promoting a more rapid decrease in error (Galea *et al.*, 2011).

Then, in the **late learning** phase the representation of the sequence is maintained as long-term memory in the motor, premotor and parietal cortices.

The cerebellum could contribute to this representation by storing information about the optimal motor control parameters for performance of the skill within a particular context. Indeed while an fMRI result showed specific increases in lobule VIII after long-term training on a motor sequence task (Steele & Penhune, 2010), the TMS study cited above shows that disruption of the lateral cerebellum during reaching does not halt movement, but rather appears to disrupt the estimate of the location of the arm in space (Miall *et al.*, 2007). This study, among others, suggests that the cerebellum does not appear to be required for the storage of the motor program itself but rather contributes to it through motor control aspects (Penhune & Steele, 2012).

The sensorimotor region of the striatum would lead to habitual execution of the sequence through combining the different elements into one chunk. Indeed a proposal for the

role of the basal ganglia in motor sequence learning is that it associates multiple movements into groups or chunks (Graybiel, 1998; 2008). Chunking is characteristic of over-learned sequences and is thought to be important for learning and maintaining longer and more complex sequences because it confers a memory advantage (Rosenbaum *et al.*, 1983; Sakai *et al.*, 2003). Consistent with this evidence, a recent fMRI study showed that activity in dorsal-lateral striatum was related to chunking in a finger-sequencing task (Orban *et al.*, 2011). Moreover multiunit recording work in rats has shown that as T-maze learning progresses the response of striatal output neurons becomes tuned to the beginning and end of the sequence of movements – indicating that corticostriatal circuits represent the sequence as one or more chunks rather than as a series of individual movements (Barnes *et al.*, 2011).

Cortico-striatal (Alexander *et al.*, 1986), cortico-cerebellar circuits (Bostan *et al.*, 2013) and basal ganglia-cerebellum disynaptic pathways (Bostan & Strick, 2010; Bostan *et al.*, 2013) would allow these structures to interact.

3. Learning stages in rodent studies

Many rodent studies show the involvement of a structure at given stages of learning through lesions, cell imaging or electrophysiology, but only a few have followed the neural dynamics across learning stages. Studies which have mostly focused on the striatum in motor skill learning or conditioning tasks, and two studies have examined the neural dynamics of brain regions in a spatial learning task.

3.1. Neural dynamics in goal-directed and habitual behaviours

The studies interested in a change of learning phase have mostly studied the transition between goal-directed and habitual learning. As mentioned earlier, in human motor sequence learning the last learning phase is often associated to the automation of the sequence, defined by its resistance to interference (can a secondary task be performed at the same time as the sequence with minimal interference?). In animal studies, especially in instrumental learning tasks, the term *habitual* is preferred to *automation*, a habitual behaviour being defined as being insensitive to the goal. This **habitual behaviour** is opposed to a **goal-directed behaviour**, which is thought to allow the acquisition of the task. Therefore, task learning is thought to start by a goal-directed phase and then may lead to a habitual phase.

The distinction between goal-directed and habitual behaviour is closely related to the distinction between flexible “cognitive” learning and inflexible stimulus-response learning. In “cognitive” learning, behaviours are thought to involve associations between an action and a particular expected outcome (goal-driven behaviour through action (or response)-outcome associations). Conversely, inflexible stimulus-response reflex were thought to lack outcome representation.

In an early experiment testing this logic (Adams & Dickinson, 1981; Adams, 1982), animals were trained on a simple operant task, pressing a lever for reward. They then received a devaluation of the reward, which involved induction of an aversion to the reward through pairings of the reward with administration of a nauseogenic agent, lithium chloride. The animals were then returned to the task and tested in a probe trial in which no reinforcement was present, called extinction. Animals that had been trained in the task but not far past their initial acquisition performance levels reduced lever presses. This finding suggested that the animals recognized the identity of the outcome that they were working for, and could flexibly adjust their behaviour, providing support for earlier notions of animal purposefulness in behaviour (Tolman, 1932). By contrast, animals that had been over-trained on the task, that is long after they had reached an initial learning criterion, continued pressing the lever. This persistence of seeking the reinforcement despite its devaluation is considered to be a defining mark of habitual behaviour. The requirement for extensive experience is key and also implies that behaviour is initially goal directed but then becomes habitual over the course of experience.

Lesion, inactivation and pharmacological experiments have investigated the neural bases of goal-directed and habitual behaviours. The **dorsomedial (or associative) striatum** circuit has repeatedly been highlighted to support **goal-directed behaviour** (Balleine, 2005; Corbit & Balleine, 2005; Yin *et al.*, 2005a). Related studies show that a circuit centred on **dorsolateral (or sensorimotor) striatum supports habit-based behaviour** (Balleine & Dickinson, 1998; Killcross & Coutureau, 2003; Yin *et al.*, 2004; Balleine, 2005; Yin & Knowlton, 2006). Lesions to dorsolateral striatum result in a maintenance of goal-directed behaviour even with extended training, a pattern that contrasts with the effect of lesions to dorsomedial striatum that result in an early emergence of habitual behaviour (Yin *et al.*, 2004; Yin *et al.*, 2005b). Disruption of the infralimbic region of the medial prefrontal cortex produces similar effects to lesions of the dorsolateral striatum (Coutureau & Killcross, 2003; Killcross & Coutureau, 2003; Smith *et al.*, 2012). The fact that the infralimbic cortex is not

directly connected with the dorsolateral striatum, along with the many other regions implicated, suggests a widespread distribution of habit-promoting regions in the brain.

There is also explicit evidence for the **transfer from dorsomedial to dorsolateral striatum** over the course of training (Yin *et al.*, 2009; Thorn *et al.*, 2010) (for review (Graybiel, 2008; Belin *et al.*, 2009)) and also from the **shell of the accumbens (or ventral striatum) to the core** (Segovia *et al.*, 2012).

In vivo recordings in behaving mice revealed that the dorsolateral striatum is engaged later in training, when performance in an accelerated rotarod task asymptoted (Yin *et al.*, 2009). Indeed task-related activity, measured through the average modulation of firing rate during running compared to a baseline when animals were still and through the proportion of neurones which activity was modulated during running, was specifically increased in the dorsolateral striatum during the late stage, compared to the early stage or naïve mice. On the contrary, the dorsomedial striatum was specifically engaged in the early phase of rotarod training. Consistently, *ex vivo* recordings from medium spiny neurons following training revealed long-lasting changes in glutamatergic neurotransmission in the dorsomedial striatum during early training and in the dorsolateral striatum during late training. These electrophysiological analyses suggest a serial involvement of the dorsomedial and dorsolateral striatum. However in the same study the authors lesioned either regions separately, which resulted in impaired performance on the rotarod specifically early in training when the dorsomedial striatum was lesioned and in impaired performance during early and late training phases when the dorsolateral striatum was lesioned. This suggests that fast and slow skill learning develop in parallel in the dorsomedial and dorsolateral striatum, and the dorsomedial striatum disengages in later stages.

These results are similar to those obtained by Thorn *et al.* (2010). In a series of studies, Ann Graybiel's lab has developed a conditional T-maze task in which rats have to associate a cue, which is presented in the departure arm, to either a left or a right turn. This task was designed to require not only skilled motor performance, but also flexible responding based on sensory cues signalling the baited end-arm, thus taxing both sensorimotor and cognitive circuitry. Unpublished data from their team has given evidence that a classical lithium chloride devaluation procedure shows that training on a similar T-maze task behaviour is initially goal-directed and becomes habitual with overtraining (Thorn *et al.*, 2010). They recorded neural activity chronically from the naive state to the extensively overtrained state. The sensorimotor striatum developed ensemble spike activity that was increased at the action

boundaries of the task. The associative striatum developed heightened ensemble spike activity mainly during the middle of the task, when the animals chose between alternate actions based on instruction cues. These striatal activity patterns developed simultaneously across training. However, the dynamics of the learning-related changes in these two striatal regions were different, and they were differently related to the behaviour of the rats. In the sensorimotor striatum, the emerging ensemble activity pattern steadily increased as training progressed and was correlated with improving performance. In the associative striatum, the activity pattern first increased and then diminished as training progressed and it was not correlated with individual behavioural parameters. These observations lead the authors to propose a model taking into account the dynamics of simultaneously active sensorimotor and associative striatal circuits during training (Figure 25).

According to this model, exploration driven by frontostriatal associative circuits would be the default mode for behaviour in a new learning environment. During the middle of training in the T-maze task, strong dorsolateral task-bracketing activity indicates that the neural bases for a habit exists, but equally strong or stronger dorsomedial activation would prevent its expression. Finally, following mastery of all aspects of the task, the subsiding of dorsomedial activation would enable dorsolaterally based habitual behaviour to be expressed. The permissive role of the associative striatum in the evolution of behaviour toward habitual performance would not require a direct transfer of information from the dorsomedial to the dorsolateral striatum. Rather, through their output connections, they could set up a competition at downstream targets (including regions of the neocortex or brainstem), enabling the disruption of habitual responses that would otherwise be driven by dorsolateral striatum-based loops (Thorn *et al.*, 2010).

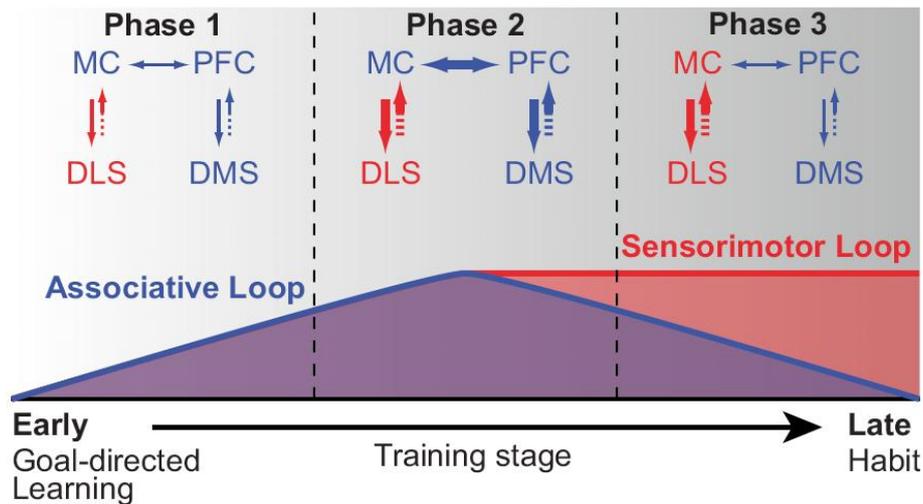


Figure 25: Schematic model illustrating hypothesized dorsomedial and dorsolateral cortico-basal ganglia loop interactions across different phases of learning. Activity in both striatal regions and their corresponding loops becomes structured simultaneously during Phase 1. In Phase 3, the reduction in structured dorsomedial striatal activity permits sensorimotor circuits to drive execution of habitual behavior. Broken arrows indicate multisynaptic connections from striatum to neocortex through pallidum and thalamus. MC, motor cortex; PFC, prefrontal cortex; DLS, dorsolateral striatum; DMS, dorsomedial striatum. *From* (Thorn *et al.*, 2010).

The parallel involvement early in training in both studies is consistent with Hikosaka *et al.* (Hikosaka *et al.*, 2002) and Penhune and Steele's (Penhune & Steele, 2012) models presented earlier. Regarding the specific involvement of the sensorimotor or dorsolateral striatum later in training it is consistent with Doyon *et al.*'s model (Doyon *et al.*, 2009) (Figure 22).

3.2. Neural dynamics in spatial learning

Two studies have looked at neural dynamics across a spatial learning task.

In the first spatial study, two groups of rats were trained for either two or five days in a radial-arm maze task (Poirier *et al.*, 2008). The study used a combined working and reference memory task of the radial arm maze which consists in retrieving pellets in four of the eight arms, thus taxing working memory within a session to avoid re-entering an arm already visited, and reference memory across daily sessions as the same four arms were baited everyday day (Olton & Papas, 1979). They measured the induction of an immediate early-gene (IEG) Zif286 in the hippocampus subfields and parahippocampal cortices. Zif286 expression is associated with both spatial memory and long-term plasticity in the hippocampus (Guzowski, 2002; Kubik *et al.*, 2007). It was compared to control rats which did not learn the task but obtained the same number of rewards, visited the same number of maze

arms and spent a comparable amount of time in the maze. Overall Zif268 levels were not different in the early, late training group and their respective control but significant correlations were found between spatial memory performance and levels of dentate gyrus Zif268 expression in the early group. Later in training both CA1 and CA3 became associated with performance, but this relationship was opposite in each field: higher Zif268 expression was associated with poorer performance in CA1 but with better performance in CA3. They also used structural equation modelling to evaluate network dynamics by deriving estimates of the influence of one site over another, based on known anatomical connections (Figure 26a) (McIntosh & Gonzalez-Lima, 1991; Friston *et al.*, 1993a). This analysis revealed that as training progressed, there was a statistical loss of dentate gyrus efferents to CA3 and CA1, and more direct functional entorhinal cortex coupling with CA1 activity, so producing a trisynaptic circuit bypass (Figure 26b).

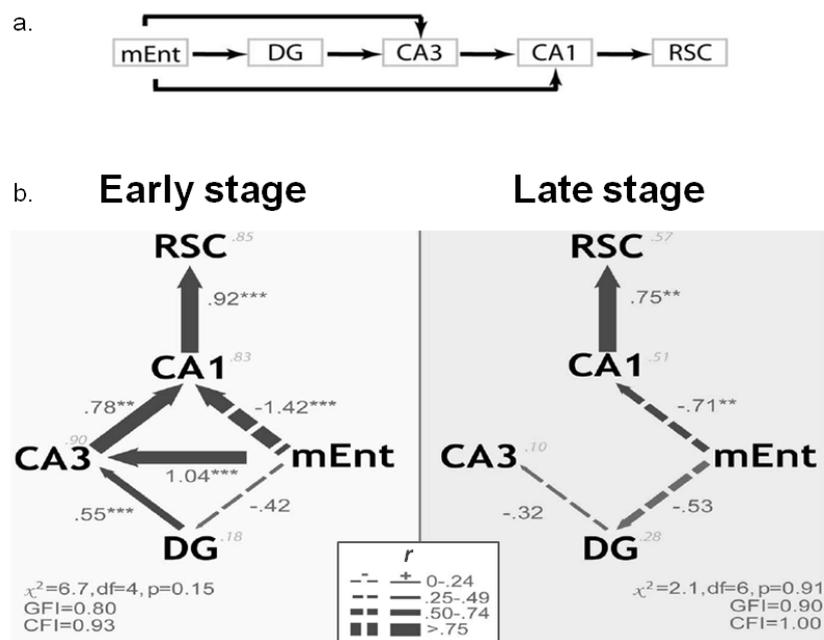


Figure 26: Qualitatively Different Hippocampal Subfield Engagement Emerges with Mastery of a Spatial Memory Task by Rats. (a) Pathways used for the anatomically derived models between the medial entorhinal cortex and the CA1–CA3 fields. (b) Path analyses for the rats trained in the radial-arm maze for either two (“early stage”) or five (“late stage”) sessions. The strength and the positive or negative relation of the causal influences represent the value of the correlation between the structures and are explained in the figure legend. For the early stage, a model containing all the anatomical connections provided the best fit to the data: it was not significantly different from the data ($\chi^2=6.7$ with $p=0.15$) and provided a good fit, close to 1 (Goodness of Fit Index (GFI)=0.8; Comparative Fit Index (CFI)=0.93). For the late stage, the best fit was a simplified model of the anatomical connections where the paths with the weakest correlations were deleted. It provided a good fit ($\chi^2=6.7$ with $p=0.91$; GFI=0.9; CFI=1). This simplified model reveals the preponderance of the temporoammonic path to CA1 over the trisynaptic circuit induced with training. * $p<0.05$; ** $p<0.01$; *** $p<0.001$. RSC, retrosplenial cortex; mEnt, medial entorhinal cortex. Adapted from (Poirier *et al.*, 2008).

In the second spatial study, Conejo et al. (2010) used quantitative cytochrome oxidase histochemistry as a metabolic brain mapping method to rats trained in a Morris water maze for one, three or five days to track the progression of brain circuits across learning. Cytochrome oxidase histochemistry is used as a marker of neuronal metabolic capacity as cytochrome oxidase activity represents an index of the energy demands of neurons after prolonged stimulation or training in behavioural tasks (Wong-Riley, 1989; Gonzalez-Lima & Cada, 1994).

Sustained changes throughout training were found in the lateral septal nucleus and anteroventral thalamic nucleus. Compared to a habituation group which performed one cued platform session, rats with one day of training in the spatial learning task showed involvement of the lateral mammillary nucleus, basolateral amygdala and anterodorsal thalamic nucleus. By five days of training, there were mean changes in the hippocampal CA3 field and the prefrontal cortex. Analysis of pairwise correlations between the regions revealed that the pattern of network interactions changed progressively over days of training (Figure 27). At one day there was an open serial network of pairwise correlations. At three days there was a more closed reciprocal network of intercorrelations. At five days there were three separate parallel networks. In addition, brain-behaviour correlations showed that CA1 and CA3 hippocampal fields together with the parietal cortex were related to the mastery of the spatial learning task.

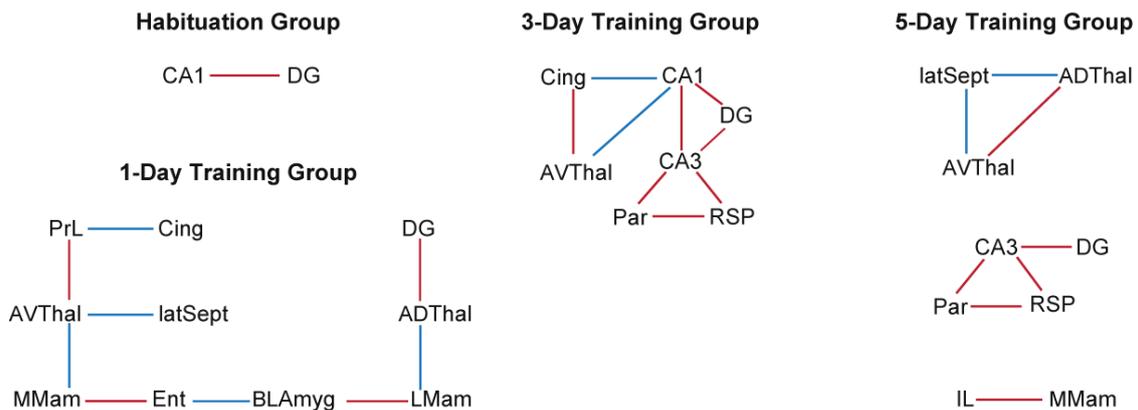


Figure 27: Progression of brain circuits mapped with cytochrome oxidase histochemistry in the Morris Water Maze. Schematic diagram showing the significant interregional correlations of cytochrome oxidase activity for the different experimental groups. Red and blue lines represent respectively highly positive and negative pair-wise Pearson's correlations ($r > 0.7$, $P < 0.05$). Note that the regions involved and their pattern of network interactions changed over days of training. At 1-day there was an open serial network of pairwise correlations. At 3-day there was a more closed reciprocal network of intercorrelations. At 5-day there were three separate parallel networks. Abbreviations: prelimbic (PrL) and infralimbic (IL) cortex, cingulate cortex (Cing), parietal cortex (Par), retrosplenial cortex (RSP), entorhinal cortex (Ent), hippocampal dentate gyrus (DG) and subfields (CA1 and CA3), septal nucleus medial lateral subdivision (latSept), anterior thalamus anterodorsal (ADThal) and (AVThal) nuclei, mammillary bodies medial (MMam) and lateral (LMam) nuclei, and basolateral nucleus of the amygdala (BLAmyg). Adapted from (Conejo et al., 2010).

PART III From mental representations of space to spatial memory

After having gone through the different processes and associated structures involved in navigation, we have seen that the neural dynamics of task learning are also an important aspect when studying navigation. Navigation is a process which involves many cognitive functions to organize and use information about one's environment to adapt our behaviour in it. Amongst these functions is the ability to memorise the information, which is referred to as **spatial memory**. As we will see in the following sections, a type of memory is defined by the way information is associated. As the information about space and one's movements in it can be memorized differently (e.g. stimulus-response or Tolman's cognitive map), spatial memory is a general term that actually refers to different types of memory. In this chapter I will introduce briefly the different types of memory and memory systems, as well as what is known on their interactions. Indeed looking at the interaction between the different structures and processes involved in navigation implies looking at the interaction between memory systems.

1. Different forms of memory

Memory processes have typically been separated into different groups depending on how long items are stored. The Atkinson-Shiffrin Model has distinguished sensory memory lasting less than a second, short-term memory lasting up to 20 seconds and long-term memory lasting up to years (Figure 28)(Atkinson & Shiffrin, 1968b). After briefly defining sensory and short-term memory, I will focus on the different forms of long-term memory.

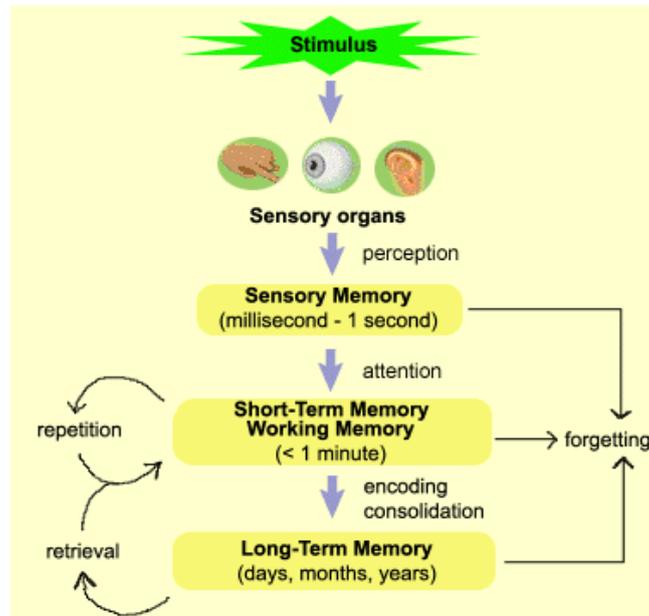


Figure 28: Different forms of memory. *From* (The brain from top to bottom).

1.1. Sensory memory

Sensory memory is the memory that automatically results from our perceptions and generally disappears in less than a second. For example remembering a tone you have just heard is a form of acoustic sensory memory. Sensory memory retains the brief impression of a sensory stimulus for just a very short time after the stimulus itself has ended.

1.2. Short-term memory

Short-term memory refers to the capacity for holding a small amount of information in mind in an active, readily available state for a short period of time. The duration of short-term memory (when rehearsal is prevented) is assumed to be in the order of seconds. Estimates of the capacity of short-term memory vary – from about 3 or 4 elements (i.e., words, digits, or letters) to about 9 elements. A commonly-cited capacity is 7 ± 2 elements, which has been historically showed by Miller: he noticed that the memory span of young adults was around seven elements regardless whether the elements were digits, letters, words, or other units (Miller, 1956). Short-term memory can help us overcome a particular problem or perform a task, like remembering a phone number before dialling it. However the amount of information one can hold in short term memory is limited and the information itself is very unstable – if one gets suddenly distracted, the retained information is lost. In contrast, long-term memory indefinitely stores a seemingly unlimited amount of information.

The concept of short-term memory was subsequently replaced by that of multi-component working memory (Baddeley & Hitch, 1974; Baddeley, 2012). When the information held in short-term memory is manipulated, it is referred to as working memory (Bird & Burgess, 2008). This model postulates the existence of three “slave” systems (the phonological loop, the visuospatial sketchpad and the episodic buffer), coordinated and supervised by an attentional component, the “central executive.” The phonological loop is responsible for storing and refreshing verbal information. The visuospatial sketchpad is involved in maintaining spatial and visual information, as well as forming and manipulating mental images. The episodic buffer acts as a temporary storage system capable of episodes whereby information is integrated across space and time. The role of the central executive is to supervise and coordinate the information supplied by the slave systems and overseeing the transfer of information to long-term memory.

Working memory may also be an important component of spatial navigation. In humans, encoding spatial information may be verbally mediated, for example, by encoding a trajectory as a series of left or right turns. Visual–spatial working memory can be divided in sequential and simultaneous components, where sequential visual–spatial working memory relates to a sequence of spatial locations presented one at a time, while simultaneous visual–spatial working memory is important for understanding the spatial relationships among locations in a single image. Verbal and sequential spatial working memory are implicated in encoding routes, while sequential and simultaneous visual–spatial working memory are likely to be relevant to survey knowledge (Garden *et al.*, 2002; Meilinger *et al.*, 2008). Frontal areas, especially the dorsolateral prefrontal cortex, are associated with working memory (Cohen *et al.*, 1997a; Courtney *et al.*, 1997).

1.3. Long term memory – storage and consolidation

Long-term memory can last as little as a few hours or as long as decades. The transition from short to long-term memory involves consolidation processes. This storage process makes encoded items less vulnerable to being forgotten. It has been divided in different types depending on the nature of the memories (see Section 2).

Consolidation is the stabilization of memory in the brain and involves two processes that occur at different levels of organization and on different timescales. **Synaptic consolidation** refers to molecular and cellular processes that occur in the minutes and hours following memory formation and that alter synaptic efficacy while **systems consolidation** occurs in the weeks, month and years after memory formation and involves the reorganization of brain regions that support the memory (Dudai, 2004).

The original and predominant view of systems consolidation is referred to as the **standard model** (Squire & Alvarez, 1995). This model proposes that hippocampus-dependent memory consolidation takes place after learning that, through interactions of hippocampal and neocortical ensembles, secures the stabilization of memory traces outside the hippocampus (Squire & Alvarez, 1995; Manns *et al.*, 2003). According to this model, experience is initially encoded in parallel in hippocampal and cortical networks. Subsequent reactivation of the hippocampal network reinstates activity in different cortical networks. This coordinated replay across hippocampal–cortical networks leads to gradual strengthening of cortico-cortical connections, which eventually allows new memories to become independent of the hippocampus and to be gradually integrated with pre-existing cortical memories. In these models, memories are assumed to decay more rapidly in the hippocampus than in the cortex (Frankland & Bontempi, 2005).

More recently, evidence that falls outside of the standard view has provided an extended framework from which systems consolidation can be accounted for. This has led to the proposal of a distinct model of systems consolidation, **multiple trace theory** that considers how the quality and amount of detail in memory changes over time (Nadel & Moscovitch, 1997; Winocur *et al.*, 2010). In this model, a subset of memories is permanently mediated by cortico-hippocampal circuitry. The theory holds that each reactivation of memory can lead to the formation of additional traces distributed in the hippocampus. There would then be multiple traces of a common past event, but these traces could entail different associations with other information that reflect their distinct provenance. Remote spatial memories are represented by a larger number of traces and so can be more accessible than recently acquired memories. According to a later version of this model (Nadel & Bohbot, 2001; Rosenbaum *et al.*, 2001), this multiple-trace theory applies particularly to “contextually rich” memories but not those that are context-free.

The standard model and multiple trace theory consider systems consolidation as a gradual, lengthy process. The **schema assimilation model** (Tse *et al.*, 2007) posits that systems consolidation could be accomplished quickly if a previously established body of related knowledge, i.e., a mental schema (Bartlett & Remembering, 1932), is available into which the new knowledge may be assimilated. The rapid schema-dependent learning was associated with up regulation of immediate-early genes in the medial prefrontal cortex (Tse *et al.*, 2011), whereas pharmacological intervention targeted at that area prevented the new learning as well as the recall of consolidated information. These findings are in agreement with the assertion of earlier models that initial memory is in both the hippocampus and the neocortex (see also (Lesburguères *et al.*, 2011)), but they are in disagreement with the assumption that the neocortex is a slow learner.

There are thus different mechanisms proposed for systems consolidation. These have emerged from different human cases and memory tasks in animals. A possibility is that the nature of consolidation could depend on the task or memory to be retained. Indeed, discrepancies about the involvement of the hippocampus, for example, are often related to different tasks, as well as the degree of complexity of the memory to be retained. Moreover, models of systems consolidation commonly refer to memories relying on the hippocampus solely but consolidation can also occur in tasks involving other structures such as the striatum (Albouy *et al.*, 2008).

The consolidation theories characterize consolidation as a one-time event, after which a memory remains fixed and resistant to subsequent disruption. However this view is challenged by studies performed as from the late 1960s reporting that the presentation of a “reminder” cue made a completely consolidated memory labile to the same agents that block consolidation (Misanin *et al.*, 1968; Schneider & Sherman, 1968). These findings suggested that the reminder reactivated the original memory trace, making it necessary to “reconsolidate” the memory to maintain it (Nader *et al.*, 2000; Sara, 2000). Several experimental parameters, or boundary conditions, have been shown to be important in determining whether reconsolidation occurs, including how memories are reactivated (Tronel *et al.*, 2005; Dębiec *et al.*, 2006), whether novelty is introduced during memory reactivation (Pedreira *et al.*, 2004), and the age and strength of a memory (Milekic & Alberini, 2002; Eisenberg *et al.*, 2003). Reconsolidation has been suggested to mediate the reorganisation of the existing mnemonic schema, thus leading to the proposal that reconsolidation might correspond to a never-ending

consolidation process (Dudai & Eisenberg, 2004; McKenzie & Eichenbaum, 2011). However, it has been proposed that reconsolidation, as opposed to consolidation, may help updating memories (Wang & Morris, 2010; Besnard *et al.*, 2012) as memories are often retrieved in situation presenting additional complementary information.

2. Different memory systems in long-term memory

The theory of memory systems has emerged following neuropsychological studies showing i) that a subject can present severe impairment affecting a given type of memory while sparing the others and ii) that the alteration of a brain structure or group of structures leads to a specific memory impairment (Scoville & Milner, 1957; Tulving & Schacter, 1990; Squire, 1998; Tulving, 2002; Eustache & Desgranges, 2008).

Memory systems have been defined at two levels. On a neuropsychological level, they are considered as specialized modules that process particular kinds of information (e.g. facts and events) (Tulving, 1972), perform particular operations (e.g. working and reference) (Olton *et al.*, 1979) or store information for a particular period of time (e.g. short term and long term) (Atkinson & Shiffrin, 1968b). On a biological level, a memory system is usually defined as a neural structure (or network of structures) and its interconnections, which together operate on a particular type of information and then participate in the storage of that information, either within the structure itself or elsewhere (Atkinson & Shiffrin, 1968a; Schacter & Tulving, 1994). The operation performed has been termed *processing style* by White and McDonald (White & McDonald, 2002). Integrating these two levels defines a memory system as a structure or group of structures that underlie a mnemonic function (Kim & Baxter, 2001).

The successful identification of a brain region specific to learning and memory was provided by Brenda Milner, who initially described the amnesia in the patient H.M. who had his two medial temporal lobes removed to treat intractable epilepsy. The severe amnesia that H.M. suffered from following medial temporal lobe resection pointed to a critical role of the region in supporting memory processes (Scoville & Milner, 1957). However although he was severely amnesic, he retained the ability to learn mirror drawing, which requires hand-eye coordination skills (Milner, 1962). These observations lead to a widely accepted taxonomy of memory that divided memory into two broad categories, declarative and non-declarative (Figure 29)(Cohen & Squire, 1980).

2.1. *Non-declarative memory*

Non-declarative memory is unconscious memory; it is expressed through performance rather than recollection (Squire, 1987). Non-declarative memory is involved in tasks such as remembering how to play handball or how to ride a bike. This is sometimes referred to as the “know how” memory. Typically, a person knowing how to ride a bike might have problems verbalizing what they are doing on the bike and why; as such non-declarative memory can often only be expressed by performing that specific skill. Non-declarative memory has been broken down into three separate groups: 1) skills and habits also referred to as procedural memory, which involve stimulus-response associations, procedural memory’s *processing style*. It has been proposed to rely on the striatum and the cerebellum (Salmon & Butters, 1995; Graybiel, 2008), 2) conditioned reflexes, like eyeblink conditioning depending on reflex pathways also including the cerebellum (Yeo & Hesslow, 1998) and 3) emotional associations like fear conditioned reflexes depending on the amygdala (Gallagher & Chiba, 1996).

2.2. *Declarative memory*

Declarative memory, which depends on the medial temporal lobe, describes what is thought of as memory in the traditional sense, the recollection of facts and events, also referred to as the “knowing what” memory (Tulving & Schacter, 1990). It relies on the flexible association of information, through the *processing style* of stimulus-stimulus (S-S) associations (White & McDonald, 2002). The hippocampus has been proposed to perform the stimulus-stimulus associations between information present in neocortical modules that could not otherwise communicate (Cohen & Eichenbaum; Cohen *et al.*, 1997b; Eichenbaum & Cohen, 2001).

It has been divided up into two major components: episodic memory (memory for past and personally experienced events) and semantic memory (knowledge for the meaning of words and how to apply them) (Tulving & Donaldson, 1972). Semantic memory comprises the general knowledge of facts and encoding often occurs multiple times, while episodic event memory is tied to the space and time associated with its acquisition, and encoding only happens once.

2.2.1. Episodic memory

Episodic memory lets you remember events that you personally experienced at a specific time and place. It includes memories such as the meal you ate last night, or the name of an old classmate, or the date of some important public event. Tulving has suggested that episodic memory “receives and stores information about temporally dated phases or events, and temporal-spatial relations among those events” (Tulving, 1972). So, episodic memory provides information about the ‘when’ of events as well as ‘what’ and ‘where’ they happened. This what-where-when criterion has been used to define episodic-like memories in animals (Clayton *et al.*, 2001). Episodic memory has also been referred to as autothetic consciousness or self-knowing (Wheeler, 2000) which above the previous elements, also includes the notion of subjective time. It is the capacity that allows adults humans to mentally represent and to become aware of their protracted existence across subjective time. It is the capacity to represent the self’s experience in the past, present and future. This definition raises theoretical issues as it cannot be tested in animals (especially for the future part). But the absence of evidence for the measure of subjective time in animal is not sufficient to demonstrate that animals are incapable of measuring subjective time.

2.2.2. Semantic memory

By contrast to episodic memory, semantic memory involves knowledge of facts in the absence of memory for the context in which they were learned. The information in semantic memory is derived from that in our own episodic memory, such that we can learn new facts or concepts from our experiences.

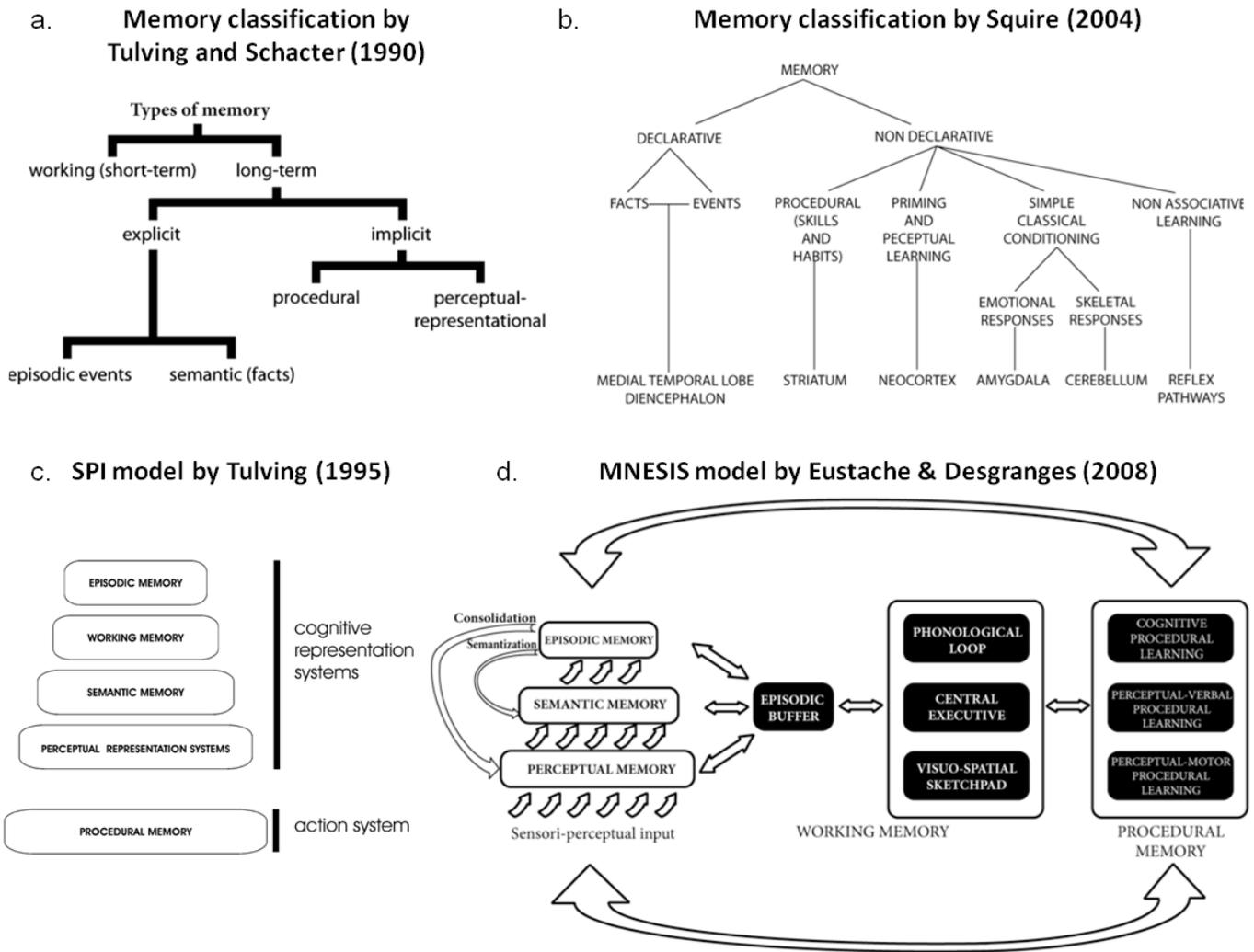


Figure 29: Different types of memory systems classification all proposing a dissociation between declarative and non-declarative memories. (a) Tulving’s model separating explicit and implicit memories (Tulving & Schacter, 1990). (b) Squire’s taxonomy dissociates declarative and non-declarative memories and details the structures associated to each type of memory (Squire, 2004). (c) The Serial-Parallel-Independent (SPI) model of Tulving identifies five systems: an action system corresponding to the procedural memory, and four representation systems (Tulving, 1995). Encoding is serial, from the perceptual representation system upwards, storage takes place in parallel in the different systems, and information retrieval takes place independently of retrieval from the other systems. (d) The Memory NEostructural Inter-Systemic (MNESIS) model dissociates representational memories (episodic, semantic, perceptive) from the working memory and the procedural memory (Eustache & Desgranges, 2008).

PART IV: Navigation Strategies: Identifying the mental representation of space

Efficient spatial navigation calls upon the ability of the subject to select the strategy that is most appropriate to the complexity of the task (Trullier *et al.*, 1997; Arleo & Rondi-Reig, 2007). The strategy selected results from the combination of various sources of information, which can be used in different reference frames and processed according to different associations, for example stimulus-response or stimulus-stimulus association. They thus call upon different memory systems depending on the processing style. Different navigation strategies have been identified, and different classifications of these strategies have been proposed (O'Keefe & Nadel, 1978; Gallistel, 1990; Trullier *et al.*, 1997; Redish, 1999; Franz & Mallot, 2000; Arleo & Rondi-Reig, 2007). Moreover the different strategies can be expressed as learning algorithms where the sensory information used (intersection, place representation...) and the way it is manipulated (stimulus-response associations, distance estimation ...) are formalized mathematically.

In this chapter I will first present the different strategies which have been characterized at a behavioural level. These behavioural strategies have been the subject of computational models to formalize the way information is processed, which will also be described. The neural basis of the different strategies will be detailed in relation to the computational processes that underlie them. Finally we will see that the nature of spatio-temporal sequence learning, revealed through the use of a sequential egocentric strategy, remains ambiguous regarding the learning processes and in this chapter I will present the different processes that can underlie sequence-based navigation and what is known about the neural basis of sequence learning in rodents.

1. Navigation strategies and computational processes

The strategies are here going to be presented in an order according to the amount of external spatial information used (Arleo & Rondi-Reig, 2007).

1.1. Path integration

As mentioned in the chapter on idiothetic information processing (Chapter 2.1.2, p. 14), **path integration**, or dead reckoning, corresponds to the ability of animals to return to the starting point of a journey directly, even if their journey was sinuous (Mittelstaedt & Mittelstaedt, 1980; Etienne *et al.*, 1998) (Figure 30a). This is performed by computing a vector (the *homing vector*) from any point of the environment to the departure (Figure 30b). The current location of an animal relative to a starting point (i.e., homing vector) is computed by integrating linear and angular self-motion signals over time. This process relies on idiothetic cues like vestibular and kinaesthetic signals, motor command efferent copies, and sensory (e.g., optic) flow information.

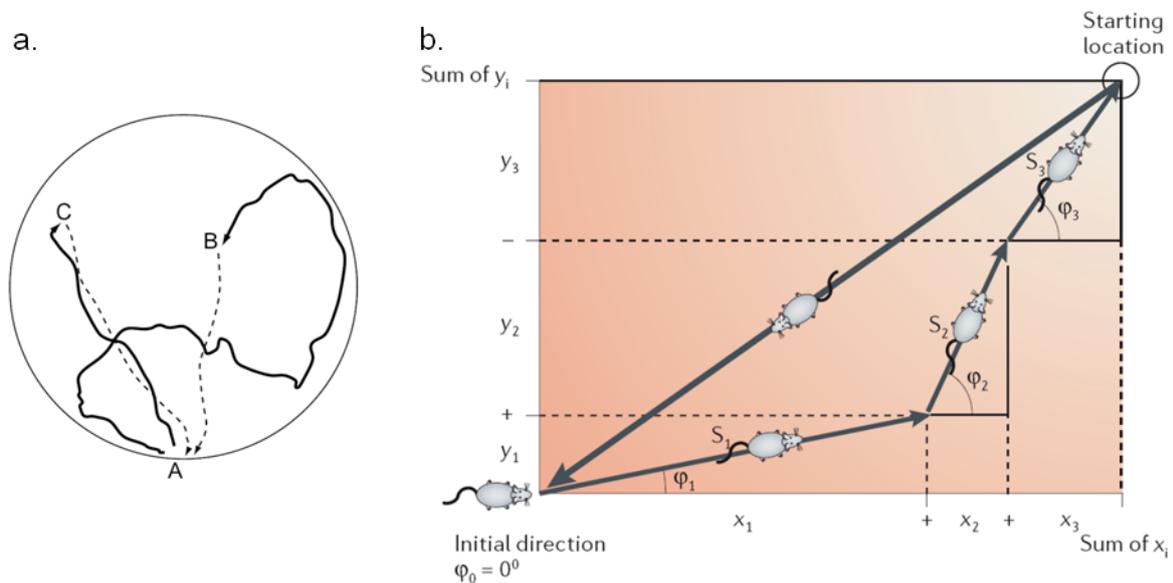


Figure 30: Homing behaviour based on path integration. (a) Two examples of homing behaviour performed by two hamsters. After having been guided by a bait from the nest location A to points B and C (solid lines), the two animals return home following direct trajectories (dashed lines). The experiment was performed in the dark in a circular arena of 2 m of diameter. *From* (Etienne *et al.*, 1998). (b) Theoretical representation of the homing process to the nest by path integration. S_{1-3} represent vectors lengths of segments of the outbound journey, and φ_{1-3} are corresponding angles relative to the departure. Variables x_{1-3} and y_{1-3} are the Cartesian components of the segment vectors which, in principle, could be summed to compute the homing vector. ‘Starting location’ refers to the beginning of the homing trajectory. *From* (McNaughton *et al.*, 2006).

Since path integration does not depend on external references, it allows a subject to self-localize in an unfamiliar environment from its very first exploring excursion (Griffin & Etienne, 1998). It is also suitable for all types of environments (i.e., with or without external cues). A limitation of path integration is its vulnerability to cumulative drift over time. Indeed, the idiothetic-based dynamics, consisting of integrating translational and rotational signals over time, is prone to accumulation of errors that quickly disrupt the position estimate (Mittelstaedt & Mittelstaedt, 1980; Etienne *et al.*, 1998). Environmental landmarks may be used to occasionally reset the integrator of self-motion signals. Thus allothetic spatial information can contribute to path integration to avoid the position assessment process from being affected by cumulative errors (McNaughton *et al.*, 1991).

As shown in Figure 30b, a minimal path integration computational model relies on three processes:

1. Identify an origin, which can be the departure point ;
2. Calculate the travelled distance and orientation relative to the departure for each step along the trajectory (or segment in Figure 30b);
3. When necessary, sum the vectors to compute the resulting homing vector to return to the origin.

The neural substrate of path integration has been proposed to be the medial entorhinal cortex as lesioning alters path integration (Van Cauter *et al.*, 2013). More specifically, it has been shown that the medial entorhinal cortex is specifically involved in coding distance information (Jacob, 2013). Errors in orientation and distance are observed when the hippocampus is lesioned (Winter *et al.*, 2013), suggesting that the hippocampus is necessary for integrating both orientation information with distance information provided by the medial entorhinal cortex to perform accurate path integration.

1.2. Goal or Beacon approaching

If the goal is visible, or if it is signalled by a single prominent cue (e.g. a flag on the platform), also named *beacon* (Leonard & McNaughton, 1990), reaching the goal relies on a simple reactive behaviour: orient towards the target or the beacon and approach it. The first strategy is termed **target approaching** and the second **beacon approaching**. Once the goal or beacon has acquired a motivational value, target or beacon approaching, grouped under the

term of taxon navigation (Morris, 1981; Redish, 1999), require limited spatial information processing (Trullier *et al.*, 1997).

The orientation behaviour towards the goal or beacon followed by the execution of movements to join it could rely on a “pre-cabled” orientation system does not require any learning. The **superior colliculus** could be involved as the main substrate of this pre-cabled system. Indeed this midbrain structure contains sensory inputs and motor outputs and is best known for its role in generating and controlling eye and head movements based on signals from different senses (Holmes & Spence, 2005). In a study using an olfactory discrimination task where rats first sample an odour presented at a central port and then move to an adjacent port on either the left or right side to receive a potential water reward, electrophysiological recordings identified neurons in the superior colliculus which predicted the upcoming choice and maintained selectivity for it after movement completion. Unilateral inactivation of the superior colliculus activity in the same task profoundly altered spatial locomotor choices, suggesting a role for this structure in sensory-guided orienting and navigation (Felsen & Mainen, 2008).

Thus to model goal or beacon strategy, the minimal system should require a visual entry to detect the position of the goal or beacon in the visual field; the system should then minimize the orientation of the body relative to the position of the goal or beacon (e.g. align the visual field to the goal or beacon); and then advance towards it until reaching it. This system reflects the saccadic behaviour of the gaze orientation once a salient stimulus is detected, followed by the motor response in the same direction. This system must also be associated to a system able to detect the valence of the goal or beacon in order to select it amongst all the visual cues detected. This motivational value associated to the goal or the beacon could be provided by the dopaminergic input of the VTA on the basal ganglia (Schultz, 1998) (as will be further detailed in section 1.5). The basal ganglia are known to exert modulatory influences on the superior colliculus to control saccadic eye movement towards the goal or beacon (reviewed in (Hikosaka *et al.*, 2006)). This would also explain the deleterious effects of **dorsolateral striatum** lesions when having to go to a visible cue in Morris water maze (McDonald & White, 1994).

1.3. Stimulus-response strategy

If the target is neither directly visible nor identified by a beacon, animals can learn to associate landmarks with given movements, thus learning **stimulus-response** associations as proposed by the behaviourist theory (Thorndike, 1911; Watson, 1913). This consists in employing a **stimulus-response strategy** (or **egocentric** strategy (Kesner *et al.*, 1989)). This strategy is characteristic of the procedural memory (White & McDonald, 2002). This procedure is suitable when the trajectory to a hidden target is composed of one or an ensemble of choice points where the spatial context (e.g., visual landmarks or geometric configurations) can be associated to specific directions of a body movement. If there are multiple choice points on the trajectory, they must be distinguishable from each other to allow associating each one to a given movement. This strategy relies on a chain of independent stimulus-response associations, thus it does not allow the subject to anticipate subsequent stimuli.

1.4. Map-based strategy

Another way of finding a goal not directly visible is by building a map-like representation of the environment, as first suggested by Tolman (Tolman, 1948) and specified by O'Keefe and Nadel (O'Keefe & Nadel, 1978).

This map-based strategy is also termed **place**, **locale** or **allocentric** strategy (O'Keefe & Nadel, 1978; Kesner *et al.*, 1989; Redish, 1999). It refers to the ability to build a cognitive map of the environment of the various parts of an environment including salient environmental cues by organizing the spatial relations (distance, direction) between them (Figure 31). Such connections are built through **stimulus-stimulus** (S-S) associations between the different parts of the environment, which are implemented as the subject explores the environment. This strategy relies on declarative memory due to its relational properties (Eichenbaum *et al.*, 1999; White & McDonald, 2002). This cognitive map allows a subject to locate it/himself and locate the goal from any point of the environment and implement a map-based strategy by determining the trajectory to a goal. Contrary to stimulus-response strategies, it allows flexible goal-oriented behaviour: if an obstacle is encountered, alternative paths can be taken to join the goal. Tolman and Honzik's study presented in the first part of this manuscript (p.7) is a perfect illustration of the flexibility of the map-based strategy (Tolman & Honzik, 1930).

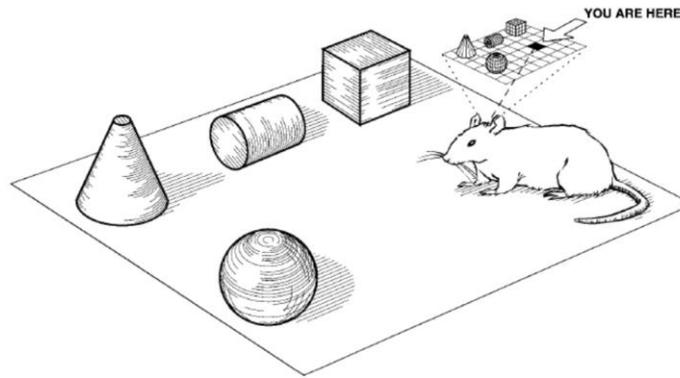


Figure 31: Cognitive Map. Conceptual model of a map-based representation of a spatial environment according to the cognitive mapping hypothesis. *From* (Eichenbaum *et al.*, 1999).

1.5. Reinforcement learning to model stimulus-response and map-based strategies

Stimulus-response and map-based strategies can be modelled by reinforcement learning models. These strategies differ from path integration and goal or beacon approaching in the sense that decisions are made along the trajectory to the goals and these decisions are learned through experiencing the environment. **Reinforcement learning** is a computational framework that focuses on an agent interacting with its environment, and addresses the question of how that agent should interact with the environment to maximize the amount of reward received in the future or minimize punishments (Sutton & Barto, 1998).

The decision-making environments in which reinforcement learning occurs consist of a set of “**states**”, which in the case of navigation can be represented by locations on a maze (e.g., an intersection would be one ‘state’, a location in a watermaze ‘state’); a set of possible **actions** to choose from (e.g., turn left or travel south); and a set of **rules** that the decision-maker must learn by interacting with the environment (e.g., the platform is in the south-west quadrant of the watermaze). The actions or behaviours that the decision-maker performs move the agent from one state to another, and produces outcomes which can be positive or negative (e.g., finding a large reward or no reward).

Reinforcement learning models are divided into **model-free** and **model-based** categories, a dichotomy which parallels **stimulus-response** and **stimulus-stimulus** associations but also goal-directed and habitual behaviours (e.g., (Daw *et al.*, 2005; Niv *et al.*, 2006)).

For “model-free” or “model-based” versions, the term *model* refers to a mental as opposed to a computational model. Model-based reinforcement learning depends on developing a *model of the world* with a representation of the various actions to be taken and the goal. An action is taken by establishing its value according to the probability of obtaining the goal by working out on-line the consequences of eventual additional actions, much as a chess player might work out which chess move to make by thinking through the consequences of various possible moves. The cognitive map is an example of *world-model*. In contrast, model-free reinforcement learning does *not form a model of the world*. The action selection is based on the reward history of a given action in a given state, and not on its consequences.

When performing a sequence of actions, **model-free** systems reinforce each action individually, as soon as one action has been performed, and without taking into account the global sequence of actions. As a consequence, each action is learned independently from preceding and succeeding actions. Thus, model-free systems are computationally very simple. However, they are much slower to learn as the association between a state and the most rewarding action to do in the state needs several repetitions.

For each state, the reinforced action is the one which has the highest probability of getting to the reward. This learning is driven by **temporal difference prediction errors**. According to such models, a reward value for an action $A_{1 \rightarrow 2}$ performed at a given state S_1 and leading to the state S_2 is estimated based on the reward history obtained in S_2 . When the reward is delivered in S_2 , it is compared to the estimated value to determine whether it is better or worse than predicted. This is called the prediction error (the difference between actual and expected outcome) and it is used to update the reward expectation when performing the action $A_{1 \rightarrow 2}$ and thus adapt the probability of performing the action $A_{1 \rightarrow 2}$: the action $A_{1 \rightarrow 2}$ will be reinforced if the reward obtained in S_2 is higher than expected, or on the contrary will not be reinforced if it is lower than expected. Thus actions are selected according to whether they are expected to produce a maximal value reward. Such learning procedure leads to progressively transferring the reinforcement signals from the time of reward occurrence to the environmental context (or state) that precedes the reward, and further to states preceding states preceding reward... (Sutton, 1988).

In terms of neural circuitry by which temporal difference computations occur, a popular idea is that there is one neural network that selects actions (the “**actor**”) and a second neural network that evaluates the outcomes of the behaviours selected by the actor, the “**critic**” (e.g. (Houk *et al.*, 1995; Sutton & Barto, 1998)). The actor stores the information about the

reward probability associated to each action, and the critic compares the outcome of the action against the expected reward probability through the prediction error. If the critic detects a discrepancy between predicted and actual rewards (i.e., a reward prediction error), the actor will update its policy for the given action.

The **striatum** has received much attention as the locus of the actor–critic function (e.g., (Joel *et al.*, 2002)). The lateral dorsal striatum is often considered to mediate stimulus–response or habit learning, while the ventral striatum is thought of as evaluators of the outcomes of actions. Thus, the actor–critic networks could correspond to the lateral dorsal striatum and ventral striatum, respectively (O'Doherty *et al.*, 2004; Bornstein & Daw, 2011; van Der Meer & Redish, 2011).

Moreover reward prediction error signals have been shown to be coded by dopamine neurons which project to the ventral striatum, thus dopamine neurons may also contribute to analysis by the critic. Indeed in a series of studies conducted in non-human primates, Schultz *et al.* (Schultz *et al.*, 1997) provided evidence that the signal provided by **midbrain dopamine neurons** mimicked error prediction. Dopamine neurons respond with phasic bursts of action potentials when an unexpected reward is delivered, and also respond to conditioned cues that predict reward (Ljungberg *et al.*, 1992; Mirenowicz & Schultz, 1994). When, however, an expected event or reward does not occur, the activity of some putative dopamine cells is inhibited. Thus, a reward that is better than predicted can generate a positive prediction error, a fully predicted reward elicits no error, and a reward that is worse than predicted can elicit a negative prediction error (Hollerman & Schultz, 1998; Hollerman *et al.*, 1998; Bayer & Glimcher, 2005). In this way, dopamine acts as a teaching signal that enables the use of flexible behaviours during learning (Schultz & Dickinson, 2000), and facilitates motivated behaviours by signalling the salience of environmental stimuli, such as cues that predict food (Berridge & Robinson, 1998; Salamone & Correa, 2002; Flagel *et al.*, 2011). In addition, the prediction error signal appears to take into account the behavioural context in which rewards are obtained (Nakahara *et al.*, 2004). Interestingly both the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc) project to the hippocampus and to the striatum, two brain structures frequently discussed in terms of goal-directed navigation and learning.

In **model-based** systems, the decision-maker builds a model of the causal structure of the world containing the whole sequence of stimuli (or places) and the actions linking them, in the form of a decision graph. At a given current state, e.g. the root of the graph if it is the

departure point, the best action to do is determined by searching the graph either forward from the root to the leaves (the terminal points) or backwards from the leaves to the root, accumulating information about the probability of obtaining the reward for each action in each state. This search can be thought as an expression of mental simulation but such deliberative decision-making can become slow and computationally expensive with an increasing number of states and possible actions (van der Meer *et al.*, 2010; Dolan & Dayan, 2013). This system is however quickly adaptable as if there is a change in the environment (e.g. change of position in the reward), as from the first experience of this change, the probability of getting a reward at the previously reinforced position is changed and the sequence of actions to do is updated.

There have been reports of neural response profile that would be predicted if an animal is evaluating an internally represented sequence of actions and their consequences at critical decision points, notably in spatial tasks (Johnson & Redish, 2007; Van Der Meer & Redish, 2009; Pfeiffer & Foster, 2013). At decision points, corresponding to a branch point in a maze, hippocampal place cell responses can be observed to sweep forward from the actual location of the subject, first down one path, then down the other. These sequences start at the rats' location and proceed to the next available goal (Johnson & Redish, 2007). In a recent study by Pfeiffer and Foster, they showed that such sweeps predicted the future trajectory (Pfeiffer & Foster, 2013). As being involved in goal-directed learning, the dorsomedial striatum is supposed to contain an explicit representation of the consequences of one's actions through action-outcome associations. It is thus in this respect also associated to model-based learning (Bornstein & Daw, 2011).

2. Tasks to identify strategies and their neural basis

In the first two parts of this introduction, I have presented the structures engaged in the various processes involved in navigation and task learning. Some of these processes are selected and used when employing a given strategy. For example the map-based allocentric strategy requires the combination of idiothetic and allothetic information to build a world-centred representation of the environment, a notion of the goal location, and structures enabling the production of the sequence of movement once the trajectory has been planned. Thus, all structures cited above may contribute to the allocentric strategy. This also holds for the other strategies, some requiring sometimes less information manipulation. This suggests that all brain regions contribute to navigation. However, lesion studies and transgenic models

have helped identify the structures necessary to the expression of the different strategies. These have been performed using navigation paradigms which allow identifying the strategies used.

During the navigation process, allothetic and idiothetic information are both available and they can be organized in two different reference frames (allocentric or egocentric) potentially leading to the simultaneous acquisition of different strategies which can each solve the task. Moreover different strategies can result in a similar trajectory. Several experimental procedures can help identify the strategy used, the main one being a change in the departure point once the task is learned.

2.1. Stimulus-response and map-based strategies

The **cross maze task**, first developed by Tolman (Tolman *et al.*, 1946), is a four-arm maze in which rodents are trained in a T-maze configuration to turn to a given arm (e.g. the east arm) to find a reward (Figure 32a). During the training phase, the rodents can either use a **stimulus-response strategy**, or **egocentric**, associating the intersection with a right turn, or a **map-based allocentric strategy**, learning to locate the position of the reward relative to the external cues. During the probe trial, the departure point is changed to the opposite arm in order to assess the strategy which was preferentially used (Figure 32b). Using the allocentric strategy brings the rodents back to the east arm whereas using the stimulus-triggered response strategy leads them to the west arm.

The neural bases underlying these two strategies were investigated by inhibiting the **dorsolateral striatum** or the **hippocampus** with lidocaine before the probe trial in rats (Packard & McGaugh, 1996). After eight training days, control rats, as well as rats with inactivated dorsolateral striatum, mostly used the map-based strategy, but inactivating the hippocampus increased the number of animals using the stimulus-response strategy. After sixteen training days, most control rats now used the stimulus-response strategy and only the inactivation of dorsolateral striatum blocked the use of this strategy (Figure 32c). This double-dissociation study shows that the allocentric map-based strategy requires the hippocampus whereas the stimulus-response strategy requires the dorsolateral striatum. Moreover, this task illustrates the switch from an allocentric to a stimulus-response response strategy across learning days (Figure 32c).

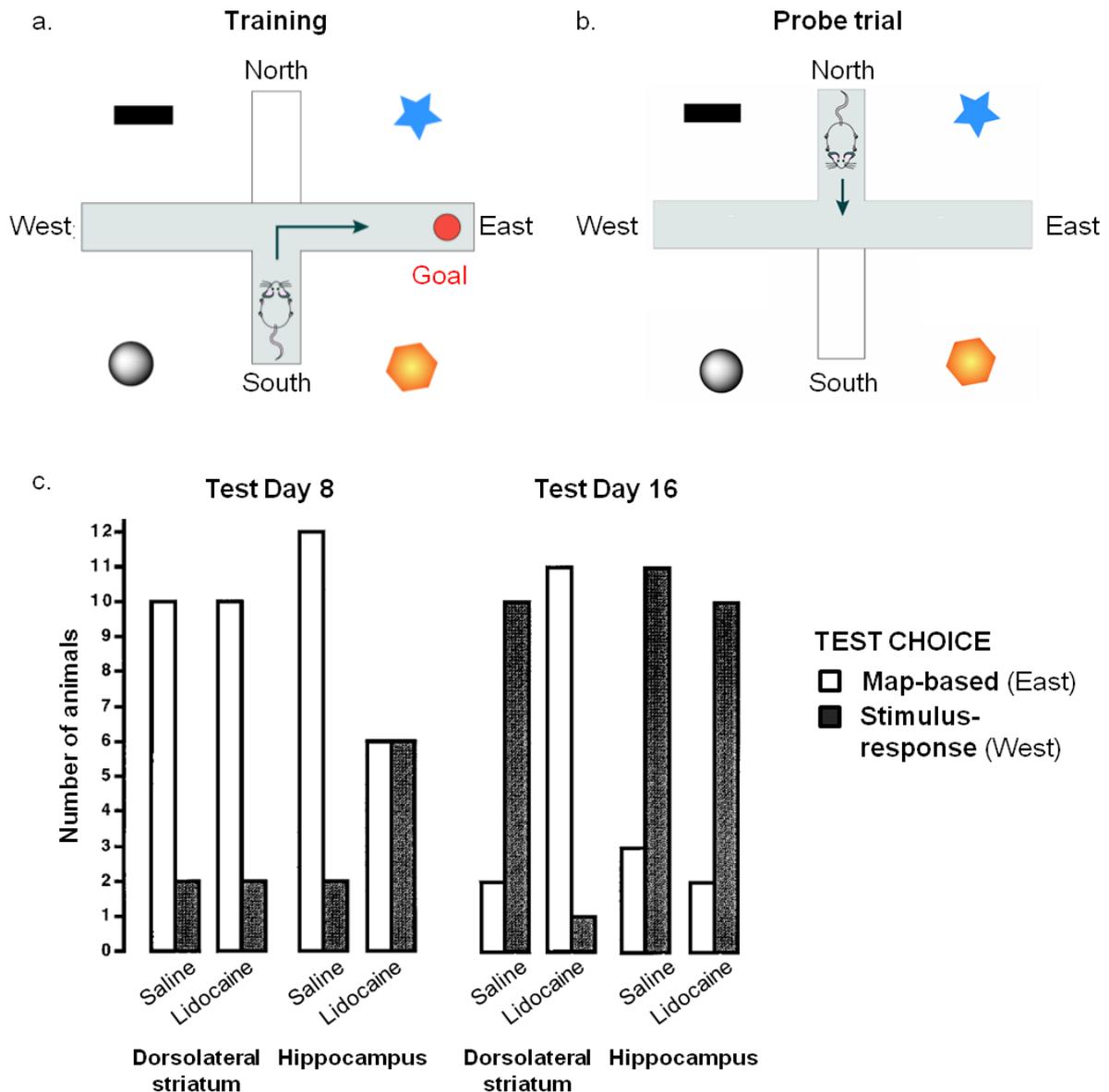


Figure 32: The cross-maze: stimulus-response versus map-based strategies. (a) During the learning phase, the north arm is blocked and the animal starts from the south arm and must find a reward, located in the east arm. The goal can be attained by using a stimulus-response or an allocentric strategy. (b) During the probe trial, the south arm is blocked and the animal starts from the north arm. Using the allocentric strategy will lead the rodent to the east arm but using the stimulus-response strategy will lead to the west arm. (c) Number of rats in each treatment group that exhibited stimulus-response or map-based strategies on both the day 8 and day 16 test trials. *Adapted from (Packard & McGaugh, 1996).*

A lesion study in rats also demonstrated a double dissociation between the **hippocampus** and the **dorsolateral striatum** in a **water maze task** (McDonald & White, 1994). Control rats, rats with NMDA-induced neurotoxic damage to the dorsolateral striatum, and rats with radio-frequency-produced damage to the fornix/fimbria, main output of the hippocampus, were trained on a visible platform version of the water maze task in which the platform remained in a fixed position in the pool. During the visible platform training, a series

of invisible platform trials was given in which a submerged platform was located in the same place. On the last day of the experiment the visible platform was moved to a new location to assess the relative strengths of the spatial cues and the cue of the platform itself as influences on the animals' behaviour.

Rats with neurotoxic damage to the dorsolateral striatum acquired both the visible and hidden platform versions of the task, but when required to choose between the spatial location they had learned and the visible platform in a new location they swam first to the old spatial location. Rats with radio-frequency damage to the fornix acquired the **visible platform** version of the water maze task but failed to learn about the **platform's location in space**. When the visible platform was moved to a new location they swam directly to it. Normal rats acquired both the visible and hidden platform versions of the task.

These findings showed that the hippocampal system allows map-based allocentric learning whereas the dorsolateral striatum is rather involved in beacon approaching.

The role of the hippocampus in the use of the map-based allocentric strategy has been widely shown and it corresponds to the electrophysiological properties of its place cells, which signal a place usually in an allocentric reference frame. The place cells' place fields are built by relating multiple stimuli to each other, a feature known as relational memory, belonging to declarative memory, possibly semantic (linking notions about what is where) (Eichenbaum *et al.*, 1999). This role also corresponds to building a model of the world, implemented in model-based reinforcement learning.

The role of the dorsolateral striatum in stimulus-response reflects its role in model-free reinforcement learning, which also corresponds to procedural memory (White & McDonald, 2002).

2.2. The starmaze task and sequence-based navigation

In 2006, Rondi-Reig *et al.* developed a task where mice had to learn a trajectory not composed of one intersection like in the cross-maze but of multiple intersections, called the starmaze task (Rondi-Reig *et al.*, 2006). The **starmaze** is a water-maze composed of five Y-intersections around a central pentagon. It is surrounded by external cues and contains proximal cues on the walls of the pentagon (Figure 33a). The trajectory to the hidden platform can either be performed using a **map-based allocentric strategy** based on the environmental

cues, or using a **guidance strategy** by following the patterns on the interior wall of the pentagon, or using a **sequential egocentric strategy** by remembering the sequence of body turns at the different choice points (Figure 33a). The guidance strategy corresponds to a stimulus-response strategy where each intersection is defined by its pattern on the wall. The egocentric strategy consists in learning the turns through the order of the intersections. During training, as the departure and goal zones are fixed, the three strategies resulted in an identical trajectory. To distinguish them the departure point is changed in a probe test, without changing the orientation of the maze in the room, in such a way that each strategy will lead the mouse to a different end point (Figure 33b). Mice can also reach the platform using a suboptimal strategy, the **serial strategy**, which consists in turning left at each intersection, thus relying on a single stimulus-response association “intersection-left turn”, where the intersections are treated as one identical stimulus despite their allocentric position in the room or their intra-maze position.

After 10 training days, most mice used either the allocentric or sequential egocentric strategy and a few used the guidance or serial strategy. By the 20th training day, mice stopped using the serial strategy, and a mouse still used the guidance strategy (Figure 33c). However it was always in combination with either the sequential egocentric and/or the allocentric strategies. Indeed the majority of the control animals (60%) developed the ability to switch back and forth between strategies, meaning that they used different strategies during the four probe tests. This task was then adapted to virtual reality in Humans, who similarly to mice, showed parallel encoding and use of both strategies (Igloi *et al.*, 2009).

In the starmaze task the relative use of the map-based or sequential egocentric strategies did not depend on the number of training days.

The **simultaneous acquisition of different strategies**, also observed in another task (Whishaw & Mittleman, 1986), gives the animal the possibility to adapt its behaviour to changes within the environment. For example, when sudden darkness eliminates the access to distant visual cues, the animal can still return to a recently visited part of the environment identifiable by the recalled locomotory movements (Fenton *et al.*, 1998). This finding is in agreement with the Whishaw and Mittleman experiment (Whishaw & Mittleman, 1986), suggesting that even not required strategies can be acquired during a task of spatial navigation.

Multiple strategies version of the starmaze

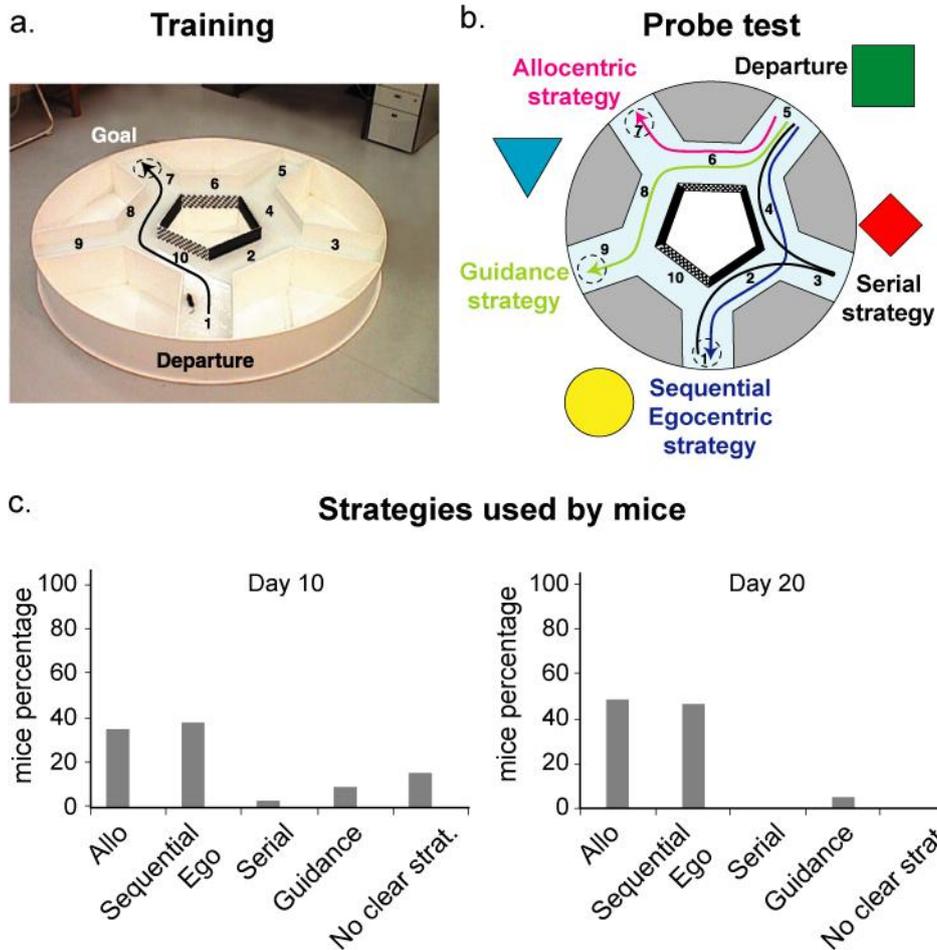


Figure 33: The multiple strategies version of the starmaze task. (a). The apparatus has five central alleys forming a pentagonal ring and five peripheral alleys radiating from this central ring, all filled with water. The animals were placed in alley 1 and must find the hidden platform located in alley 7 (dashed circle). Once an animal had learnt the task, it used the shortest path indicated with an arrow and corresponding to the 1–10–8–7 sequence of alleys. (b). To distinguish which strategy the animal used to solve the task, the departure point was changed to the alley 5. The position of the distal cues remained constant. The chessboard-like and black walls were viewed in a reversed position by the mouse compared with the departure in alley 1. Therefore, when departing from alley 5, an animal had to choose between: using the distal visual cues (5–6–7 trajectory corresponding to an allocentric strategy); executing a sequence of body movements (left–right–left) (5–4–2–1 trajectory indicating a sequential-egocentric strategy); following the intramaze cues (5–6–8–9 trajectory corresponding to guidance); visiting all radiating alleys successively (5–4–3–2–1 trajectory indicating a serial strategy). Other behaviours were considered as no clear strategy. (c). The percentage of animals using a given strategy is represented on day 10 and day 20. *Adapted from (Rondi-Reig et al., 2006).*

During my PhD I have studied specifically the sequential egocentric strategy, or sequence-based navigation, to characterize it through its neural bases and learning processes. The following section focuses on this strategy and what is generally known about rodent sequence learning.

3. Sequence-based navigation (or sequential egocentric strategy): what computational processes and what neural basis?

3.1. Sequential egocentric strategy

In the sequential egocentric strategy, the subjects do not identify the intersections through their allocentric position in the room (this would result in an allocentric strategy) or their visual patterns (leading to guidance). Rather the intersections are identified through their position along the trajectory, or in other their order in the sequence.

In Rondi-Reig *et al.*'s study (2006), they used mice that lack NMDA receptors (NMDARs) in the CA1 area of the hippocampus and present a decrease of NMDARs in the deep cortical layers (NR1-KO mice). NMDARs are involved in long-term potentiation (LTP) in the hippocampus and the NR1 KO mice lacking functional NMDARs do not show hippocampal LTP (Tsien *et al.*, 1996a). These mice had already been shown to be deficient in learning an allocentric strategy in a water maze (Tsien *et al.*, 1996b). In the star maze task, they were deficient in the allocentric but also in the sequential egocentric strategy (Rondi-Reig *et al.*, 2006). In the virtual reality star maze task, human also activated their hippocampus in the sequential egocentric strategy (Iglói *et al.*, 2010).

The NR1 mice were tested in a simple egocentric version of the star maze task having to learn one turn and were successful (Rondi-Reig *et al.*, 2006). Thus, they could learn one stimulus-response. This highlights the difference between stimulus-response learning and the sequential egocentric strategy, relying in the spatio-temporal organization of multiple turns. The role of the hippocampus in the sequential egocentric strategy was proposed to allow the organization of the sequence of turns. This corresponds to the proposed role of the hippocampus in relational organization of information, may this information be of spatial nature (as in the allocentric strategy or for creating place fields) or of another nature (Eichenbaum, 1999). Moreover, remembering the spatio-temporal organization of turns requires the retrieval of 'what' movement has to be done (to turn right or left), 'where' it has to be done (at one of the three intersections encountered along the path) and 'when' it has to be done (according to its order in a sequence). By combining these three aspects, it has been proposed that the sequence-based navigation could be a model of episodic memory (Fouquet *et al.*, 2010). A study in our team tested the use of the sequential egocentric navigation in evaluating episodic memory in normal aged subjects and patients suffering of Alzheimer's disease or fronto-temporal dementia and the results revealed a selectivity of this strategy to detect episodic memory deficits linked to Alzheimer's disease (Bellassen *et al.*, 2012).

At the computational processes level, it was proposed that **Stimulus-Response-Stimulus** associations (S-R-S) could underlie the sequence-based navigation, which has been called a **route strategy** (O'Keefe & Nadel, 1978; Redish, 1999). Learning a chain of Stimulus-Response-Stimulus associations allows ordering the different stimuli one another (Arleo & Rondi-Reig, 2007). Stimulus-Response-Stimulus associations enable the navigator to predict the next stimulus based on the current stimulus-action association. It can thus be modelled by a **model-based reinforcement learning algorithm**, where the *world model* is build by organizing the different parts on the maze not based on their allocentric position but on the physical relations between one another, i.e. two parts of the maze will be linked in the *world model* if an action directly leads from one to another.

However mice could also learn independent stimulus-response associations if they use another mechanism than the allocentric position to differentiate the intersection, as for example a counting mechanism or a memory of the previous actions. In the latter case, when doing the correct trajectory, the first intersection is preceded by going straight from the departure point whereas the second is preceded by a left turn and the third intersection is preceded by a right turn. If each stimulus is defined as the actual position in the maze and a memory of the last actions performed, they become differentiated and can each be associated to a given response.

Another possibility is that the mice are using path integration to find the platform. Indeed they could estimate the distance and direction to the platform relative to the departure point.

During my PhD I have tested the three types of learning to see if one of them could reproduce the mice's behaviour when learning sequence-based navigation.

3.2. Neural basis of sequence learning in rodents

Several paradigms have been developed to study sequence learning in rodents. They involve learning actions in a temporal order or recognizing elements based on their temporal order.

One way of studying sequence learning is testing the memory for the temporal order in which **objects** are presented. Object exploration tasks rely on the spontaneous tendency of rats to explore novel aspects of their environment more than familiar aspects (Ennaceur & Delacour, 1988). Several versions of spontaneous exploration exist (for review see (Dere *et al.*, 2007)).

The first paradigms used relied on remembering the order in which **odours** are presented. In Kesner *et al.* (Kesner *et al.*, 2002) and Fortin *et al.* (Fortin *et al.*, 2002), rats were presented with a series of five randomly selected odours presented individually (each mixed in sand with a buried reward). Memory of the sequence was tested by presenting two odours at a time and the rat had to choose the odour that occurred earliest in the sequence. Rats learned the task but if the **hippocampus** was lesioned after training, the rats could not remember the sequential ordering of odours despite recognizing encountered odours from unknown odours (Figure 34). The lesions included both **dorsal and ventral** areas of the hippocampus.

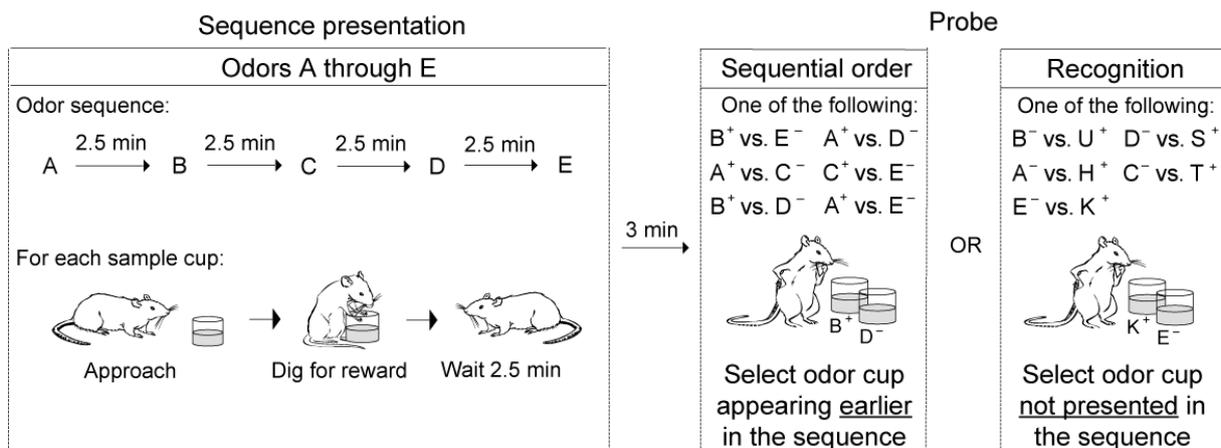


Figure 34: Sequential order and recognition tasks. Cups containing specific odours are presented to the rat one after another in a defined order. A–E designates the order of presentation for odours in each series, with odour A presented first and odour E last. During each test the rat must approach the cup, find and consume the reward then wait 2.5 min before the next odour is presented. During the sequential order probe the rat is presented a pair of odours previously presented and it must select the one that appeared earlier in the sequence. During the recognition test, the rat must simply choose the odour that has never been presented in the sequence. Signs denote the odours associated (+) or not (-) to the reward. *From* (Fortin *et al.*, 2002).

In a follow-up experiment in mice, DeVito *et al.* confirmed the involvement of the hippocampus and showed that the **medial prefrontal cortex** was also necessary in detecting the temporal order of a sequence of odours (DeVito & Eichenbaum, 2011). The lesions extended across the infralimbic, prelimbic and cingulate cortices, consistent with previous

experiments performed in rats with **medial prefrontal cortex** lesions spanning over the prelimbic and cingulate regions (Mitchell & Laiacona, 1998).

Following studies used the temporal order version of spontaneous exploration tasks where pairs of identical objects (e.g. A–A, B–B and C–C) are presented one after another. After the third pair of objects, the animals receive a “temporal order” test where one copy of object A (i.e. a “remote” object) and one copy of object C (i.e. a “recent” object) are presented to the animal (Figure 35b). Rats show a significant preference for the least recently presented object (A). Using this task, Hoge and Kesner showed that dorsal CA3 lesions did not modify the preference for the least recently presented object whereas dorsal CA1 lesions did, while still showing significant memory for Object A when presented with an unknown object (Hoge & Kesner, 2007). This suggests that the dorsal CA3 is not required for temporal processing for non-spatial information whereas the dorsal CA1 is.

In a later study, Hunsaker et al.(Hunsaker *et al.*, 2008) examined the effects of dorsal or ventral CA1 lesions on memory for the temporal order of objects (using the task described by Hoge and Kesner above), of odours and of spatial locations (Figure 35). Control animals showed a significant preference for the least recently presented object, odour and spatial location (orange arrow in Figure 35). Rats with dorsal CA1 lesions showed normal preference for the least recently presented item in the odour task, but not in the object (as previously shown) and spatial location tasks. In contrast, rats with ventral CA1 lesions showed normal preference for the least recently presented item in the spatial task, but not in the object and odour tasks. These data provide evidence that the CA1 is involved in temporal order processing, but that dorsal and ventral CA1 play a different role depending on the type of information being processed: **the dorsal CA1 is required for temporal processing of spatial locations**, the **ventral CA1 for temporal processing of olfactory information**, and **both for temporal processing of object information**.

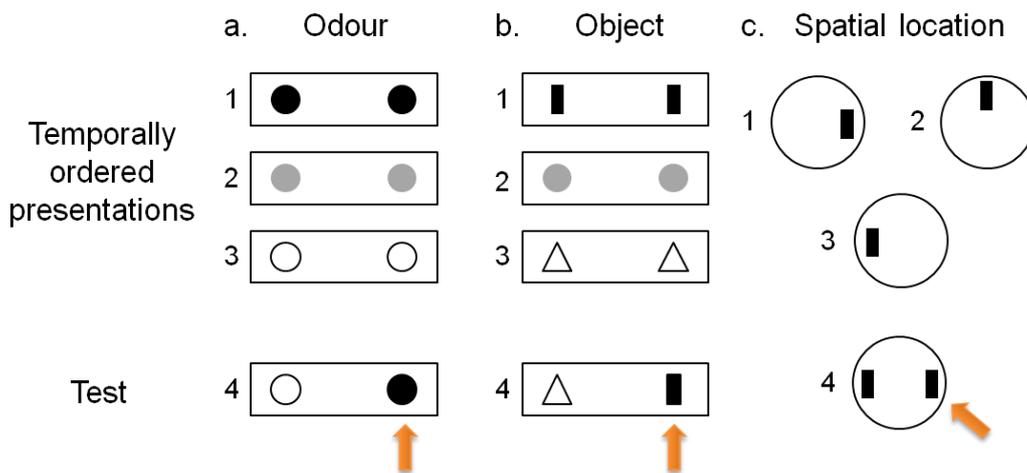


Figure 35: Behavioural paradigms for testing temporal order based on spontaneous exploration. (a) Temporal order for olfactory information. The black, grey, and white circles represent distinct odours. (b) Temporal order for objects. Each shape represents a different object. (c) Temporal order for spatial locations. The objects used in each session are identical so the spatial location information is all that differs. For each configuration, the odour or objects are presented in three consecutive sessions. During the fourth test session, rats tend to explore the least recently presented item (indicated with an orange arrow). *Adapted from* (Hunsaker *et al.*, 2008).

Another way of testing sequential knowledge is by testing the memory for a sequence of spatial locations on a **radial-arm maze** (Figure 36).

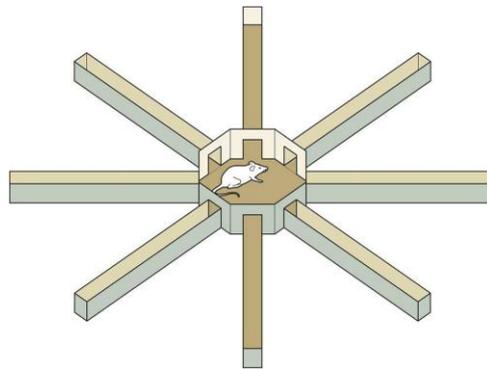


Figure 36: Radial arm maze

In Gilbert *et al.*'s study (Gilbert *et al.*, 2001), rats visited the eight arms of the maze in a given order, by sequentially opening one door at a time, letting the animal eat a food reward at the end of it and opening another one when he went back to the central platform of the radial arm-maze. The rats were then tested on the temporal order between two arms by having to identify the one which occurred earliest in the sequence, similarly to the odour sequence tasks (Hoge & Kesner, 2007; Hunsaker *et al.*, 2008). Rats with dorsal DG lesions performed as well as controls, whereas those with **dorsal CA1** lesions were significantly impaired, and

performed close to chance levels (Gilbert *et al.*, 2001).

In a similar study by Gaytan-Tocaven and Olvera-Cortés (Gaytan-Tocaven & Olvera-Cortés, 2004), rats had to visit four arms of the radial arm maze in a given order to find food pellets twice a day for 13 days and the number of wrong alleys visited to retrieve all four pellets. Rats with a lesioned **cerebellar dentate nucleus** presented a delayed learning of the task. Whereas control rats improved their performance as from the fourth training day, lesioned rat started improving their performance on the twelfth day.

Starmaze and radial arm mazes both allow testing temporal order memory. However what distinguishes them is that in the starmaze the decision points are spatially distinct. Thus the radial arm maze relies on temporal ordering whereas the starmaze relies on spatio-temporal ordering of the decision points.

Domenger & Schwarting (Domenger & Schwarting, 2005) devised an instrumental test in rats to serve as a model for the classical human **serial reaction time task** (SRTT). In this rodent serial reaction time task, rats have to respond to sequentially, or randomly, presented stimulus locations by nose-poking to obtain food (Figure 37). They were able to show that, similarly to humans, rats display superior performance (faster reaction times and higher response accuracies) under sequential condition compared to random conditions.

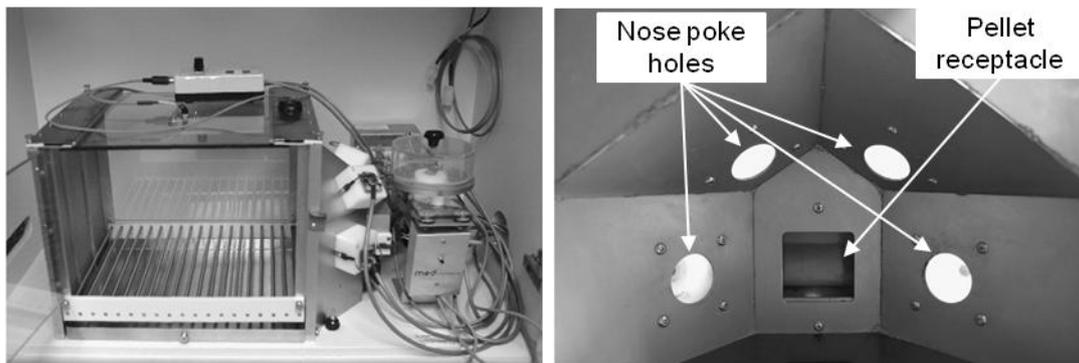


Figure 37: Rat serial reaction time task. Left: Complete instrumental set-up, with on the right of the operant chamber devices for illuminating the nose-poke holes and dispensing pellets. Right: View of the alcove-like sidewall containing the four nose-poke holes around the pellet receptacle. The rats had to respond to the illumination of a nose-poke hole by quickly poking their nose into this illuminated hole. They were trained to respond to series of such illuminated holes to obtain a pellet. At the final level they were reinforced by food-reward on a fixed ratio schedule of 13 nose-pokes. *Adapted from* (Schwartzing, 2009).

These authors were interested in the role of **striatal dopamine** in sequential learning and showed that dopamine depletion in the striatum led to a general instrumental impairment in terms of reduced speed (response latencies) and response rate. These deficits were observed

with dopamine depletion performed before training (Eckart *et al.*, 2010) or once the rats were well-trained (Domenger & Schwarting, 2008). These results suggest that dopaminergic-striatal networks play an important role in the acquisition and the execution of sequential behaviour.

Another instrumental learning task to test sequence learning is through used **lever press** learning tasks (Yin, 2009; 2010). In these tasks, mice had to learn to press on two levers in a given order (right then left, or the opposite) to obtain a food reward. They differ from the previous Serial Reaction Time task as successful performance relies on an internal representation of serial order and not on following cues. Lesion experiments showed that the **secondary motor cortex M2** (Yin, 2009) and the **dorsolateral striatum** (Yin, 2010), but not the primary motor cortex M1 or dorsomedial striatum, are necessary in realizing the sequence. Lesion of the dorsolateral striatum did not prevent acquisition of single lever press but, interestingly, these mice repeated twice the press closest to the reward in the sequence (e.g. left-left when the correct sequence was right-left). Dorsolateral striatum-lesioned mice had a selective deficit in binding the different actions to form a performance unit (Yin, 2010). The lack of deficit early in training when the dorsomedial striatum was lesioned is surprising regarding previous publications by the same author (for review (Yin & Knowlton, 2006) and see Section 3.1). The author suggests this could be due to differences between mice and rats but it is unlikely as in another of his studies in the Rotarod, lesions in the dorsomedial striatum impaired the acquisition (Yin *et al.*, 2009). This rat-mice difference could thus be specific to lever pressing tasks.

Table 1 summarizes the tasks testing temporal order learning and the structures identified as underlying them.

Tasks testing temporal order		Structures
Spontaneous exploration	Odours	Ventral CA1 Medial PFC
	Objects	Dorsal CA1 Ventral CA1
	Spatial locations	Dorsal CA1
Radial Arm Maze		Dorsal CA1 Cerebellar dentate nucleus
Serial Reaction Time task (nose-poking)		Dopaminergic-striatal network
Lever presses		Secondary motor cortex Dorsolateral Striatum

Table 1: Summary of tasks testing temporal order and structures.

The different paradigms used to test sequential learning often involve the hippocampus, suggesting it supports the ability to encode the temporal order of events. Earlier in this manuscript we have described the spatial activity of the hippocampal place cells (p.27). Place cell's activity studies have revealed that their firing activity coded for more than the current position of the animal.

3.3. Hippocampus and sequential activity

3.3.1. Retrospective and prospective firing

In 1991 Richard Morris had pointed out the question: “as place cells are defined as cells that fire only when an animal occupies a specific position in space, how can the mapping system access information pertaining to places other than the one presently occupied?” (Andersen *et al.*, 2006).

A solution can be found in hippocampal place cell activity. Indeed in addition to reporting the instantaneous position of the animal, neurons in the hippocampus can also predict where the animal is coming from (**retrospective** coding) or where it is going

(**prospective coding**) (Frank *et al.*, 2000; Wood *et al.*, 2000; Ferbinteanu & Shapiro, 2003). The influence of the past or the future on place cell activity is visible in tasks that promote directional firing and require the rat to traverse the same part of the apparatus as part of two different paths. For example, Wood and colleagues trained animals on a continuous alternation task in a T-maze that had return tracks from each goal to the start of the stem so the animal could run in a continuous figure-of-eight path by turning left or right alternatively at the choice point of the T junction (Wood *et al.*, 2000). Activity in two-thirds of the place fields in the stem of the T varied markedly depending on whether the animal entered the stem following a return from the left-hand or right-hand goal (Figure 38).

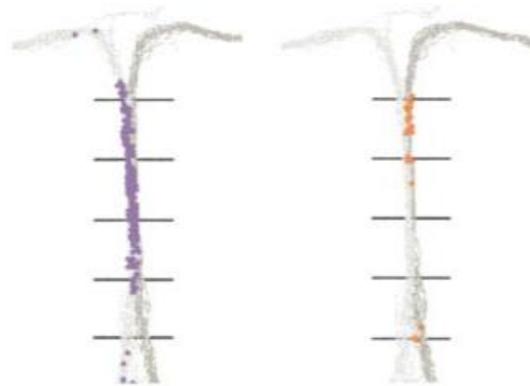


Figure 38: Example of a hippocampal cell that was differentially active when the rat was traversing the central stem. The paths taken by the animals on the central stem are plotted in grey (light grey, left-turn trial; dark grey, right-turn trial). The location of the rat when individual spikes occurred is indicated separately for left-turn trials (purple dots) and right-turn trials (orange dots). This cell fired almost exclusively during either left-turn trials. Adapted from (Wood *et al.*, 2000).

In the Wood *et al.* study, it was not possible to distinguish between firing owing to the previous part of the path (retrospective coding) and the future part of the path (prospective coding). Two other studies (Frank *et al.*, 2000; Ferbinteanu & Shapiro, 2003), however, did allow for this distinction and reported that, in addition to the retrospective effect of the previous path on place cell firing, the subsequent path (i.e., the upcoming turn to be made at the T junction) also had an effect on firing in the stem (a prospective effect).

It has been proposed that prospective coding could be involved in elaborating choices in route planning. Catanese *et al.* directly tested this hypothesis using a modified version of the alternation T-maze task where, after five to seven alternation trials, a cue indicated the rat to change its intended trajectory (Catanese *et al.*, 2012). In alternation trials, they observed similar turn-specific place cells as in (Wood *et al.*, 2000). When the cue was presented, a

processing delay of 420 ms was observed between the cue presentation and the onset of the prospective firing. This delay is greater than the trajectory-selective responses in rat superior colliculus neurons which appear at ~150 ms (Felsen & Mainen, 2008; 2012) suggesting that this activity is not implicated in the early stages of elaborating a trajectory choice. The authors propose that this prospective activity is rather a consequence of a decisional activity performed in other regions (e.g. the prefrontal cortex or the striatum) which would then return signals to the hippocampus to help establish prospective activity (Catanese *et al.*, 2012).

Nonetheless, retrospective and prospective representations could help solving tasks by serving as a short-term memory buffer to instruct the choice for the next trial (Ainge *et al.*, 2008). For example, in a radial arm maze animals may switch from a retrospective coding (based on the arms already visited) to a prospective coding (anticipating the remaining arms to visit) once half of the baited arms have been sampled, thus decreasing the number of items to manipulate and keep in mind (Shapiro *et al.*, 2006).

Retrospective and prospective coding highlight the ability of the hippocampus to distinguish locations based on previous or future events. This mechanism could participate in the sequential encoding of events and the temporal organization of spatial information and could participate in the processes underlying episodic memory (Shapiro *et al.*, 2006).

3.3.2. Sequence representation

In addition to prospective and retrospective coding, it is also known that hippocampal neurons respond to events organized according to a temporal sequence (Lee & Wilson, 2002; Huxter *et al.*, 2003). Temporal sequences in the hippocampus may be observed at different scales:

- at a behavioural scale: when animals go successively through different fields of activity corresponding to different place cells (Figure 39);
- at the level of EEG theta oscillations (seconds scale), called phase precession;
- at the level of ripples (milliseconds scale): when large populations of neurons fire at the same time in a short time frame .

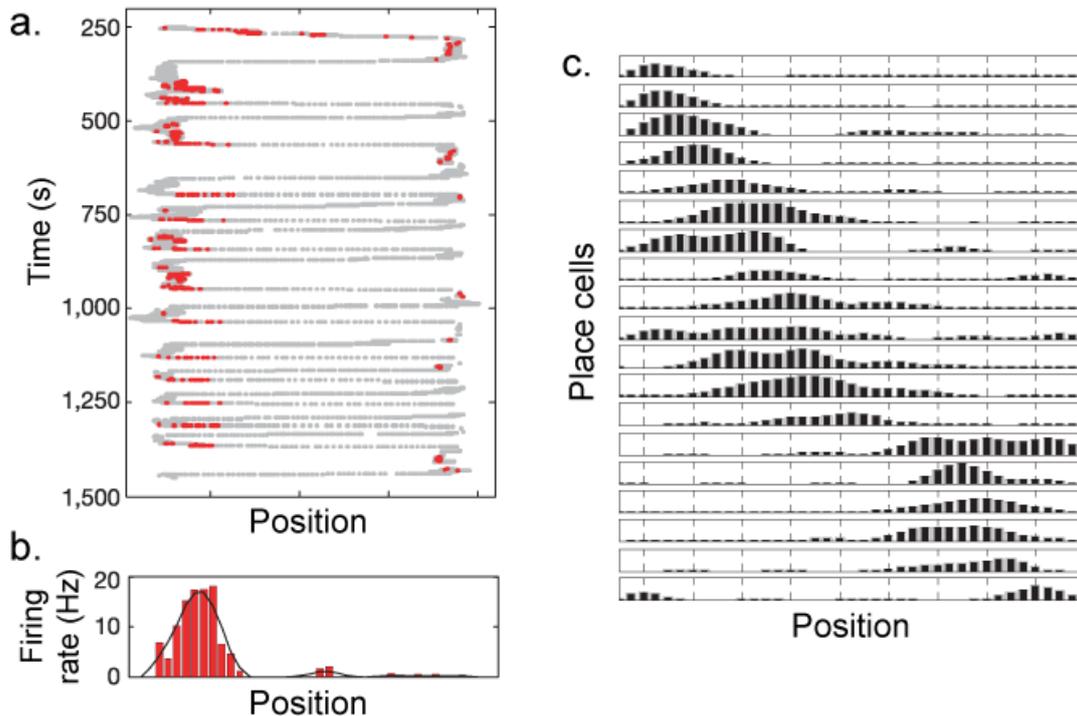


Figure 39: A sequence of place fields. (a) The position of a rat running up and down a linear track during one recording session is shown in grey as a function of time. Spikes emitted by a single hippocampal place cell while the animal faced rightwards are shown in red. (b) The place field of the single cell shown (a). (c) Amongst 128 cells recorded, 26 cells had place fields on the track. The nineteen cells with fields in the rightward direction are ordered by peak to generate a probe sequence. From (Foster & Wilson, 2006).

Hippocampal place cells do not fire in a continuous pattern when the rat runs through a place field but burst with a frequency close to that of the EEG theta rhythm (4-12 Hz). Studying phase correlates on narrow tracks as the rat runs through a cell's place field, O'Keefe and Recce first noted that instead of remaining correlated to a constant phase of the EEG theta cycle, as on treadmills, the phase of firing changed in a systematic way (O'Keefe & Recce, 1993). When the rat entered the cell's place field, the cell began firing at a particular phase of theta. However, as the animal progressed through the field, the bursts of unit firing occurred on an earlier phase of each successive theta cycle (Figure 40). This is called **phase precession phenomenon**.

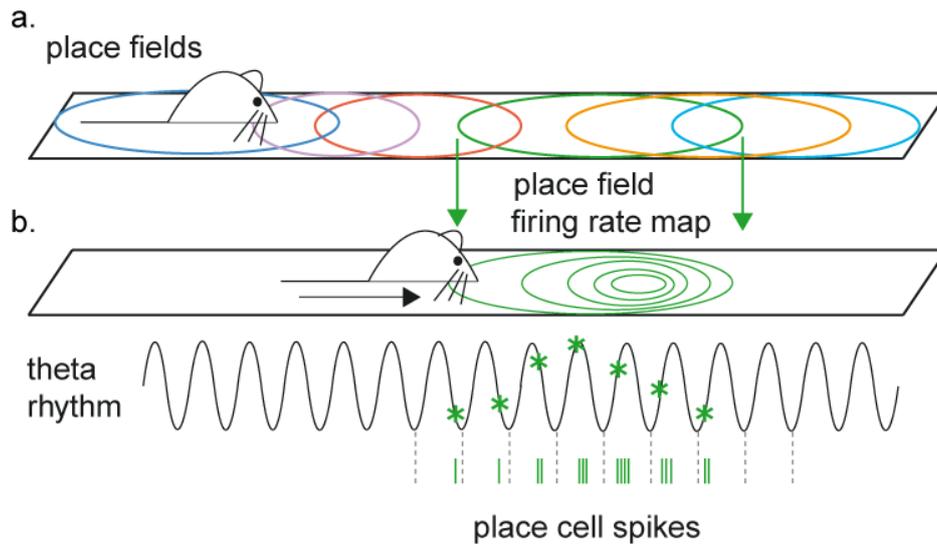


Figure 40: Theta phase precession. (a) A rat is depicted running left to right on a linear track. Each oval on the track represents the borders of the spatial firing field ('place field') of a single hippocampal place cell. (b) The green place field of (a) is shown in more detail. The contours indicate increasing firing rates of the neuron as the rat runs through the place field which is here directional as seen after repeated trajectories in a stereotyped direction. Below the track is indicated the theta rhythm under which are shown spikes from the "green" place cell as the rat proceeds through the place field. The precise timing of the spikes relative to the phase of the theta cycle reveals a temporal code for location within the place field. The cell fires in bursts of activity (indicated by the asterisk) at a slightly faster rate than the theta rhythm of the field potential. From (Foster & Knierim, 2012).

An important consequence of the phase precession phenomenon is that cells with spatially neighbouring place fields will fire at close phases of the theta cycle. When the animal is about to exit the place field of a cell and at the same time is entering an overlapping place field of a second cell, the first cell will fire few milliseconds before the second cell. Thus, the sequence of place fields crossed by the animal can lead, within each theta cycle, to an orderly and sequential activation of place cells associated with these fields (Figure 41) (Dragoi & Buzsaki, 2006; Foster & Wilson, 2007).

Theta sequences have been proposed to compress behavioural spatiotemporal sequences into a timescale conducive to LTP-induction mechanisms (Skaggs *et al.*, 1996). Moreover, since the sequences tend to be repeated over multiple theta cycles as an animal passes through a region of space, the chunking of behavioural sequences into multiple, repeated theta sequences effectively turns one-trial learning into multiple trials, which may help to solidify the sequence memory (Foster & Knierim, 2012).

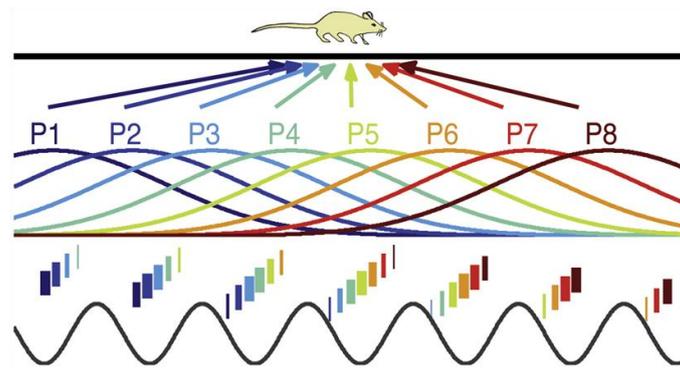


Figure 41: Theta sequences. Each position (P1 to P7) is defined by the most active place cell firing. At any given position on the trajectory, cells with overlapping fields will fire at different moments of the theta phase thus resulting in a compressed representation of a sequence of places in each theta cycle. From (Buzsáki, 2010).

Theta sequences are restricted in spatial extent to overlapping place fields. Much longer sequences of place cells coding of entire trajectories have been shown to occur, first shown during sleep (Lee & Wilson, 2002), where they were hypothesized to be involved in long-term memory consolidation (O'Neill *et al.*, 2010). These are called **forward replays** and they appear during slow wave ripples, short-lasting high-frequency (150-200Hz) hippocampal EEG oscillations. Replays have also been shown to happen during some waking states when the animal is still, in the same order as actually experienced (forward replay), before the animal performs the trajectory, or in the reverse order (**reverse replay**), after having performed the trajectory (Figure 42)(Foster & Wilson, 2006; Diba & Buzsaki, 2007). Consistent with a role in learning, reverse replay appears to be more prevalent on a novel track than a familiar one (Foster & Wilson, 2006), whereas forward ordered sequences display the opposite pattern (Diba & Buzsaki, 2007).

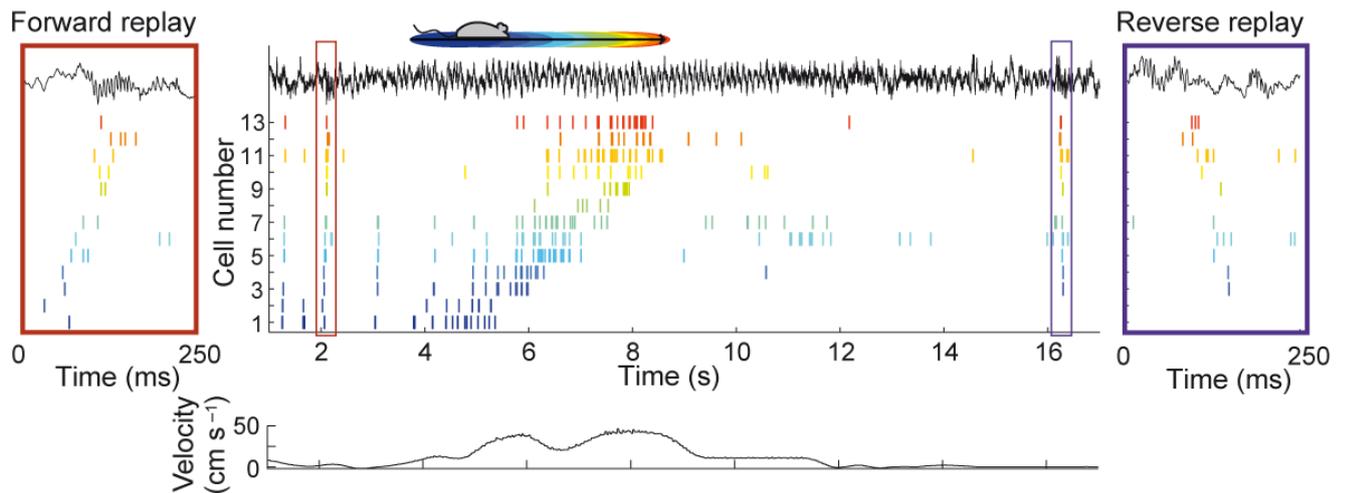


Figure 42: Forward and reverse replay. Spike trains for 13 neurons with place fields on the track are shown before, during and after a single traversal. Sequences that occur during running (centre) are reactivated during awake slow wave ripples (SWR). Forward replay (left inset, red box) occurs before traversal of the environment and reverse replay (right inset, blue box) after. The CA1 local field potential is shown on top and the animal's velocity is shown below. *Data from (Diba & Buzsaki, 2007), figure adapted from (Carr et al., 2011).*

Recently, Dragoi and Tonegawa have shown that in naïve mice, temporal firing sequences expressed in association with sharp-wave ripples during sleep or rest can *preplay* future spatial sequences of place cells encoding novel environments (Dragoi & Tonegawa, 2011). The order of firing on the track resembled firing sequences both before and after the running session. There were roughly three times as many replay events as preplay events. It seems, therefore, that some sequences might be hardwired, and others are shaped by recent experience. In a follow-up experiment, they showed that place cell sequences encoding novel spatial experience are selected from an existing larger repertoire of temporally organized sequences (Dragoi & Tonegawa, 2013). This confers the hippocampal network with the capacity to rapidly encode multiple parallel spatial experiences.

Through the temporal compression of neural sequences in theta cycles and ripples, phase precession and replay phenomenon could participate at different time scales to the emergence of a representation of sequences (Diba & Buzsaki, 2007). These mechanisms for joint encoding of place and behaviour characterizing an event could explain how the hippocampus is involved in both the memory of space and episodes, episodes relying on sequential organisation of events (Huxter *et al.*, 2003).

3.3.3. Time cells

Recently, it has been shown that some cells in the hippocampus represent not only sequences but also elapsed time (Pastalkova *et al.*, 2008). These cells have later been named “**time cells**” (MacDonald *et al.*, 2011). In these experiments, a rat performs a working memory task with one important characteristic: during the delay portion of the task, the rat must stay in one place for several seconds before making its choice, effectively keeping the rat’s location constant. Many cells were active only during brief intervals of time, and the preferred interval of the cell was constant from trial to trial (Figure 43).

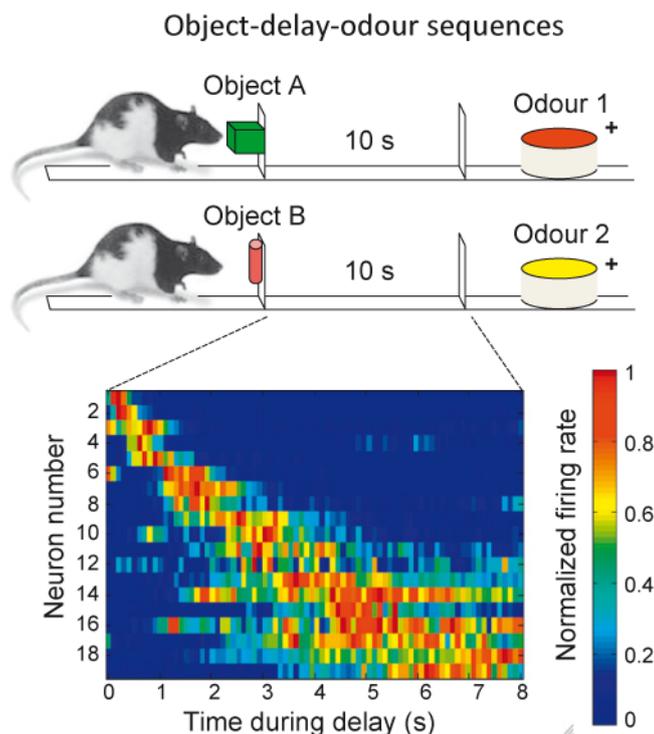


Figure 43: Time cells in the hippocampus. Above: in the object-delay-odour sequence task, rats are initially presented with one of two objects and then, following a 10 s delay, must respond to one of two odours to receive reward. Below: during the delay, hippocampal neurons fire sequentially; the normalized firing rate of each neuron is shown in successive rows. *Adapted from* (Eichenbaum, 2013).

In a follow-up study, Kraus *et al.* used a new behavioural paradigm to examine the relative contribution of time and distance of the time cells (Kraus *et al.*, 2013). In this task, a rat ran through a modified version of the alternating T-maze. In the stem part of the maze, where the rat must hold in working memory whether to go right or left, the rat was required to run on a treadmill. In some trials, the rats ran for a prescribed amount of time (“time-fixed”), while in others they ran for a prescribed distance (“distance-fixed”). By changing the speed of the treadmill, time and distance could be sufficiently dissociated from trial to trial. They found

that firing of most of the cells on the treadmill were best explained by a **combination of time and distance**, but 8% of the cells responded **exclusively to time** and 11% **exclusively to distance**. Analysing these cells in other portions of the maze revealed that they could also have place field, suggesting that time cells are not distinct cell types from place cells (Kraus *et al.*, 2013). Rather place and time cells encode spatial and temporal regularities of experience and the activity of a cell would be associated to space or time depending on the dimensions of the context in which learning occurs (Eichenbaum, 2013).

Time cells have only been observed in short delay periods in a working memory task, representing time on the order of seconds, and have been proposed mainly as a way to bridge small gaps in discontinuous events (MacDonald *et al.*, 2011). It is thus not known whether time cells appear in a wide range of tasks or whether they specialize in working memory (Rowland & Moser, 2013).

Conclusion and experimental question

Navigation is thus a function involving **multiple processes**: integrating allothetic and idiothetic information concerning the world surrounding us and our movements in it, to build a mental representation of space and use it efficiently to reach a goal. This representation is built through reference frame manipulations of the sensory inputs and can be in an egocentric or allocentric reference frame. Head-direction, grid, boundary and place cells are several elements of the mental representation of space and contribute to it by each conveying a specific type of information.

Reaching efficiently a goal may be achieved through different ways of manipulating the information in the mental representation of space. The use of strategies and computational models are means to understand what information is being manipulated and how, in a given situation: is the subject using a map-like representation of the environment and searching the best path in it? Is the subject learning the best action to do in each place? Is the subject tracking distance? Or is the subject using one reliable cue to move towards it? Depending on the type of manipulation performed, different memory systems will be involved in the storage of the information.

Navigation, through the multiple processes it requires, relies on **several structures**. Furthermore, learning about one's environment and the optimal path to reach a goal is a **dynamic process** and studies on motor learning have shown that it is underlied by dynamic reorganization of brain networks.

I have in this introduction gathered studies performed at various scales (structural through imaging and lesion studies, neuronal through electrophysiology) and in various disciplines (navigation, motor sequence learning, computational learning). During my PhD, I focused on **sequence-based navigation** and combined several approaches to characterize it through a holistic approach.

Why focus on sequence-based navigation specifically? This navigation relies on the temporal organization of movements at spatially distinct choice points. Spatio-temporal processing of information allows recognizing and generating serially ordered temporal sequences (Lashley, 1951). Although this capability contributes to almost every neural function, from recognizing speech to generating muscle movements, the underlying neurophysiology is poorly understood (Mauk & Buonomano, 2004). Cellular imaging, lesion

and computational approaches have been used to characterize sequence-based navigation. The results are presented in two articles in the following pages. These articles are preceded by a methodological section focusing on cellular imaging and the associated network analyses.

METHODS FOCUS:
FOS IMAGING

1. Fos imaging

Expression of *c-fos* is used as an **index of cellular activity**. Comparing the level of activation of this gene in experimental animals to its level in control animals allows identifying the neural structures that were specifically activated during a task. Density of nuclei containing Fos protein, the product of *c-fos* gene, was thus measured using an immunohistochemical technique (with an antibody directed against Fos protein) (Guzowski, 2002; Maviel *et al.*, 2004).

IEGs and plasticity

Immediate early genes (IEGs) were first described in non neuronal cells as genes that were rapidly and transiently induced in response to growth factors. *c-fos* was one of the first IEGs to be identified. Its appearance within minutes, and disappearance thirty minutes later was, at the time, the fastest response to growth factor application that had ever been described (Greenberg & Ziff, 1983; Müller *et al.*, 1983). *c-fos* had previously been identified as a proto oncogene, meaning that its mutation or deregulation resulted in cell transformation (Herdegen & Leah, 1998). Subsequent characterization of *c-fos* activation in neuronally differentiated cells demonstrated that in addition to being induced by growth factors, it was also induced in response to depolarizing conditions mediated through voltage gated calcium channels (Morgan & Curran, 1986). This suggested that early response genes such as *c-fos* may play a more general role in coupling cell stimulation to long-term changes in gene transcription.

Other IEGs known to be expressed in neuronal cells and playing a role in plasticity are Zif268 (or *egr1*) and Arc. The pattern of expression of *C-fos*, Zif268 and Arc share similarities (Guzowski *et al.*, 2001), which may be due to common binding sites on their promoter regions, offering some insight to the simultaneous activation of several IEGs in response to the same stimuli (Davis *et al.*, 2003).

Fos protein functions by dimerizing with other IEG protein products to form the AP-1 (activating protein 1) complex, a transcription factor (Curran & Franza Jr, 1988). This transcription factor recognizes the common AP-1 DNA binding site and can interact with responsive elements that regulate downstream expression of many different genes (Karin *et al.*, 1997) (Figure 44).

It has been shown that IEGs are involved in the transition from the early phase to the late phase of **long-term potentiation** (LTP). The early phase of LTP is under the control of

second messengers and kinases. It is independent of protein synthesis and involves post-translational modifications of existing proteins (He *et al.*, 2002). The late phase, occurring 3 to 6 h after induction, induces long-term changes of synaptic connections through mechanisms of synaptogenesis and neurite outgrowth which both require activation of the transcription and translation processes (He *et al.*, 2002). This late phase allows memory consolidation and is initiated by the action of IEGs (up to 30 to 40 IEGs are involved). Their transitory expression occurs within minutes of stimulation. IEGs, usually activated by kinases (involving CREB pathway), act in signalling cascades (Figure 44). These cascades lead to the activation of genes coding for synaptic proteins that are required for the long-term changes of cells. IEGs are key players in LTP, long-term depression (Kemp *et al.*, 2013), maintenance of synaptic plasticity (Kubik *et al.*, 2007) and are involved in consolidation and long-term storage of long-term memory (Guzowski *et al.*, 2001; Hall *et al.*, 2001; Ramírez-Amaya *et al.*, 2005; Teather *et al.*, 2005).

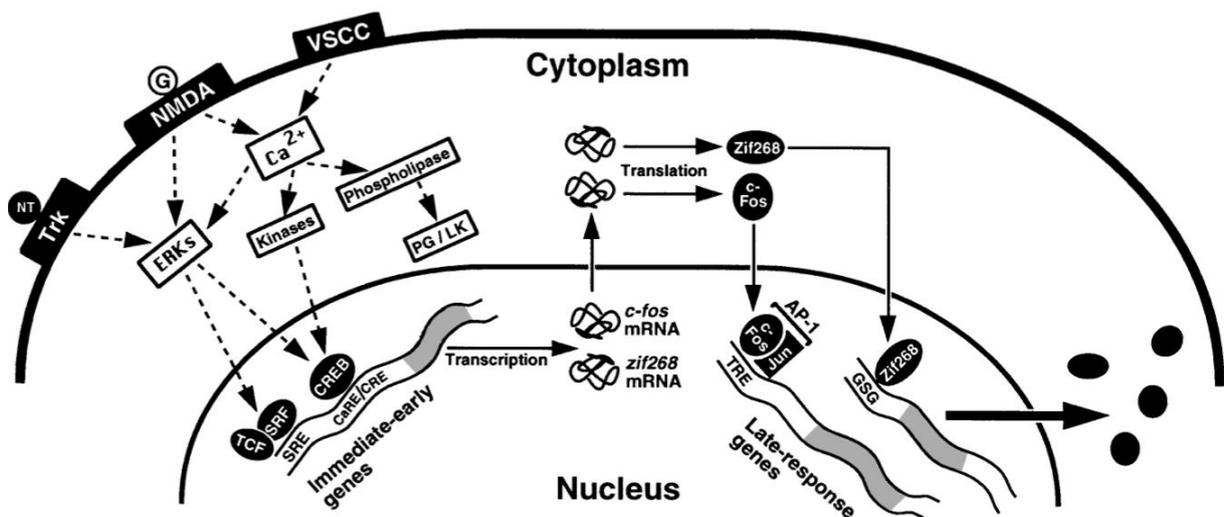


Figure 44: One activation pathway of *c-fos*. Cell stimulation induces activation of kinases that phosphorylate CREB and so will activate it. CREB induces the transcription of *c-fos*. Once the translated Fos protein is translocated in the nucleus, it forms the AP1 complex with Jun protein. The complex will then activate the expression of genes involved in long-term potentiation. *From* (Chaudhuri, 1997).

The role of *c-fos* in **memory** has been demonstrated using antisense oligonucleotide (ODN) infusion technique. Injecting antisense strand of the mRNA of *c-fos* blocks the translation of Fos protein. *c-fos* ODN injected in the amygdala caused learning and retention deficits in a conditioned taste aversive task (Yasoshima *et al.*, 2006). In the hippocampus, it produced long-term memory deficits in a food preference transmission task (Countryman *et al.*, 2005) and in the Morris water maze task (Guzowski *et al.*, 2001).

IEG imaging

Due to its involvement in learning and memory in a variety of tasks, Fos, as well as Zif268 and Arc, have been used to analyse memory processes occurring in the intact brain of animals performing a learning task (Guzowski *et al.*, 2001). This cellular imaging technique therefore uses the pattern of expression of these genes as an index of cellular activity. This is based on the idea that the level of activation of IEGs in different structures following a learning paradigm may indicate the relative contribution of these structures to the observed behaviour (Gill *et al.*, 2007). It has indeed been shown that the expression of *c-fos* was induced in the hippocampus after spatial learning (Vann *et al.*, 2000; Guzowski *et al.*, 2001; Colombo *et al.*, 2003; Teather *et al.*, 2005). This method, which has been widely used for the past 15 years, not only reveals regions that are active during a specific behaviour but also those in which neuronal plasticity occurs (Kubik *et al.*, 2007). As IEGs can be detected and quantified at a cellular resolution throughout the brain, this method also allows for brain-wide mapping of recent neuronal activity.

The optimal use of an IEG as an activity marker requires i) the consideration of its activation properties and ii) the implementation of appropriate controls.

i) The very low constitutive level of *c-fos* expression facilitates the observation of an increase in its activity. *c-fos* expression is induced rapidly and transiently and is very sensitive to new stimuli (Papa *et al.*, 1993). Furthermore, to ensure that the measured level of *c-fos* expression is indeed the result of an activation linked to a specific behaviour, it is important to take into account the **induction kinetics** of this gene. *c-fos* mRNAs are observed 30 minutes after stimulation and the maximum level of Fos protein expression is achieved 60 to 90 min after gene induction. *c-fos* expression then returns to its basal level after a period of 2-3 h (Guzowski *et al.*, 2001; Guzowski *et al.*, 2005). Cell imaging studies measuring *c-fos* as an index of neuronal activity typically use a range of 60 to 90 min between the completion of learning and the sacrifice of animals (Maviel *et al.*, 2004).

ii) *c-fos* expression is not only related to plasticity but also to general neuronal activity (Morgan & Curran, 1991) which can be triggered in particular by stress and motor activity. Stress and motor activity have been shown to induce a strong activation of *c-fos* (Tischmeyer & Grimm, 1999). It is therefore necessary to identify non-specific activity changes due to independent aspects of learning using **appropriate controls**. These animals, although not learning the task, must be exposed to the same experimental conditions. A control used in the water maze tasks are matched animals called "yoked control", which swim the same time as

their matched experimental animal in the absence of a platform (Santin *et al.*, 2003; Teather *et al.*, 2005). It may also be a control group whose swimming time is the average time taken by the experimental animals to find the goal. In both cases, this control allows seeing *c-fos* expression changes due to swimming behaviour, stress and other factors non-associated to the actual task learning.

2. Network analysis

Brain regions activated during a task compared to a control condition are considered to participate in that function. However, inconsistencies emerge from this approach. For example, in some cases there is a lack of activation in areas thought to be critical for particular function based on lesion data (reviewed in (McIntosh, 2004)) as well as substantial overlap in brain areas attributed to different functions (e.g. (D'Esposito *et al.*, 1998)). These apparently disparate findings can be reconciled by taking the status of interconnected brain areas into consideration when assessing brain function. The idea, that the activation of brain areas relative to other brain areas determines the cognitive state, was termed neural context (McIntosh, 1999). Information about the functional connectivity of brain regions can provide insight concerning the context in which a brain region is activated (i.e. how it is activated in relation to the activation state of other brain regions). These ideas about functional connectivity and neural context account for the possibility that regions can show changes in their interactions without associated change in activity (McIntosh, 2004). As a result, experiments that only consider the activation of brain regions may falsely conclude that a brain region is not involved in the cognitive state being studied.

2.1. Functional connectivity

Global imaging techniques can be used to provide information about structural and functional connectivity in the brain. Structural and functional connectivity are related but distinct: structural connectivity in the brain consists of anatomical connections while functional connectivity at the macro scale reflects the coordinated activation of brain regions.

While structural connectivity in the brain is conceived as anatomical connections, functional connectivity is a more elusive concept (Horwitz, 2003). Functional connectivity is defined as a statistical association between elements of a system and involves looking for **correlations** between brain activity in distinct regions. This approach has its origins in the analysis of spike trains obtained from multiunit electrode recordings (Gerstein & Perkel,

1969). To assess dependency in the brain, neural data must be collected simultaneously from multiple structures. Functional imaging techniques, such as fMRI and PET (Positron emission tomography) or *post mortem* with cellular activity markers as IEG expression, allow simultaneous global mapping. The correlations can be measured within a subject across time or between subjects in a single epoch. The major underlying assumption in this approach is that when these neural units have measured activity that is correlated, they function together in some way (Friston *et al.*, 1993b).

2.2. Graph theory

Data on brain connectivity can be rendered in the form of networks, also referred to as **graphs** (Bullmore & Sporns, 2009; Sporns, 2011), which are simplified representations of brain systems as sets of neural elements and their interconnections. Such network models allow the application of a quantitative theoretical framework for an objective and data-driven analysis of network attributes (Sporns, 2014) to provide insight specific aspects of brain structure and function.

Graph theory is a branch of mathematics that is used to formally describe and analyze networks and has recently been applied to structural and functional brain connectivity datasets (Bullmore & Sporns, 2009). This data-driven approach to examination of brain connectivity allows for analysis of emergent properties of connectivity architecture.

Networks consist of nodes and links between nodes. The definition of the **nodes** in the network depends on the methodology used to collect the data. Nodes represent brain regions or voxels in the case of metabolic or fMRI data, electrodes or sensors in the case of EEG or MEG data or neurons in the case of small scale microcircuit data. The **links** in the network represent the measures of connectivity described above, either structural or functional, and depending on the nature of the data can contain information about directionality or strength of connectivity. Strength of correlation, but not directionality, can be extracted with IEG imaging. In the case of functional connectivity weak and negative associations are often discarded by applying a threshold to produce a clearer topology (Rubinov & Sporns, 2010). Increasing the threshold eliminates weaker connections that are more likely to be contributing noise to the network. Since the level of thresholding is somewhat arbitrary, it is often done for a range of values in order to establish the robustness of network properties. Although network theory has a long history dating back to the 1700s (Biggs *et al.*, 1976), it was first used in conjunction with functional connectivity data just over ten years ago (Stephan *et al.*, 2000) and has

recently first been used with functional connectivity data obtained from interregional correlations in markers of neuronal activity in animal models (Wheeler *et al.*, 2013).

Several **graph theory measures** allow characterizing properties of the network as a whole (e.g. degree distribution, segregation, integration), while other graph theory measures are well suited to describe properties of individual nodes or connections in network and are useful for identifying key elements in the network. I have used measures belonging to the second category during my PhD, referred to as measures of **centrality**. These measures are useful for assessing the importance of individual nodes in the network and identifying highly central “hub” regions. The most basic measure of centrality is **node degree** which is the number of connections that a node has, indicating how much that node is interacting with other nodes in the network. **Betweenness centrality** calculates the number of shortest paths that pass through a node suggesting that it is important for controlling the flow of information in the network (Rubinov & Sporns, 2010). Using these measures cortical hub regions have been identified and characterized using fMRI functional connectivity methods (Achard *et al.*, 2006) as well as in tract tracing structural connectivity data from the cat (Zamora-López *et al.*, 2010).

RESULTS

Article 1: Complementary Roles of the Hippocampus and the Dorsomedial Striatum during Spatial and Sequence-Based Navigation Behaviour

1. Introduction

In this study, the aim was to investigate the neural bases of the map-based and sequence-based navigation strategies. We used the multiple strategy version of the star-maze in which mice could learn the path to the platform by either an allocentric strategy (using the environmental extra-maze cues) or the sequential egocentric strategy, remembering the sequence of turns (Rondi-Reig *et al.*, 2006). There were no intra-maze cues on the walls so mice could not learn the path to the platform through a guidance strategy.

Rondi-Reig *et al.*'s study had shown that the hippocampus was necessary for learning both strategies (Rondi-Reig *et al.*, 2006). This study aimed at identifying whether other regions were similarly or differentially engaged in each strategy. This study particularly concentrated on the dorsomedial striatum, as it was shown to be involved in goal-oriented learning in instrumental conditioning (Yin *et al.*, 2005a) and navigation tasks (Yin & Knowlton, 2004) (for review see (Yin & Knowlton, 2006)).

To map the neuronal activity of the hippocampal, striatal and cortical regions, we used cellular imaging of the activity-dependent gene *c-fos* (Guzowski, 2002; Maviel *et al.*, 2004). We then adopted an invasive approach by performing region-specific excitotoxic lesions of either the dorsal hippocampus or the dorsomedial striatum to specifically determine the role of the dorsomedial striatum relative to the hippocampus in goal-directed navigation.

2. Main results

The Fos imaging analysis revealed that an overlapping network including the dorsal hippocampus, the dorsomedial striatum and the medial prefrontal cortex supported both strategies. A significant higher activation of the ventral CA1 subregion was observed when mice used the sequential egocentric strategy.

Dorsal hippocampus lesioned mice were unable to optimally learn the sequence but improved their performances by for the most part developing a serial strategy, consistent with the results obtained with the NR1-KO mice without functional NMDA receptors in the dorsal CA1 (Rondi-Reig *et al.*, 2006). In contrast, mice with a dorsomedial striatum lesion were

severely impaired: 50% learned suboptimal paths to the goal and the other 50% failed to learn any path to the platform.

3. Discussion

These results show that additionally to the hippocampus, the dorsomedial striatum and prefrontal cortex are also involved in performing either map-based or sequence-based strategies.

Prelimbic and infralimbic cortices, which have been shown to code for goal position (Hok *et al.*, 2005; Spiers & Maguire, 2007), are known to be involved in a variety of executive processes such as working memory for spatial location information, decision-making, planning and strategy selection (see review in (Chudasama, 2011; Kesner & Churchwell, 2011)).

Dorsal hippocampus' increased Fos expression when mice used either strategy together with the deficits provoked by its lesion are consistent with previous findings showing that the hippocampus is crucial for the acquisition of relationships between multiple stimuli (Eichenbaum, 1999). Its role is well known in learning the representation of the spatial relationships among landmarks, which is essential to the allocentric strategy (Morris *et al.*, 1982). These results also further strengthen its role in the retrieval of sequences (e.g. (Fortin *et al.*, 2002; Kesner *et al.*, 2002; Kumaran & Maguire, 2006)), which are consistent with electrophysiological recordings in rodents reporting sequential patterns of firing of hippocampal place cells during spatial navigation (Foster & Wilson, 2006; Diba & Buzsaki, 2007).

While most hippocampal mice developed the serial strategy and therefore improved their performances, most dorsomedial striatum lesioned mice were unable to adopt any clear strategies. These data suggest that a functional dorsomedial striatum is required to learn the correct actions leading to the goal, irrespective of the representation used, i.e. spatial or sequential. Our result corroborates previous studies arguing that the dorsomedial striatum is engaged in the cognitive control of behaviour (Ding & Gold, 2010; Devan *et al.*, 2011) especially in the selection of action in goal-directed behaviours (Yin & Knowlton, 2006) and plays a role in spatial navigation tasks (Devan & White, 1999; Yin & Knowlton, 2004; Moussa *et al.*, 2011).

Finally, the specific activation of the ventral hippocampus in sequential egocentric strategy strengthens its functional contribution to temporal order memory (Howland *et al.*,

2008).

These results demonstrate that the hippocampus and the dorsomedial striatum are both necessary for optimally performing in a complex goal-directed navigation task and could potentially cooperate to perform either allocentric or sequential egocentric strategies successfully.

Complementary Roles of the Hippocampus and the Dorsomedial Striatum during Spatial and Sequence-Based Navigation Behavior

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Abstract

We investigated the neural bases of navigation based on spatial or sequential egocentric representation during the completion of the starmaze, a complex goal-directed navigation task. In this maze, mice had to swim along a path composed of three choice points to find a hidden platform. As reported previously, this task can be solved by using two hippocampal-dependent strategies encoded in parallel i) the allocentric strategy requiring encoding of the contextual information, and ii) the sequential egocentric strategy requiring temporal encoding of a sequence of successive body movements associated to specific choice points. Mice were trained during one day and tested the following day in a single probe trial to reveal which of the two strategies was spontaneously preferred by each animal. Imaging of the activity-dependent gene *c-fos* revealed that both strategies are supported by an overlapping network involving the dorsal hippocampus, the dorsomedial striatum (DMS) and the medial prefrontal cortex. A significant higher activation of the ventral CA1 subregion was observed when mice used the sequential egocentric strategy. To investigate the potential different roles of the dorsal hippocampus and the DMS in both types of navigation, we performed region-specific excitotoxic lesions of each of these two structures. Dorsal hippocampus lesioned mice were unable to optimally learn the sequence but improved their performances by developing a serial strategy instead. DMS lesioned mice were severely impaired, failing to learn the task. Our data support the view that the hippocampus organizes information into a spatio-temporal representation, which can then be used by the DMS to perform goal-directed navigation.

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Introduction

Extensive research in rodents using navigation tasks has made a distinction between simple egocentric (response learning based on stimulus response-like associations) and allocentric (or place-learning) navigation [1]. In such tasks, the dorso-striatal system mediates habit or response learning [2], [3], [4] and the hippocampal system predominantly supports place learning [5], [6].

This parallel functioning of the dorsal striatum and the hippocampus is however not always clear-cut as revealed by recent findings. On one hand, the dorsal striatum has been shown to be anatomically [7] and functionally divided in a dorsolateral and a dorsomedial part, the former being related to response learning and the latter mediating goal-directed learning [8]. On the other hand, using a more complex paradigm, the starmaze

task, we previously demonstrated that an additional strategy we called *sequential egocentric* is encoded concomitantly with the allocentric strategy [9], [10]. Sequential egocentric strategy differs from a simple egocentric strategy as it requires a temporal order memory of successive choice points [11]. Due to its sequential nature, this strategy depends on the hippocampus in both rodent [9] and human [12]. In this study, we hypothesized that the hippocampus and the dorsomedial striatum (DMS) could support together a spatial task which can be solved by mice using either an allocentric or a sequential egocentric strategy.

One fundamental characteristic of hippocampal function is to enable the relational organization of declarative memory [13], [14], [15], explaining its involvement in the sequential egocentric strategy. In rodents, place cell properties provide physiological correlates of such relational organization of the spatio-temporal representation in the hippocampus. For example, the experience

of moving from one location to another along a route can be represented by the resulting sequence of place fields traversed [16]. Moreover, there has been a growing body of evidence that the hippocampus is essential to memorize sequences of events [17], [18], [19], [20], [21], [22]. Likewise in humans, functional magnetic resonance imaging (fMRI) studies provided converging evidence that retrieving the temporal order of a series of events recruits preferentially the hippocampus [23], [24], [25], [26], [12].

Concerning the DMS, the first demonstration of its implication in goal-directed learning comes from instrumental conditioning [27], see review in [28]. In a spatial task, actions need to be organized to reach a specific goal as well, thus questioning the possible role of DMS in spatial learning. Indeed rats with a lesion of the DMS were found to be impaired in a water maze [29] and Yin and Knowlton [30] nuanced Packard and McGaugh experiment [2] by showing that the DMS is needed to solve the simple cross-maze experiment by using place learning. Using a spatial alternation task, Moussa et al. [31] proposed that the DMS is necessary to link the goal with the suitable spatial behavior. From a computational point of view, this has been formalized as a role of the DMS in navigation strategies based on an internal model of the full sequence of movements to reach the goal, no matter if such internal model is allocentric or egocentric [32].

Functional connectivity between the DMS and the hippocampus was demonstrated in rodents during the choice period in a T-maze task [33] and in human for successful contextually dependent navigation [34]. Interaction between the human hippocampus and the caudate nucleus (homologous to the rodent DMS) has also been shown during route recognition [35]. No direct anatomical connectivity is known between the DMS and the hippocampal formation however these structures have been shown to interact through the prefrontal cortex on the one hand [36], [37], [38] and through the ventral striatum and substantia nigra (pars compacta) on the other hand [39] (see review in [7] and [40]). Gruber and McDonald [41] suggested that the DMS is an important node for translating hippocampal information into optimal goal-directed navigation.

We first examined the possible co-activation of the DMS with the hippocampus in the allocentric as well as the sequential egocentric strategies in the starmaze task. The use of either strategy can be detected accurately by analyzing the response made in a subsequent probe trial for which the start point is changed [9]. Thus mice can reach the hidden platform by remembering either its spatial position using the allocentric strategy, or the sequence of successive choice points leading to the goal, using the sequential egocentric strategy. To map the neuronal activity of the hippocampal and DMS memory systems, we used cellular imaging of the activity-dependent gene *c-fos* [42], [43]. We then adopted an invasive approach by performing region-specific excitotoxic lesions of either the dorsal hippocampus or the DMS in order to determine the effects of these selective lesions on learning the goal-directed navigation task in the starmaze. Our results suggest that the hippocampus organizes information into a spatio-temporal representation, which can then be used by the DMS to link a goal to an optimal path.

Materials and Methods

Ethics Statement

All behavioral experiments were performed in accordance with the official European guidelines for the care and use of laboratory animals (86/609/EEC) and in accordance with the Policies of the French Committee of Ethics (Decrees n° 87-848 and n° 2001-464). Animal housing facility of the laboratory is fully accredited

by the French Direction of Veterinary Services (n°B-75-05-24, 18/05/2010). Animal surgery and experimentation are authorized by the French Direction of Veterinary Services for LRR (# 75-752, 2009) and for AW (# 75-1634, 2009).

All efforts were made to minimize suffering and animal discomfort. Prior to surgery, mice were anesthetized by intraperitoneal injection of ketamine/xylazine. After surgery, mice were allowed 15-day rest and were observed regularly during this period to check if there was no infection and no weight loss.

At the end of the experiment, mice were sacrificed for Fos imaging and lesion analyses (see *Brain extraction for Fos imaging and histological verification of lesions* section). Mice were deeply anesthetized by intraperitoneal injection of ketamine/xylazine and perfused transcardially to extract the brain.

Experimental Subjects

Seventy one male C57BL/6J mice (3-month-old; Janvier, France) were used throughout the experiment ($n = 24$ in the Fos imaging study and $n = 47$ in the lesion study). Mice were housed in groups of 5 in standard conditions: 12 h light/dark cycle, with *ad libitum* access to water and food. Seven days prior the beginning of sensory-motor tests, mice were separated and housed individually to limit the inter-boxes variability resulting from social relationships. All behavioral experiments took place during the light cycle.

Behavioral Studies

Prior to training in the starmaze task, motor coordination and balance were evaluated in an accelerating rotarod (see [44]).

The starmaze is a complex goal-directed navigation task which consists of five alleys forming a central pentagonal ring and five alleys radiating from the vertices of this pentagonal ring (see [9] for details). All alleys were filled with water made opaque with an inert nontoxic product (Accuscan OP 301, Brenntag, Lyon, France) (Fig. 1A). White noise (50–60 dB) was used to cover all other sounds that the mice could have used to orientate themselves. The maze was surrounded by a square black curtain with 2-D and 3-D patterns affixed to provide configurations of spatial cues. To solve the starmaze task, mice had to swim to a platform hidden 1 cm below the water surface. The departure (alley 1) and arrival (alley 7) points were fixed (Fig. 1A). When a mouse reached the platform, it was allowed to spend 30 sec on it. If an animal did not locate the escape platform within the maximum swimming time (60 sec), the experimenter placed the animal on the platform where it remained for 30 sec.

The starmaze task: training schedule (Fig. 1C). The starmaze task relied on a massed training phase given over one day (day 1), composed of 10 sessions of 4 trials in the presence of all visual cues (see Fig. 1C for the training schedule).

The day before the training phase (day 0), all mice were given a pretraining session of 4 trials in the starmaze to limit stress and habituate them to swim and climb on the platform. The pretraining session was a cued version of the starmaze in which a proximal cue (a flag) was placed on the top of the submerged platform in the absence of any other visual cues (the starmaze was surrounded by a circular black curtain). On day 0, an additional training session was run on all mice included in the lesion study to insure optimal learning during the training phase.

Probe trial (Fig. 1B). The day following training (day 2), a probe trial was run to identify the strategy spontaneously used by each animal (Fig. 1B), namely the allocentric or the sequential egocentric strategy. To be interpretable the probe trial requires a perfect acquisition of the task. Thus, only the probe trials of mice which had reached the learning criterion were analyzed. This

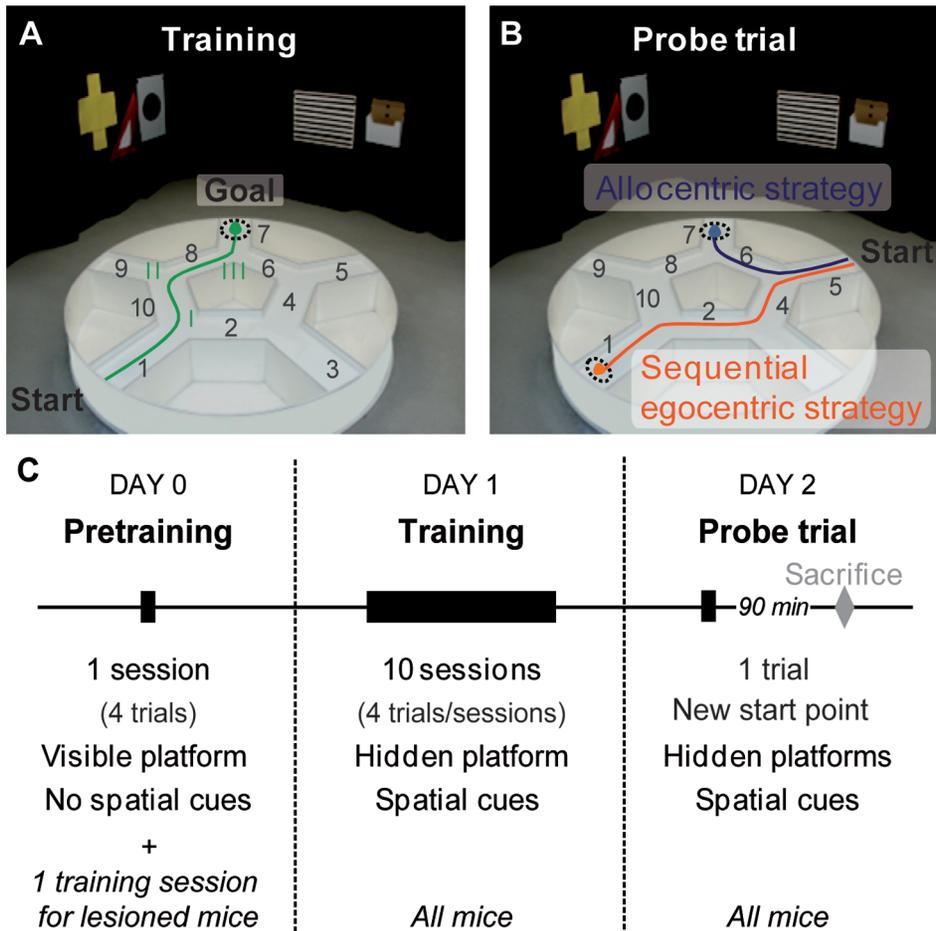


Figure 1. Experimental procedures in the starmaze. (A) Mice placed in a fixed departure alley (1) were trained to reach a fixed escape platform (dashed circle in alley 7) submerged under opaque water in the presence of visual spatial cues. The direct path to the platform is drawn in green. Intersections are numbered in roman numerals. (B) The probe trial. The day after (Day 2) the training day (Day 1), each mouse underwent a probe trial allowing to identify the strategy spontaneously used during training. The animal was placed in a new departure alley (alley 5) and could reach one of the invisible platforms located either in alley 1 or alley 7 in the presence of visual spatial cues. Mice that reached the habitual goal location (blue line) used an allocentric strategy whereas mice reproducing the temporal sequence of body movements (turning left, right and left; orange line) reaching alley 1 used the sequential egocentric strategy (orange line). (C) Design of the behavioral assay. The pretraining phase consists in reaching a visible platform (cued with a flag) from different departure points during a session of 4 trials the day before training, in the absence of any spatial cues (Day 0). The training procedure (Day 1) was composed of 10 sessions of 4-trials with an inter-trial-interval of 10 min and an inter-session interval of 40 min. On day 2, a single probe trial was given prior to processing the brains for Fos immunostaining. For the lesioned mice, a training session (4 trials with a hidden platform and visual spatial cues) is included on Day 0, after the pretraining to insure an optimal learning during the training phase. doi:10.1371/journal.pone.0067232.g001

criterion was defined as no more than 1 error (i.e. 1 wrong turn) during the last 4 trials on day 1.

The departure point was changed (alley 5). In addition to the habitual platform located in alley 7, another hidden platform was placed in alley 1 so that both strategies were equally rewarded. If a mouse used the configuration of distal visual cues, it performed the [5–6–7] trajectory revealing the use of an allocentric strategy. Executing the temporal sequence of body movements (left–right–left) led to the [5–4–2–1] trajectory indicating a sequential egocentric strategy. Any other path was classified as ‘other strategy’.

Analysis of learning: direct path score and behavioral strategies used. To evaluate the mouse’s ability to learn the correct sequence of turns and thus to elaborate a direct path towards the platform (Fig. 1A), we computed the direct path score relying on the turn scores for the intersection I, II and III. The turn score reflects the ability of making the correct turn at the first encounter with a given intersection only when following the ideal

path (i.e. when coming from alley 1 for intersection I, alley 10 for intersection II, alley 8 for intersection III; Fig. 1A). If the mouse makes a correct turn, it is given a score of 100. A score of 0 is given otherwise. To calculate the direct path score, each turn score is normalized by the number of alleys visited between the evaluated intersection and the first encounter with the previous one. The normalized scores for the three intersections are then averaged. This enables to evaluate the ability of the mouse to navigate directly from one intersection to another. This score thus takes into account the ability of doing the correct turns, but also more generally the ability of mice to orientate themselves towards the platform, especially at the first intersection. Indeed the configuration of the starmaze is such that when a mouse turns right at the first intersection, it goes towards the opposite direction from the location of the platform. The direct path score ranges from 0 to 100 and equals 100 when the path is direct (alleys 1-10-8-7) [45]. Additional examples are given in table S1.

The mice were classified according to their most used path during the last five training sessions, i.e. the second part of training. Different categories were used: “Direct path” corresponding to the most direct path to the platform (alleys 1-10-8-7, see Fig. 1A, green arrow) which can be achieved using either optimal strategy, allocentric or sequential egocentric. This analysis revealed additional non optimal ways of performing the task: “Long path” corresponding to a path along the alleys 1-2-4-6-7, “Serial strategy” consisting in visiting all radiating alleys successively until finding the platform (alleys 1-10-9-8-7), and “No strategy”, when mice did not repeat any clear path.

Control Animals Used for the Fos Imaging Study

In order to evaluate Fos expression specifically related to task learning, free swimming control mice were employed. These control mice were placed in the departure alley (31×25 cm) blocked with Plexiglas walls in presence of all visual cues (Fig. S1) and allowed to swim for the averaged escape latency of the experimental group. No escape platform was present. As Fos expression is known to be sensitive to environmental novelty [46], placing the control animals in the same new alley as the experimental mice for the probe trial, i.e. alley 5 (Fig. 1B and Fig. S1), allowed to take into consideration Fos expression induced by the change of view point and novelty effect. Thus, these animals allowed to estimate Fos expression related to the non mnemonic aspects of the testing procedure such as the change of view point, stress and motor behavior. Contrasting the mice using the allocentric or sequential egocentric strategy to the control group allowed us to identify structures involved in both memory reactivation and use of a strategy.

Surgery

Mice were randomly assigned to one of four groups: hippocampus sham [Hipp PBS] (n = 15), hippocampus lesion [Hipp IBO] (n = 14), dorsomedial striatum sham [DMS PBS] (n = 10), dorsomedial striatum lesion [DMS IBO] (n = 8). Excitotoxic lesions were performed by means of bilateral microinjections of ibotenic acid (Sigma, St. Louis, MO, USA) dissolved in phosphate-buffered saline (pH 7.4; 10 g/l) and sham lesions consisted in PBS 1X (Phosphate Buffer Saline) solution injections. Mice were anesthetized with ketamine (Imalgène 1000, Merial, Lyon, France; 100 mg/kg i.p.) and xylazine (Rompun, Bayer, KVP Kiel, Germany; 10 mg/kg i.p.) and placed in a stereotaxic frame (Stoelting). The skull was exposed and holes were drilled above injection sites. Targeting coordinates were determined from the atlas of Franklin and Paxinos [47]. Coordinates were measured in relation to bregma and the skull surface. For the hippocampus, 0.3 µL was injected per side (Antero-Posterior [AP], -2 mm; Medio-Lateral [ML], +/-1.4 mm; Dorso-Ventral [DV], -1.8 mm). For the dorsomedial striatum, 0.48 µL was injected per side (AP, +0.75 mm; ML, +/-1.3 mm; DV, -3.0 mm). Injections (80 nL/min) were made through a glass capillary 1 min after lowering it into the target region using a hydraulic micromanipulator (Narishige, Japan). After each injection, the capillary was left in place for another minute. After completing the injections, the scalp was sutured, and the mouse returned to its home cage for two weeks of resting. The mice were then handled daily (approximately 5 min/day) for a week and tested in the rotarod task at the end of the week. Starmaze testing began three weeks after surgery.

Brain Extraction for Fos Imaging and Histological Verification of Lesions

Ninety minutes after the completion of the last probe trial (or free swimming session) in the starmaze, mice were deeply anesthetized with an intraperitoneal injection of a mixture of Ketamine (150 mg/kg) and Xylazine (12 mg/kg) and perfused transcardially with saline (0.9%), followed by an ice-cold solution of 4% paraformaldehyde in phosphate buffer (PB 0.1 M, pH 7.4). After postfixation overnight in the same fixative at 4°C, brains were cryoprotected for 48 hours in a sucrose solution (30% in PB 0.1 M, pH7.4) at 4°C. 50 µm-thick coronal sections were cut on a freezing microtome and stored in PB 0.1 M solution containing 0.02% of sodium azide.

Fos Imaging

Free floating sections were rinsed in 0.1 M PB and then incubated for 30 min with H₂O₂ hydrogen peroxide (0.3% in PB). After four 10 min PB-rinses, sections were incubated overnight with a Fos-specific primary rabbit polyclonal antibody (1:5000, Santa Cruz) diluted in blocking solution (PB 0.1 M, 0.1% BSA, goat serum 2%, 0.2% Triton X-100). A biotinylated goat anti-rabbit antibody (1:2000, Jackson ImmunoResearch) was used as secondary. After washing, staining was revealed using the avidin-biotin peroxidase method (ABC kit, Vectastain Elite kit, Vector Laboratories, Burlingame, CA, USA) coupled to diaminobenzidine as chromogen. Sections were mounted on gelatin-coated slides. Quantitative analyses of Fos-positive nuclei were performed by using a computerized image processing system (Mercator, Exploranova, La Rochelle) coupled to an optical microscope. The quantification of Fos positive nuclei was carried out at 10x magnification. Structures were defined according to the Franklin and Paxinos atlas [47]. Immunoreactive neurons were counted bilaterally using a minimum of three sections, spaced 200 µm from each other. The number of Fos-positive nuclei was quantified in the following areas of interest: subfields CA1, CA3 and dentate gyrus (DG) of the dorsal and ventral hippocampus (dCA1, dCA3, dDG, vCA1, vCA3, vDG), dorsomedial (DMS) and dorsolateral (DLS) parts of the striatum, nucleus accumbens shell (AccS) and core (AccC), prelimbic (PL), infralimbic (IL), parietal (Par), lateral entorhinal (LatEnt) and granular and dysgranular retrosplenial cortices (DysRSP and GrRSP, respectively). The mean count in each structure for each animal (number of Fos positive nuclei per mm²) was divided by the mean count in that region of the respective control group to generate a normalized count for each animal. Results expressed as a percentage were averaged to give the final means of each group.

Histological Verification of Lesions

Free floating sections were incubated overnight at room temperature with a mouse primary antibody against neuronal-specific nuclear protein NeuN (anti-NeuN Alexa Fluor 488 conjugated; 1:1000; Chemicon, Temecula, CA, USA) in blocking solution (PB 0.1 M, 0.1% BSA, goat serum 2%, 0.2% Triton X-100). Sections were mounted on gelatin-coated slides and coverslipped with Vectashield mounting medium (Vector labs, Burlingame, CA, USA). Analyses of lesion extent were performed using a computerized image processing system (Mercator, Exploranova, La Rochelle) coupled to a fluorescence microscope. One mouse injected with ibotenic acid in the dorsal hippocampus and five mice injected with ibotenic acid in the dorsomedial striatum (DMS) were excluded of the study due to absence of lesion.

Data Analysis

Results were expressed as means \pm standard error mean (S.E.M.). Statistical analyses were run using the Statview 5.0 software. Learning performances were compared using analyses of variance with repeated measures (two-way repeated ANOVA and one-way ANOVA). Differences in normalized Fos density were assessed using Kruskal-Wallis non parametric tests followed by Mann-Whitney comparisons when indicated (values of $p < 0.05$ were considered as significant).

Results

Fos Imaging Study

Identification of the navigational strategies used in the starmaze. Upon completion of training, learning using either the allocentric or the sequential egocentric strategy led to the same direct path (see arrow in Fig. 1A). Each mouse was categorized according to the strategy used during the probe trial performed after the acquisition phase on day 2 (Fig. 1B, C). No significant strategy preference was observed in this experiment as equivalent proportions of mice used allocentric ($n = 7$ i.e. 44%) or sequential egocentric ($n = 9$ i.e. 56%) navigational strategies. Their learning profile was similar regardless of the strategy used during navigation as shown by comparable escape latencies (two-way repeated ANOVA, $F_{1,14} = 0.01$, $p = 0.91$; Fig. 2A) and direct path score, reflecting the ability of mice to execute the direct path to the platform (two-way repeated ANOVA, $F_{1,14} = 0.7$, $p = 0.41$; Fig. 2B). In addition, no difference in swimming speed was found (unpaired t-test, $t_{14} = 0.23$, $p = 0.82$; Fig. 2C).

An overlapping network supports allocentric and sequential egocentric strategies. Fos immunoreactivity was quantified in different structures known to be critical for learning spatial tasks, i.e. the dorsal hippocampus [dCA1, dCA3 and dentate gyrus (dDG) Fig. 2D], the ventral hippocampus [vCA1, vCA3 and dentate gyrus (vDG), Fig. 2E], the dorsal striatum [dorsomedial (DMS) and dorsolateral (DLS) Fig. 2F], the ventral striatum [nucleus accumbens core (AccC) and shell (AccS) Fig. 2G], and different cortices [infralimbic (IL), prelimbic (PL), parietal (Par), lateral entorhinal (LatEnto), dysgranular and granular retrosplenial (GrRSP and DysRSP, respectively) Fig. 2H, I]. To isolate changes in gene expression associated with the non mnemonic aspects of the testing procedure (e.g. locomotor activity, contextual arousal, and change in viewpoint during the probe test), we added a group of control mice which could swim freely in one alley (31 \times 25 cm) of the starmaze without a platform (Fig.S1). Number of Fos-positive nuclei in allocentric ($n = 7$) and sequential egocentric ($n = 9$) groups were normalized with respect to the level of Fos expression in control mice ($n = 8$).

Fos expression analysis in the hippocampus revealed that the dorsal CA1 and CA3 regions were conjointly recruited regardless of the strategy adopted by the mice (Kruskal-Wallis, $p < 0.01$, Mann-Whitney U , $p < 0.01$ for all comparisons to the swimming controls, allocentric versus sequential egocentric Mann-Whitney U , $p = 0.79$ for dCA1 and $p = 0.96$ for dCA3; Fig. 2D). However, only sequential egocentric strategy was associated to a significant increase in ventral CA1 (Kruskal-Wallis, $p < 0.01$, sequential egocentric versus swimming controls Mann-Whitney U , $p < 0.01$; Fig. 2E). No significant increase in Fos expression was observed in the DG in either dorsal or ventral subregion as well as in the ventral CA3 compared to the control group (Fig. 2 D, E). When examining Fos expression in the striatum (Fig. 2F), we observed that only the dorsomedial part is recruited, and this in both allocentric and sequential egocentric mice (Kruskal-Wallis, $p < 0.01$, Mann-Whitney U , $p < 0.01$ for all comparisons to the

swimming controls for the DMS). We did not observe any Fos activation in the dorsolateral striatum compared to the control group. As for Fos counts in the dorsal CA1 and CA3, Fos counts in the DMS were similar in allocentric and sequential egocentric group (allocentric versus sequential egocentric Mann-Whitney U , $p = 0.63$; Fig. 2F). Interestingly, Fos expression in hippocampal areas correlated positively with that in the DMS (Spearman correlation $r = 0.61$, $p < 0.01$ for CA1 and $r = 0.74$, $p < 0.01$ for CA3; Fig. S2).

There was no clear difference in Fos activation in AccS between controls and mice performing the task while a significant activation was seen in the AccC of mice using the sequential egocentric strategy (Kruskal-Wallis, $p = 0.04$, sequential egocentric versus swimming controls Mann-Whitney U , $p < 0.01$, allocentric versus swimming controls Mann-Whitney U , $p = 0.1$ for AccC; Fig. 2G). Fos activation was significantly higher in IL and PL cortices of mice learning the task compared to controls (Kruskal-Wallis, $p < 0.05$, Mann-Whitney U , $p < 0.05$ for all comparisons to the swimming controls; Fig. 2H). The DysRSP was activated in mice using the sequential egocentric strategy, its recruitment being also close to significance in allocentric mice (Kruskal-Wallis, $p = 0.04$, sequential egocentric versus swimming controls Mann-Whitney U , $p = 0.02$, allocentric versus swimming controls Mann-Whitney U , $p = 0.06$ for DysRSP; Fig. 2I).

Taken collectively, these results show that allocentric and sequential egocentric strategies in the starmaze were supported by an overlapping structural network which includes the dCA1, dCA3, DMS and medial prefrontal brain regions. Only the vCA1, the accumbens core and the dysgranular retrosplenial cortex were preferentially activated during the sequential egocentric strategy.

Hippocampal and DMS Lesion Study

The Fos imaging results reported above suggest that the hippocampus and the DMS are part of a common anatomofunctional basis for allocentric and sequential egocentric strategies and raise the possibility that the hippocampus and the DMS play complementary roles during learning of the starmaze goal-directed task. To test this hypothesis, we performed region-specific brain lesions using the excitotoxic agent ibotenic acid prior the starmaze procedure. Motor coordination and balance were evaluated in a rotarod [44]. We did not find any deleterious effect of ibotenic acid injections on motor abilities in either hippocampal or DMS-lesioned mice. The performances of lesioned and sham control mice (injected with PBS) were comparable to those of the mice trained in the Fos imaging study (One-pair ANOVA $F_{5,57} = 2.23$, $p = 0.06$ for time spent on the rod; Fig. S3). The DMS PBS group exhibited the lowest score (60 \pm 6 sec on the Rotarod compared to approximately 80 sec in the other groups). However such difference did not affect the starmaze performances of this group (see Fig. 4 B, C and D).

Dorsal hippocampus lesion impairs learning in the starmaze task and results in serial strategy learning. We first targeted the dorsal hippocampus and found that our lesion procedure resulted in a near complete neuronal depletion in the dorsal hippocampus with no detectable damage to surrounding areas (Fig. 3A).

The direct path score differed significantly between hippocampal mice ($n = 14$) [Hipp IBO] and the sham control mice ($n = 15$) [Hipp PBS] (two-way repeated ANOVA, $F_{1,27} = 10.61$, $p < 0.01$; Fig. 3B). There was a significant difference in swimming speed, the control mice swimming at a higher pace (unpaired t-test, $t_{27} = -2.39$, $p = 0.02$; Fig. 3C). However the swimming speed and the direct path score were not correlated (Spearman correlation $r = 0.25$, $p = 0.18$). Thus, the possibility that the difference in direct

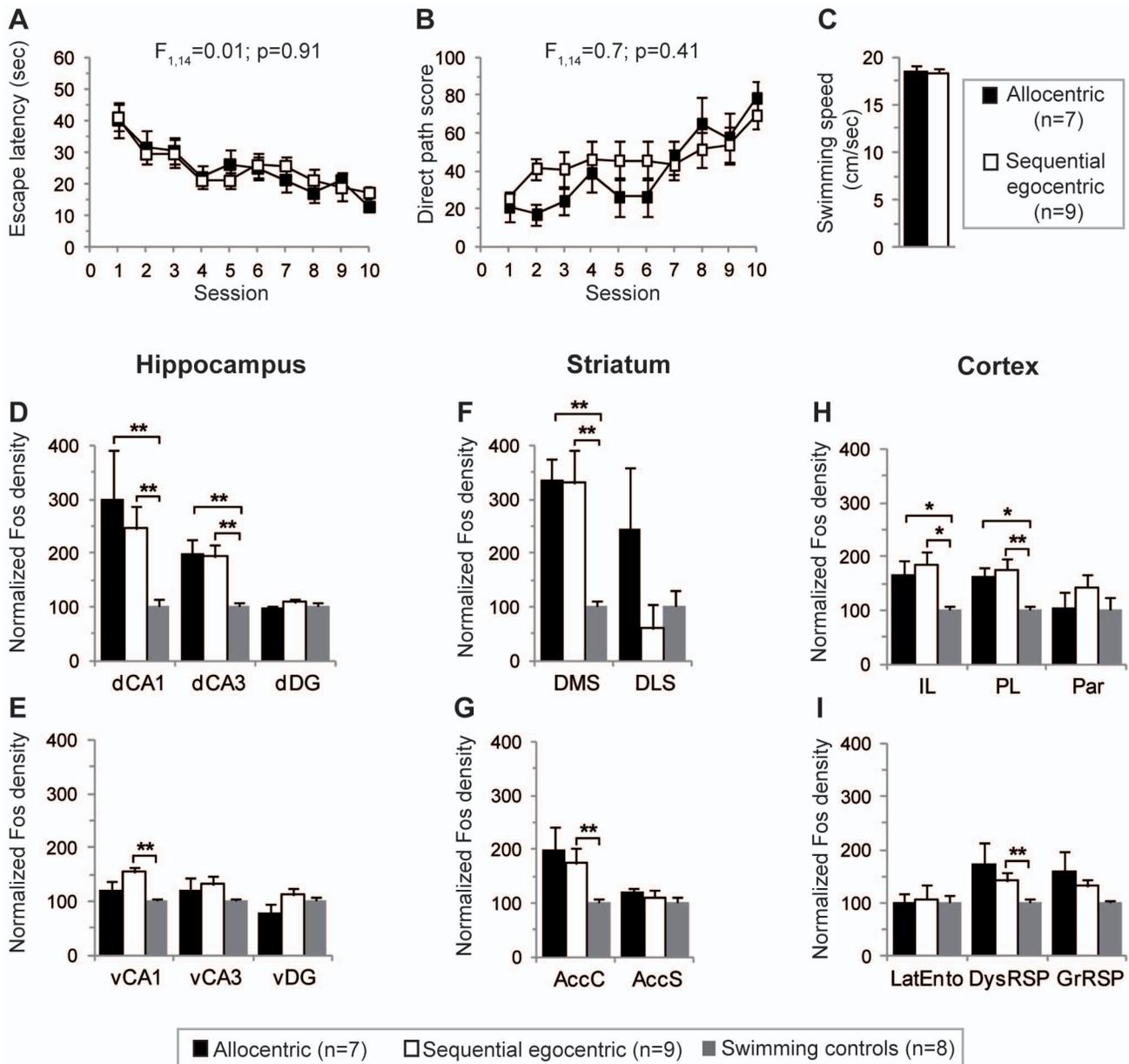


Figure 2. Identification of the network supporting allocentric and sequential egocentric strategies. Mice were categorized as allocentric ($n=7$) or sequential egocentric ($n=9$) according to their pattern of search in a probe test given one day following training in the star maze. **(A)** The escape latency to reach the hidden platform declined similarly across sessions in allocentric (closed squares) and sequential egocentric (open squares) mice. **(B)** Their learning profiles were similar as shown by direct path score across learning. **(C)** There was no difference in swimming speed. **(D–I)** Normalized Fos density relative to controls in hippocampal **(D, E)**, striatal **(F, G)** and cortical **(H, I)** brain regions of allocentric (black bars, $n=7$), sequential egocentric (white bars, $n=9$) and swimming control mice (grey bars, $n=8$). Note the increased Fos expression in the dorsal CA1 and CA3 fields of the hippocampus, in the dorsomedial striatum (DMS) and the infralimbic (IL) and prelimbic (PL) cortices of the allocentric and the sequential egocentric mice compared to the swimming control group. Compared to control mice, sequential egocentric mice have supplementary increased Fos expression in the ventral CA1 field, the core of the accumbens and the dysgranular retrosplenial cortex. No significant increase in Fos expression was observed in the dentate gyrus (Dorsal DG) and dorsolateral striatum (DLS). Error bars represent s.e.m. * $p<0.05$, ** $p<0.01$ Mann Whitney. doi:10.1371/journal.pone.0067232.g002

path score was due to the difference in swimming speed was unlikely. When analyzing the evolution of the direct path score across sessions, control and lesioned groups both improved their scores during training (one-way repeated ANOVA across sessions for control mice, $F_{10,154}=3.37$, $p<0.01$; for lesioned mice, $F_{10,143}=3.95$, $p<0.01$; Fig. 3B).

To further characterize the nature of the deficit of hippocampal mice, we examined how mice behaved during the second part of

the training. Two strategies were quantified: the direct path toward the goal or the serial strategy. All other types of behavior were characterized as no clear strategy. There was a significant difference in the distributions of strategies between hippocampal and control mice (Fisher's exact test, $p=0.04$). Control mice with PBS injection essentially relied on the direct path (60%). 27% of them used a serial strategy and 13% no clear strategy. By contrast, only two mice (14% of the hippocampal mice) used the direct path.

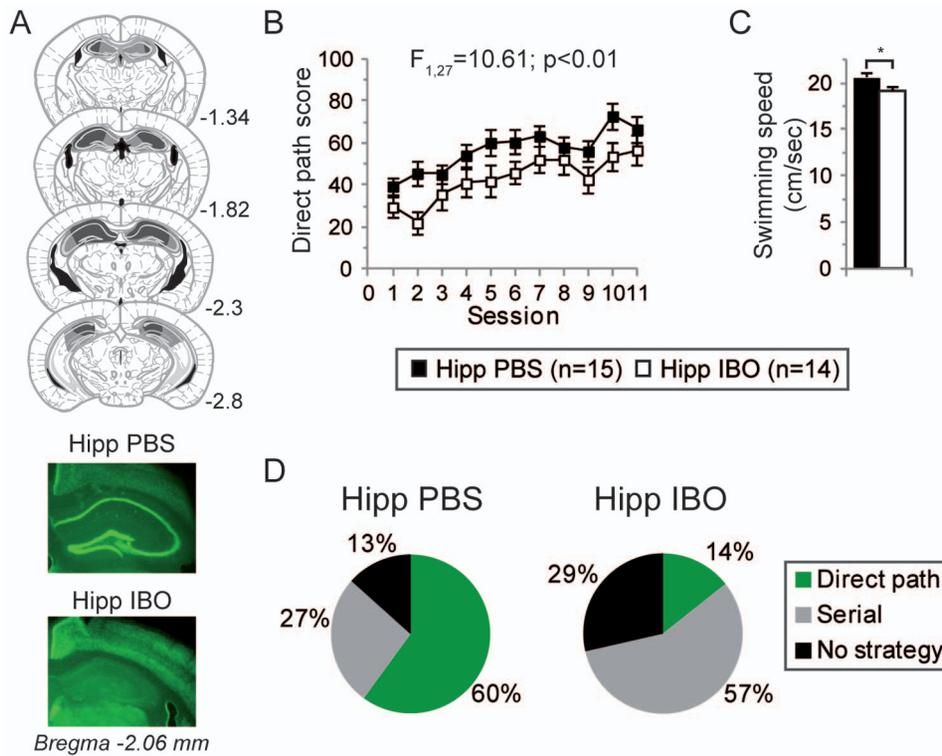


Figure 3. Learning performances of dorsal hippocampal lesioned mice in the starmaze. (A) Upper. Schematic representation of excitotoxic lesions of the dorsal hippocampus. Shaded areas represent the minimum (dark gray) and the maximum (light gray) extent of the lesions. Ventricles are in black. Numbers indicate distance from Bregma in mm. Lower. Representative coronal sections from control (injected with PBS as vehicle, Hipp PBS) and hippocampal mice (injected with ibotenic acid, Hipp IBO) stained for the neuron-specific marker NeuN (mm posterior to bregma). Infusion of ibotenic acid resulted in a near complete neuronal depletion in the CA fields and the dentate gyrus of the dorsal hippocampus. (B) Corresponding learning profiles in the starmaze. Compared to PBS-injected mice (closed squares, $n = 15$), lesioned mice (open squares, $n = 14$) exhibited an impaired direct path score. (C) There was a significant difference in swimming speed (black bar: control mice; white bar: hippocampal mice) but which was not correlated to the direct path score (see Results section). (D) Paths most used by the mice during the second half of the training day. Control mice injected with PBS essentially relied on the direct path (60%) whereas 57% of hippocampal mice relied on the serial strategy (turning always left at all intersection) and 29% expressed no clear strategy. doi:10.1371/journal.pone.0067232.g003

However during the probe test, one of these two mice used a serial strategy while the other did not use any clear strategy. Thus in the hippocampal group, no mice were clearly identified as using the allocentric or the sequential egocentric strategy. 57% of them relied on the serial strategy (visiting all radiating alleys until finding the platform) and 29% even expressed no clear strategy (Fig. 3D).

Dorsomedial striatum lesion impairs starmaze task learning. We next examined the effects of DMS lesions in the starmaze task. DMS-lesioned mice displayed neuronal depletion restricted to the dorsomedial part of the striatum with no observable damage to the dorsolateral part (Fig. 4A).

The direct path score of DMS-lesioned mice ($n = 8$) [DMS IBO] was significantly lower than that of sham control mice ($n = 10$) [DMS PBS] (two-way ANOVA, $F_{1,16} = 15.11$, $p < 0.01$; Fig. 4B) and there was no difference in swimming speed (unpaired *t*-test, $t_{16} = -0.04$, $p = 0.95$; Fig. 4C). Notably, the direct path score presented no evolution across sessions contrary to hippocampal mice (one-way repeated ANOVA across sessions for control mice, $F_{10,99} = 4.22$, $p < 0.01$; for DMS lesioned mice, $F_{10,77} = 0.32$, $p = 0.97$; Fig. 4B).

When comparing the paths used during learning by the DMS-lesioned mice and the control mice, DMS mice presented a significant difference of distribution with the control mice (Fisher's exact test, $p < 0.01$). 70% of the control mice used the direct path while no DMS lesioned mice did. Instead, half of them

demonstrated no clear strategy (compared to 10% for the PBS mice), a quarter used the serial strategy (compared to 20% for the PBS mice), and the last quarter adopted a different path, the long path to the goal (alleys 1-2-4-6-7) (Fig. 4D).

Comparing dorsomedial striatum versus hippocampal lesion. Although both dorsal hippocampus and DMS lesions impaired learning in the starmaze, the behavior exhibited by the lesioned animals was clearly different depending on the lesioned structure, as revealed by the distribution of the paths used (Fig. 3D, 4D). Hippocampal mice were able to develop a serial strategy to reach the goal whereas the DMS mice were lost as shown by the majority of no clear path used. Notably no DMS-lesioned mice learned the direct path to the platform. 25% of them used the non optimal long path to reach the platform. In addition to being non optimal, this path also reveals an inability of the mice to orient themselves towards the platform. Indeed, the configuration of the starmaze is such that when a mouse turns right at the first intersection, it goes towards the opposite direction of the location of the platform (Fig. 1A).

Discussion

We investigated the structures involved in using the allocentric and sequential egocentric strategies in the starmaze task. Both strategies are encoded in parallel [9], [10] but can be used

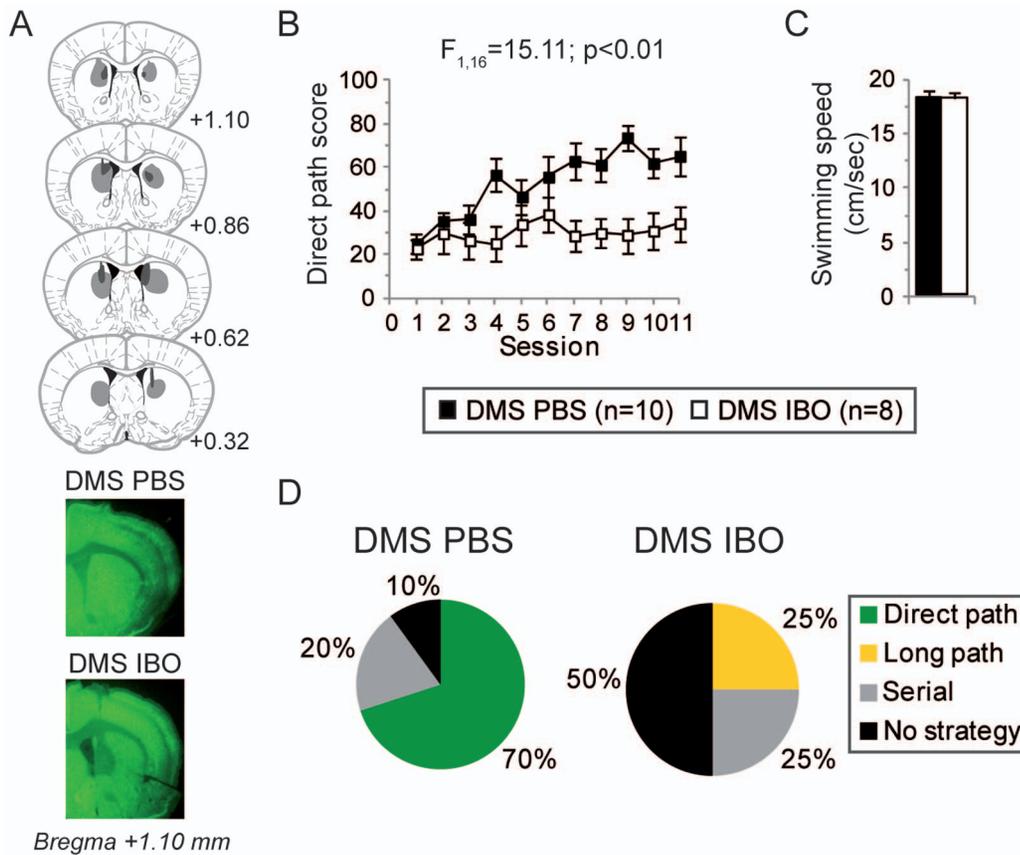


Figure 4. Learning performances of DMS lesioned mice in the starmaze. (A) Upper. Schematic representation of excitotoxic lesions of the DMS. Shaded areas represent the minimum (dark gray) and the maximum (light gray) extent of the lesions. Ventricles are in black. Numbers indicate distance from Bregma in mm. Lower. Representative coronal sections from control (injected with PBS as vehicle, DMS PBS) and dorsomedial striatum-lesioned mice (injected with ibotenic acid, DMS IBO) stained for the neuron-specific marker NeuN (mm anterior to bregma). Infusion of ibotenic acid led to extended neuronal depletion in the dorsomedial part of the striatum. (B) Corresponding learning profiles in the starmaze. Compared to PBS-injected mice (closed squares, $n = 10$), DMS-lesioned mice (open squares, $n = 8$) exhibited an impaired direct path score. (C) There was no difference in swimming speed (black bar: control mice; white bar: DMS lesioned mice). (D) Paths most used by the mice during the second half of the training day. PBS mice essentially relied on the direct path (70%) whereas 50% of IBO mice exhibited no clear strategy, 25% used the serial strategy (turning always left at all intersection) and 25% used the long path to the platform (1-2-4-6-7). Only DMS IBO mice displayed the long path. doi:10.1371/journal.pone.0067232.g004

separately to achieve complex goal-directed navigation in the starmaze task. Regardless of the strategy being adopted, mice were equally rewarded during the training procedure and had to perform the same sequence of body turns to reach the goal. Moreover, mice revealed as allocentric or sequential egocentric learners showed similar learning performances. Therefore, the main difference between using the allocentric and the sequential egocentric strategies resided in what was retrieved by the mice: the association of extra-maze landmarks in the former, and a temporal sequence of body turns in the latter.

Using Fos imaging, we first identified the structures involved in the use of the strategies during the probe test. We then focused on the role of the hippocampus and the DMS in learning the task by lesioning each of these structures.

The profile of Fos expression revealed a common neural network supporting both allocentric and sequential egocentric strategies. This network included the dorsal hippocampus, the DMS and the medial prefrontal cortex (infralimbic and prelimbic areas).

The higher levels of Fos density in infralimbic and prelimbic cortices of mice achieving the starmaze task compared to swimming controls is consistent with the role of these areas in a

variety of executive processes such as working memory for spatial location information, decision-making, temporal order memory and planning (see review in [48], [49]) as well as strategy selection [50], [51]. Moreover, the medial prefrontal cortex is part of the associative loop which also includes the DMS and which has been shown to be involved in behavioral flexibility required to solve a goal-directed task [52], [53].

Compared to control mice, Fos activation in the accumbens core was significantly higher only in the sequential egocentric strategy. However a similar tendency was observed in the allocentric strategy, supporting the view that the accumbens subregion is a structure involved in the control of spatial behavior [54], [55], [40].

Interestingly, in the sequential egocentric strategy Fos imaging revealed a specific activation of the ventral CA1 subfield of the hippocampus. As mentioned previously, what distinguishes the sequential egocentric strategy from the allocentric strategy is the recall of a temporal sequence of body turns. Besides the known role of the ventral hippocampus in stress and emotion [56], its differential activation specifically in sequential egocentric mice suggests its functional contribution to temporal order memory as has been shown previously [57].

Elevated Fos expression in the CA1 and CA3 subfields of the dorsal hippocampus of mice using either allocentric or sequential egocentric strategies shows that these areas are involved in the use of either strategies.

Mice with selective dorsal hippocampal lesions were still able to improve their performance in the starmaze task, however they displayed a delayed learning of the direct path to the goal compared to sham controls and never learned the correct sequence to the goal. This deficit was characterized by an inability to learn the correct turn at the second intersection in the starmaze, a turn which is crucial for the temporal organization of the sequence of three body movements (i.e. sequential egocentric strategy) required to ensure successful navigation to the goal. Indeed the hippocampal mice adopted a serial strategy consisting in visiting all radiating alleys successively and systematically reaching the goal. Notice that the serial strategy does not require any learning of the sequential organization of the body movements, an animal using this strategy just explores all encountered alleys by turning toward a defined direction independently of specific choice points. The use of this non-optimal strategy in the starmaze task nevertheless allows reaching the goal doing a small number of errors thus explaining the improvement of the direct path score.

These results, indicative of a navigation deficit affecting both allocentric and sequential egocentric strategies, highlight the role of the dorsal hippocampus in the spatio-temporal organization of information [9]. They are consistent with previous findings showing that the hippocampus is crucial for the acquisition of relationships between multiple stimuli [58], [18] and its well-known role in spatial navigation, namely the representation of the spatial relationships among landmarks which is essential in allocentric strategy [59], [5]. Furthermore these results strengthen the role of the hippocampus in temporal order memory, i.e. for the retrieval of the sequence of self centered body turns required in sequential egocentric strategy [24], [25], [26], [12], see review in [11]. Electrophysiological studies in rodents also reported sequential patterns of firing of hippocampal place cells during spatial navigation [60], [61], [62] as well as firing dependant on the events which occurred earlier or later thus providing temporal information to the spatial representation, such as required in spatio-temporal learning [17], [63].

Our Fos imaging data also revealed the implication of the DMS in the allocentric and sequential egocentric strategies used in the starmaze task. Whatever strategy spontaneously chosen by mice to reach the goal, Fos levels were significantly higher in DMS compared to swimming controls. On the contrary we did not observe any significant DLS activation during the probe test whatever the strategy chosen. To investigate that Fos activation in the DMS highlights its functional involvement in learning the starmaze task, we disrupted the DMS's function and examined the effects on learning performance in the starmaze. Mice with selective lesions of the DMS were unable to learn the starmaze task. Unlike hippocampal mice, there was no improvement of the direct path score. More specifically, the examination of the paths used during training showed that the majority of DMS mice exhibited no clear strategy. These results bring to light the role of the DMS in learning and using allocentric and sequential egocentric strategies.

The DMS has been shown to play a crucial role in processes mediating goal-directed behavior and decision-making such as action-outcome associations, behavioral flexibility and action selection [27], [64], [65], [66]. Supporting the role of the DMS in goal-directed behaviors, this region has been shown to contain reward-responsive neurons, stimulus-related neurons as well as

location-related neurons [67], [68], [69], [70]. In addition, electrophysiological recordings from the dorsomedial striatal neurons in rodents performing a Go/No go reaction time task [71] and caudate neurons in monkeys performing a reaction-time visual motion direction-discrimination task [72] suggested that the caudate nucleus provides necessary signals to evaluate and influence the decision process.

The failure of DMS lesioned mice to learn the starmaze task may be explained by the inability to create a link between a goal localized far from the animal and the spatio-temporal sequence needed to reach that goal. Indeed our data suggest that a functional DMS is required to learn the correct actions leading to the goal, irrespective of the representation used, i.e. spatial or sequential. While most hippocampal mice developed the serial strategy and therefore improved their performances, most DMS mice were unable to adopt any clear strategies. Our result corroborates previous studies arguing that the DMS is engaged in the cognitive control of behavior [28], [73], [74], especially in the selection of action in goal-directed behaviors [8], and plays a role in spatial navigation tasks [29], [30], [31], [35], [68].

Goal-related information has been shown to influence hippocampal place fields [75], [76], [77]. By comparing, in two different tasks, the influence of motivational state (hunger and thirst), memory demand and spatial behavior, Kennedy and Shapiro [78] reported that beyond coding the spatio-temporal context, hippocampal representations can integrate the relationships between internal states, the external environment and actions, thus providing a mechanism coordinating motivation and memory to control goal-directed behavior. This is consistent with findings of Mizumori and colleagues [79], [80] which emphasize that the default mode of hippocampal processing is to continually integrate perceptions of sensory, movement and motivational information within a spatial context.

Early studies on the DMS by Devan et al. [29] led the authors to the conclusion that the DMS was part of a system that includes the hippocampus and may contribute to behavior based on cognitive-spatial forms of information processing. Indeed when given a choice between a visible or an invisible platform, rats with DMS lesions preferentially went to the visible platform, suggesting an inability to learn the position of the invisible platform. At the cellular level, some studies reported in the striatum neurons with firing properties quite comparable to that of hippocampal place cells [68], [81], [82] that are recruited under conditions in which space carries information about the availability of reward [83].

Our data show on the one hand that the goal-related information coding in the hippocampus is not sufficient to allow optimal goal-directed behavior as no mice learned the direct path when their DMS was lesioned, and on the other hand that the DMS does not process spatial information sufficiently to allow learning the direct path to the goal.

Taken together, our results demonstrate that the hippocampus and the DMS are involved in learning a complex goal-directed navigation task: the spatio-temporal organization of information performed by the hippocampus can be processed by the DMS to perform optimal goal-directed navigation and both structures cooperate to perform either allocentric or sequential egocentric strategies successfully.

Supporting Information

Figure S1 The control group used to evaluate the nonspecific aspects of the training procedure on expression of the c-fos activity-dependent gene. Mice were allowed to swim in only one alley, corresponding to the departure

alley of the experimental group, namely alley 1 during training trials and alley 5 during probe trials. Swimming occurred in the presence of all visual cues for a duration matching the mean amount of swimming time of the experimental group. (PDF)

Figure S2 Significant correlations were found between normalized Fos counts measured in the CA1 (A) or the CA3 (B) fields of the hippocampus and the DMS for all mice groups. (Black squares: Allocentric mice; Open squares: Sequential egocentric mice; Gray squares: Swimming control mice.) (PDF)

Figure S3 Accelerating Rotarod performances. Performances on the accelerating rotarod were not significantly different for all mice groups. In particular, lesions did not affect motor performances on the rotarod test. (PDF)

Table S1 Examples of direct path score calculation for different trajectories. The direct path to the goal is represented by the sequence of three successive turns following the 1, 10, 8, 7 alleys. A turn score is given for each of the three intersections encountered along the direct path: intersection I (1;10), intersection II (10;8) and intersection III (8;7). The intersection turn score is equal to 100 for a correct turn and 0 for a wrong turn. Each intersection turn score is normalized by the number of alleys visited between the evaluated intersection and the

first encounter of the previous one. The normalized turn scores for the three intersections are averaged to obtain the direct path score. This direct path score enables to evaluate the ability of the mouse to navigate directly toward the platform. This actually corresponds to making the correct turn as from the first encountered intersection (intersection I). Not turning to the alley number 10 at the first intersection also reveals an inability of the mouse to orient itself towards the platform. Indeed, the configuration of the starmaze is such that when a mouse turns right at the first intersection, it goes towards the opposite direction from the location of the platform. Thus when considering two serial behaviors, namely left and right serial paths, the former corresponds to a turn towards the platform's location whereas the latter indicates the mouse is swimming away from it. (PDF)

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Author Contributions

Conceived and designed the experiments: CF BB LRR. Performed the experiments: CF BMB AW BB CT LRR. Analyzed the data: CF BMB LRR. Contributed reagents/materials/analysis tools: BB LRR. Wrote the paper: CF BMB CT LRR.

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Supporting Information

Path	Intersection I turn score	Intersection II turn score	Intersection III turn score	Direct path score
1-10-8-7 (Direct path)	100/1	100/1	100/1	100
1-10-8-6-7	100/1	100/1	0	66.7
1-10-9-8-7 (Left serial path)	100/1	0	100/2	50
1-2-10-9-8-7	0	0	100/2	16.7
1-2-4-6-7 (Long path)	0	-	-	0
1-2-3-4-5-6-7 (Right serial path)	0	-	-	0

Table S1. Examples of direct path score calculation for different trajectories. The direct path to the goal is represented by the sequence of three successive turns following the 1, 10, 8, 7 alleys. A turn score is given for each of the three intersections encountered along the direct path: intersection I (1;10), intersection II (10;8) and intersection III (8;7). The intersection turn score is equal to 100 for a correct turn and 0 for a wrong turn. Each intersection turn score is normalized by the number of alleys visited between the evaluated intersection and the first encounter of the previous one. The normalized turn scores for the three intersections are averaged to obtain the direct path score. This direct path score enables to evaluate the ability of the mouse to navigate directly toward the platform. This actually corresponds to making the correct turn as from the first encountered intersection (intersection I). Not turning to the alley number 10 at the first intersection also reveals an inability of the mouse to orient itself towards the platform. Indeed, the configuration of the star maze is such that when a mouse turns right at the first intersection, it goes towards the opposite direction from the location of the platform. Thus when considering two serial behaviours, namely left and right serial paths, the former corresponds to a turn towards the platform's location whereas the later indicates the mouse is swimming away from it.

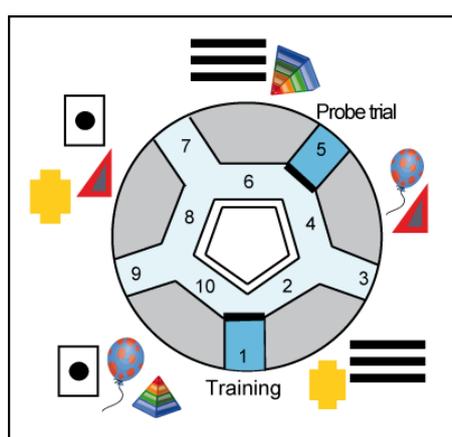


Figure S2. The control group used to evaluate the nonspecific aspects of the training procedure on expression of the c-fos activity-dependent gene. Mice were allowed to swim in only one alley, corresponding to the departure alley of the experimental group, namely alley 1 during training trials and alley 5 during probe trials. Swimming occurred in the presence of all visual cues for a duration matching the mean amount of swimming time of the experimental group.

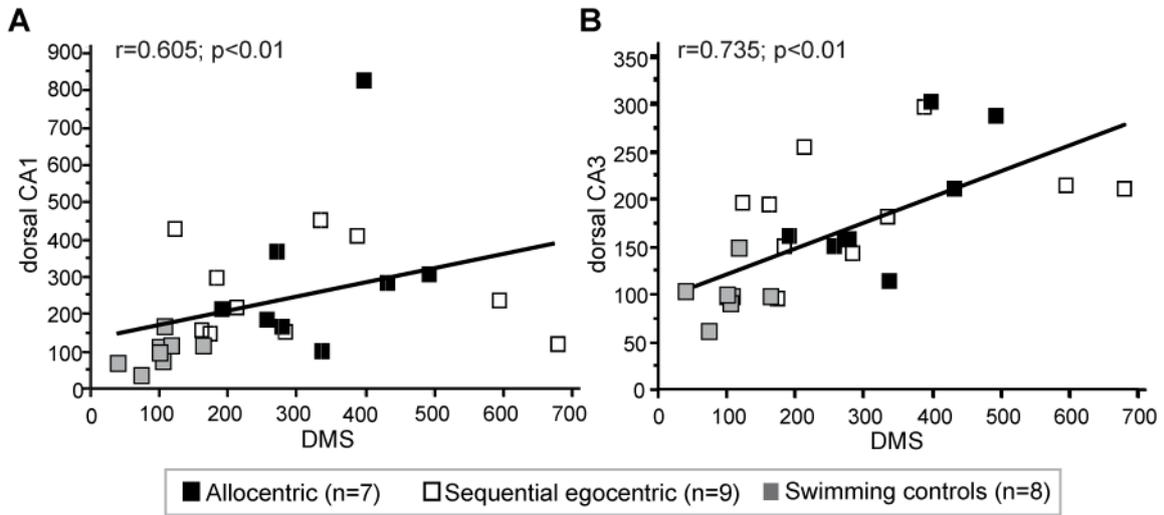


Figure S3. Significant correlations were found between normalized Fos counts measured in the CA1 (A) or the CA3 (B) fields of the hippocampus and the DMS for all mice groups. (Black squares: Allocentric mice; Open squares: Sequential egocentric mice; Gray squares: Swimming control mice).

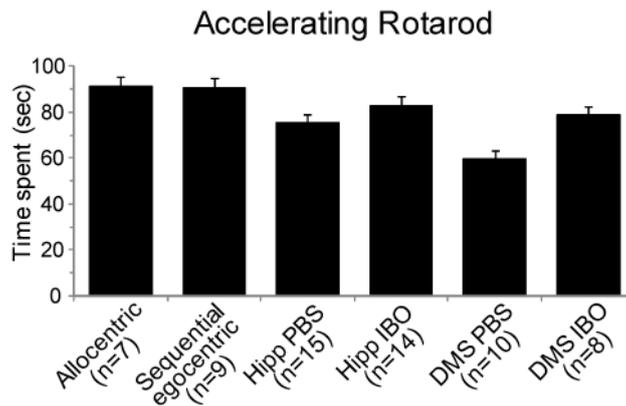


Figure S4. Accelerating Rotarod performances. Performances on the accelerating rotarod were not significantly different for all mice groups. In particular, lesions did not affect motor performances on the rotarod test.

Article 2, in preparation: Functional connectome and learning algorithm for sequence-based navigation

This second article is in preparation. Its' authors will be:

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1. Introduction

This study specifically focused on sequence-based navigation. We conducted two different approaches, one focusing on the neural circuits and the other investigating the learning algorithm of the task (Figure 45). We used a modified version of the starmaze with three Y-maze intersections and trained the mice in the absence of environmental cues to learn a path composed of two turns to the platform (Figure 45a). Due to the absence of environmental cues, mice could not use a map-based strategy to find the platform.

We characterized the neural circuits of sequence-based navigation in mice using Fos imaging. The dorsal hippocampus and the dorsomedial striatum have both been shown to be required for learning sequence-based navigation (Rondi-Reig *et al.*, 2006; Fouquet *et al.*, 2013). Fouquet *et al.* (Fouquet *et al.*, 2013) also showed that when mice used sequence-based navigation, these two structures were engaged with additional regions, namely the medial prefrontal cortex, the accumbens core, the ventral CA1 and the dysgranular retrosplenial cortex. However in this protocol mice could learn in parallel sequence-based and map-based navigation strategies. Our aim was here to specifically identify the neural circuits engaged in sequence-based navigation *per se*, thus using a protocol where mice could only use sequence-

based navigation to find the platform efficiently.

Results from the team suggest that the cerebellum contributes to building and then using a mental representation of space (reviewed in (Rocheffort *et al.*, 2013)). Specifically, cerebellar plasticity has been shown to be involved in hippocampal place cell properties when exploring an environment based on self-motion information in the absence of light (Rocheffort *et al.*, 2011). It has also been associated with trajectory optimization when performing goal-directed behaviour in a spatial task and a conditioning task (Burguière *et al.*, 2005; Burguière *et al.*, 2010). We thus also examined its contribution to sequence-based navigation. The mutant mice used in the navigations studies lacked LTD at the parallel fibre-Purkinje cell synapses (L7-PKCI mice) in all cerebellar regions. Activity mapping using Fos imaging will give us the opportunity to characterize cerebellar involvement in sequence-based navigation with higher spatial precision, at the lobule scale.

Exploration of the environment occurs mainly during the early stages of task learning. During exploration, the information about the environment can be used to build a mental representation of space (O'Keefe & Nadel, 1978; Alvernhe *et al.*, 2012). Exploration also allows discovering the rule of the task, i.e. reaching a platform to get out of a watermaze in a spatial task or finding a lever in a conditioning chamber and pressing on it to get a reward. Therefore, in rodent navigation tasks, the early learning phase of a task involves multiple processes.

We analysed the brain networks engaged during early learning and during late learning, when the sequence is well learned, using the activity-regulated gene *c-fos* (Guzowski, 2002; Maviel *et al.*, 2004). Memory expression is thought to depend upon network-wide, coordinated activation of cell assemblies (McIntosh, 1999; Buzsáki, 2010). Imaging-based approaches can detect coordinated activity across distributed and spatially remote brain regions, and therefore have been useful in defining functional networks (Wheeler *et al.*, 2013). Thus additionally to quantifying net increase in network activity, we analysed inter-regional correlations to identify collections of brain regions where Fos expression co-varies across mice and which presumably form components of a network that are co-active in early and late learning stages of sequence-based navigation (Figure 45b).

We also investigated the learning algorithm, which the mice could use to perform sequence-based navigation (Figure 45c).

Sequence-based navigation has been proposed to correspond to route learning (O'Keefe & Nadel, 1978; Redish, 1999; Arleo & Rondi-Reig, 2007), a process defined to rely on stimulus-response-stimulus associations, where successive stimuli can be predicted based on the current stimulus detected. Such learning relies on building a representation or *model*, in which the different areas of the maze (or stimuli) are represented and are linked to one other by the actions performed between them. This would allow learning the temporal order of the intersections to distinguish them and associate to each the correct turn (Fouquet *et al.*, 2010). Traditionally in the reinforcement learning field, such learning is termed *model-based* and two of its substrate are thought to be the hippocampus and the dorsomedial striatum (see for review (Khamassi & Humphries, 2012; van der Meer *et al.*, 2012; Dolan & Dayan, 2013)). The involvement of these two structures was thus an additional indication to the use of model-based reinforcement learning by the mice (Rondi-Reig *et al.*, 2006; Fouquet *et al.*, 2013). However the functions these structures underlie, relational organization of information (Eichenbaum *et al.*, 1999) and goal-directed learning (Yin & Knowlton, 2006), do not restrict them to model-based reinforcement learning. Moreover, other learning processes could underlie sequence-based navigation.

Indeed mice could also learn independent stimulus-response associations, as proposed originally by Hull and as shown in the cross-maze tasks in what is termed an “egocentric strategy” (Tolman *et al.*, 1946; Tolman *et al.*, 1947). Stimulus-response associations do not allow predicting subsequent events. By this aspect, they do not rely on building a *model* of the world and have been formalized by model-free reinforcement learning models. In the triple Y-maze, where intersections are indistinguishable, stimulus-response learning would probably require a mechanism to differentiate the intersections, as a counting mechanism or a memory of the previous actions. In the latter case, when doing the correct trajectory, the first intersection is preceded by going straight from the departure point whereas the second is preceded by a left turn and the third intersection is preceded by a right turn. If each stimulus is defined as the actual position in the maze and a memory of the last actions performed, they would become differentiated and could each be associated to a given response.

Another possibility for the mice to perform sequence-based navigation is by using path integration to find the platform. Path integration, or dead reckoning, corresponds to the ability of animals to return to the starting point of a journey directly, even if their journey was sinuous (Mittelstaedt & Mittelstaedt, 1980; Etienne *et al.*, 1998). This is performed by

computing a vector (the *homing vector*) from any point of the environment to the departure. This vector is calculated by integrating idiothetic cues such as vestibular and kinaesthetic signals, motor command efferent copies, and sensory (e.g., optic) flow information to estimate a given location relative to a starting point and has been shown to require the hippocampus (Maaswinkel *et al.*, 1999), amongst other structures (Etienne & Jeffery, 2004). In sequence-based navigation, mice could estimate the distance and direction to the platform relative to the departure point (Etienne & Jeffery, 2004).

Thus, as several learning algorithms can be proposed to allow sequence-based navigation, we tested whether model-based reinforcement learning, classical model-free reinforcement learning, model-free with a memory of the last actions performed reinforcement learning and path integration could reproduce the mice learning dynamics, at the group and individual levels (Figure 45c).

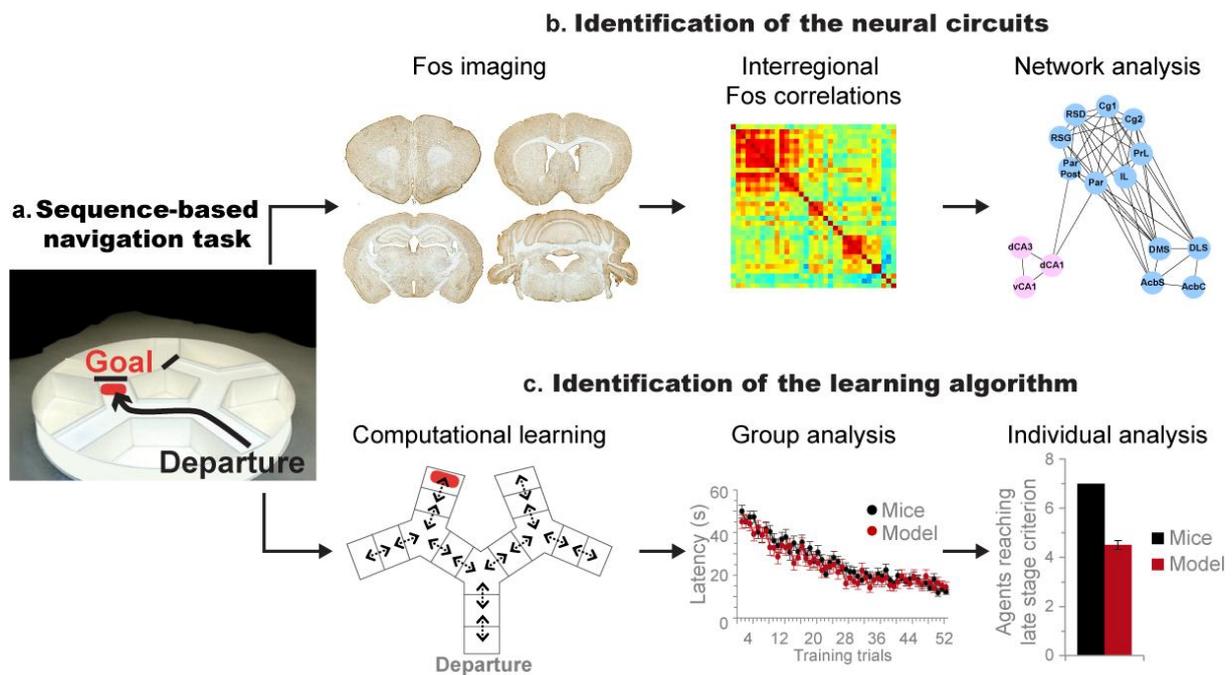


Figure 45: Overview of the experimental approach. We adopted a double approach to identify the neural circuits and learning algorithms underlying sequence-based navigation learning. (a) Mice learned a sequence of two successive turns in the triple y-maze. (b) Fos activated neurons were then quantified in 34 structures of mice at early or late learning stages. Inter-regional correlations were computed in order to identify brain regions where Fos expression co-varied across mice. The most robust correlations were then used to generate functional networks using graph theoretical approaches. (c) The behavioural performances were in parallel used to identify the learning algorithm which best reproduced the mice's behaviour, at the group and individual levels.

2. Methods

2.1. Behavioural study

Seventy-four male C57BL/6J mice (12–14 weeks old) from Janvier (France) were used in this study. All experimental procedures were carried out in accordance with international (European parliament Directive 2010/63/UE) and national legislations (Decree n° 2013-118) on laboratory animals care and use and were approved by the Animal Ethics Committee of the University of Paris-6 (n°00899.01). They were housed in groups of 5 in standard conditions: 12h light/dark cycle, with ad libitum access to water and food. Seven days prior the beginning of the behavioural tests, mice were separated and housed individually to limit inter-boxes variability resulting from social relationships. All behavioural experiments took place during the light cycle.

Prior training in the triple Y-maze task, mice performed a series of S.H.I.R.P.A. protocol tests ((Crawley, 2000), see also (Rondi-Reig *et al.*, 1997; Rondi-Reig & Mariani, 2002)) to ensure their general good health and motor performances and habituate them to being manipulated. They included general observations (appearance, spontaneous behaviour and neurological reflexes), anxiety and motor abilities tests (motor coordination, balance, rotarod and muscular strength tests) and were performed within five days (details in ((Fouquet *et al.*, 2011))).

The triple y-maze is composed of a central stem from which two y-mazes originate. It corresponds to a simpler version of the starmaze task (Rondi-Reig *et al.*, 2006; Fouquet *et al.*, 2011; Fouquet *et al.*, 2013) (Figure 45a). Alleys are 41 cm long and 25 cm wide and filled with water made opaque with an inert nontoxic product (Accuscan OP 301, Brenntag, Lyon, France) to hide a platform 1 cm below the surface. Water temperature was maintained between 19 and 21°C. A round black curtain without cues surrounded the maze and white noise (50-60 dB) was added to cover sounds that the mice could have used to orientate themselves. The departure and arrival points were fixed. To solve the triple y-maze task, mice had to swim remembering a sequence of turns: left then right (Figure 45a). Trials were grouped in sessions of four trials. Each trial lasted up to 60 sec with an intertrial interval of 30 s. When trials were unsuccessful, the mice were placed back into the departure alley and guided to the platform.

Mice were divided in four groups: early stage mice (n=15) and their early stage swimming control mice (n=15), late stage mice (n=30) and their late stage swimming control

mice (n=14).

Free-swimming control mice used to evaluate *c-fos* expression related to the non-mnemonic aspects of the testing procedure, such as stress and motor behaviour, were placed in a 2-alley corridor (with no intersection) blocked with PVC walls. They were randomly paired to early (n=15) or late (n=14) stage mice. They went through the same training schedule as their paired mice and swam the same duration as them. No escape platform was present so the animal was removed from the pool by the experimenter when the time was over. Free-swimming control mice that tried jumping out of the maze the day they were sacrificed were excluded from the study (n=1).

The early stage group performed one session of 4 trials in the triple-y maze (Figure 46a). To avoid *c-fos* expression related to discovering the features of the task (such as swimming), the early stage group and their swimming controls did a pre-training session the previous day (Figure 46a) in which they all swam 4 trials of 60 sec each in a two-alley corridor with no platform. At the end of each trial the early stage mice were habituated to climbing on the platform.

The late stage group mice were trained up to six days, doing four sessions of four trials per day, except for their last day where mice did one session (Figure 46b). This unique session on the last day allowed having a comparable amount of trials performed before doing the Fos immunohistochemistry amongst experimental groups. It also allowed verifying the quality of mice's sequence knowledge. To have equivalent task mastery amongst the mice in the late stage group and limited inter-individual variability, only mice reaching 75% of correct trials during one training day (within 3 to 5 training days) and 100% on the following day's first session were included in the Fos imaging analysis.

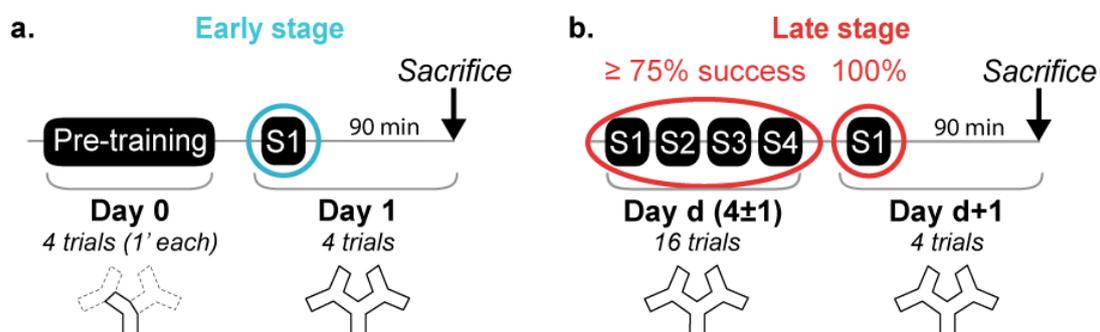


Figure 46: Design of the behavioural assay. (a) The early stage group went through a pretraining session of 4 trials (1 min each) in the 2-alley corridor. The following day mice swam for a session in the triple Y-maze. (b) The late stage group swam 4 sessions per day for 3 to 5 days until performing over 75% successful trials in one day. The following day they performed one session and were included in the group if the 4 trials were correct. Both groups performed one session the day they were sacrificed for Fos imaging.

Data acquisition was performed by means of a video recording system and tracking software, SMART (BIOSEB, Chaville, France) and data processing was automated via a MATLAB batch program developed in our laboratory (Navigation Analysis Tool (Jarlier *et al.*, 2013)).

2.2. Fos imaging

Fos immunohistochemistry

Ninety minutes after the last trial, mice were deeply anesthetized with an intraperitoneal injection of ketamine (150 mg/kg) and xylazine (12 mg/kg) and perfused transcardially with saline (0.9%), followed by an ice-cold solution of 4% paraformaldehyde in phosphate buffer (PB 0.1 M, pH 7.4). After postfixation overnight in the same fixative at 4°C, brains were cryoprotected for 48 hours in a sucrose solution (30% in PB 0.1M, pH7.4) at 4°C. Before being cut, the right side of the brains were marked to distinguish left from right. 50 µm-thick coronal sections were cut on a freezing microtome and stored in PB 0.1 M solution containing 0.02% of sodium azide.

Free floating sections were rinsed in 0.1M PB and then incubated for 30 min with H₂O₂ hydrogen peroxide (0.3% in PB). After four 10 min PB rinses, sections were incubated overnight with anti-Fos primary rabbit polyclonal antibody (1:1000, Santa Cruz) diluted in blocking solution (PB 0.1M, 0.1% BSA, goat serum 2%, 0.2% Triton X-100). A biotinylated goat anti-rabbit antibody (1:500, Jackson Immunoresearch) was used as secondary antibody. After washing, staining was revealed using the avidin-biotin peroxidase method (ABC kit, Vectastain Elite kit, Vector Laboratories, Burlingame, CA, USA) coupled to diaminobenzidine as a chromogen. Sections were mounted on gelatin-coated slides.

Fos positive nuclei quantification

Quantitative analyses of Fos-positive nuclei were performed by using a computerized image processing system (Mercator, Exploranova, La Rochelle) coupled to an optical microscope. The quantification of Fos positive nuclei was carried out at 10x magnification. Structures were defined according to the Franklin and Paxinos atlas (Paxinos & Franklin, 2008) and Allen Brain Institute Atlas for cerebellar regions (2012). Immunoreactive neurons were counted bilaterally using three consecutive sections spaced 200 µm apart. The brains were marked to allow differentiating right from left hemispheres. The quantifications were conducted 'blind' with respect to assignment of mice to groups.

The number of Fos-positive nuclei was quantified in 34 areas of interest, chosen because of their likely involvement in goal-directed navigation processes. These included cortices: prelimbic (PrL), infralimbic (IL), cingulate 1 and 2 (Cg1, Cg2), dysgranular and granular retrosplenial (RSD, RSG), parietal and posterior parietal (Par, PostPar), medial entorhinal (MEC); striatal regions: dorsomedial (DMS) and dorsolateral (DLS) striatum, nucleus accumbens core and shell (AcbC, AcbS); dopaminergic nuclei: ventral tegmental area (VTA) and substantia nigra pars compacta (SNc); hippocampal subfields: dorsal CA1, CA2, CA3 and dentate gyrus (dCA1, dCA2, dCA3, dDG) and ventral CA1, CA3 and dentate gyrus (vCA1, vCA3, vDG); cerebellar regions: lobules IV/V, VI, VII, IX, X; hemispheres VI (HVI), Crus I and II; dentate, fastigial and interpositus nuclei (Dent N, Fast N, IntP N). We also counted a region that was not expected to be involved in solving the task as a comparison site, the primary auditory cortex (Au1) because auditory information was not relevant for solving the task.

To allow direct comparison between all groups, Fos densities have to be expressed as a percentage relative to one of the control groups. We chose the late stage swimming control mice as control group for the analysis. These mice have been swimming four to six days in the same maze; their Fos expression was expected to control for motor activity and general experimental set-up.

The immunohistochemical procedure was performed in two cohorts each containing mice belonging to each experimental group. Raw cell counts were normalized within cohorts by the late stage swimming control group as follows: for each animal, each brain region's raw count (mean number of Fos positive nuclei per mm² across three consecutive sections) was divided by the same region's mean raw count across the late stage swimming control group of the same cohort. Homogeneity of normalized counts within experimental groups across cohorts was checked by Mann-Whitney U tests. Results were then averaged per group and expressed as a percentage.

Differences in normalized Fos density between the experimental groups were assessed using Kruskal-Wallis for each structure and post-hoc comparisons were performed using the Mann-Whitney U test. To test the effect of travelled distance or swimming speed on Fos densities across groups, we performed a covariance analysis (ANCOVA) using mice group as a categorical factor and travelled distance or swimming speed as a continuous factor on Fos densities.

Functional connectivity analysis

To investigate the potential interactions between the structures engaged in each learning phase, we analysed inter-regional correlations, such as previously shown in (Wheeler *et al.*, 2013). Inter-regional correlations allow us to identify brain regions where Fos expression co-varies across mice. For each experimental group (early stage, late stage, and their respective swimming controls), all pairwise correlations between the normalized Fos signal in the 34 regions were determined by computing Spearman's correlation. Each set of correlations was displayed as color-coded correlation matrices using R software (R, 2008).

To test whether two matrices came from the same population, we performed a permutation test using Matlab software (Mathworks, Natick, MA). This consisted in resampling two groups of 15 subjects within the 30 early stage mice and their swimming control, or 14 subjects within the 29 late stage mice and their swimming control, 10000 times and calculating each time the sum of differences between the two resampled correlation matrices. The 95th percentile was calculated by ranking the 10000 resampled correlation coefficients. If the correlation coefficient between the two original matrices was inferior to the 95th percentile of the 10000 sums of differences of resampled pairs of matrices (corresponding to a one-tailed significance level of $p < 0.05$), the hypothesis of identical populations was rejected.

Network graphs were constructed by thresholding inter-regional correlations in each group of mice. Networks graphs were constructed by considering correlations with Spearman's ρ at a two-tailed significance level of $p < 0.01$ and $\rho \geq 0.64$. In addition, networks were generated using either less ($\rho \geq 0.51$, corresponding to a two-tailed significance level of $p < 0.05$) or more ($\rho \geq 0.73$, corresponding to a two-tailed significance level of $p < 0.002$) conservative thresholds to evaluate whether network properties were stable across different thresholds. While potentially interesting, we did not consider negative correlations in the current network analyses. Negative functional connectivity in the brain may represent regional activity suppression, but it is not handled in the functional connectivity analysis used here (Rubinov & Sporns, 2010).

To identify hub regions, we used two measures of centrality, degree and betweenness, as previously described in (Wheeler *et al.*, 2013). They were computed for all regions in the

network using functions from Olaf Sporns' brain connectivity toolbox (<https://sites.google.com/site/bctnet/>). Degree corresponds to the number of regions a region is significantly correlated to. Node betweenness is the number of all shortest paths in the network that pass through a given node. Nodes with high values of betweenness centrality participate in a large number of shortest paths. All regions were ranked by degree and betweenness, and candidate hub regions were considered to be regions that were ranked >80th percentile for both measures in all three confidence levels' networks.

Cluster analysis was conducted with the Markov Cluster Algorithm (inflation parameter set at 2.1), a scalable, unsupervised cluster algorithm for networks based on simulation of stochastic flow in graphs (<http://www.micans.org/mcl/>). They were performed on the networks thresholded at $p < 0.01$. Additionally, we validated our results using hierarchical clustering using R software (R, 2008). Markov clustering has previously been used on Fos imaging (Wheeler *et al.*, 2013) and previous studies indicated that this procedure is significantly more tolerant to noise and behaves more robustly than other algorithms (Vlasblom & Wodak, 2009).

Cytoscape (<http://www.cytoscape.org/>) was used to perform the clustering and to visualize the graph networks and clusters. In the network graphs, the nodes represented brain regions and their size was proportional to the region's degree and the connecting lines width was proportional to the strength of the correlation.

2.3. Computational learning study

The aim of this part was to propose a theoretical model of the spatio-temporal learning process by finding algorithms that best describe the learning dynamics.

We tested three existing models that can be proposed to model spatio-temporal sequence learning: model-free reinforcement learning; model-based reinforcement learning; path integration.

Models tested

Reinforcement learning (RL) (Sutton & Barto, 1998) is based on creating associations between a given state (intersection, corridor, dead-end) and the most rewarding action. We investigated two different models for doing such associations: model-based RL or model-free

RL. In the former the agents (virtual mice) build an internal representation of all the experienced transitions (which action allowed the transition from one perception to another) whereas they did not in the later.

Model-based reinforcement learning

The internal representation of the environment was learned by repeated exploration of the maze. It contained information about the location of the reward. The agent used this graph to plan the shortest path to the reward using search algorithms (Martinet *et al.*, 2008). Two parts of the maze (intersection, corridor, dead-end) were linked because of the existence of one action (straight, left turn ...) between them, but as there were no cues in the environment they were represented independently from their allocentric position in a map representation (see Supplementary material, p.165).

Model-free reinforcement learning

A given state was defined as the configuration of the maze at the current position (intersection, corridor, dead-end) and the memory of the n previous actions performed. The short-term memory component was added to help differentiate the states that have identical configurations, such as the different intersections. This model used an actor-critic temporal-difference learning algorithm to associate by trial and error the most rewarding action to do at a given state (see Supplementary material, p.165).

Path integration

Agents calculated the displacement vector to be generated from the initial position to the reward and integrated their movements to monitor the movements to it. From a constant starting point, and given the actions performed, the agents evaluated the probability distribution of their position $P(Pos)$. When the goal was encountered, the probability distribution of the position of the goal $P(Goal)$ was updated based on the current $P(Pos)$. Finally, the direction of the next movement was chosen by drawing in the probability distribution of the direction of the goal $P(Dir)$, computed using the current $P(Pos)$ and $P(Goal)$ (see Supplementary material, p.165).

Reproduction of behavioural results

Simulation procedure

The simulated triple y-maze was represented by 15 discrete environmental sections: dead-end, corridor or intersection (Figure 45c). The departure and reward (platform) zones were dead-end sections of the maze located as in the real maze.

At the beginning of each trial, the agent was placed at the starting position (Figure 45a, c). The moving speed of the agent was set to 19.6 cm/s, corresponding to the mean speed of late stage mice on their last session, with a simulation time step equivalent to 1.05 s. If the agent was not able to reach the platform in 60 s (or 57 steps), it was automatically put back to the starting position and guided to the reward zone along the correct path, similarly to the real mice in the experiment. Reaching the goal was rewarded by $R = 1$.

The agents were simulated with one learning model at a time, set at given values for the learning parameters (η , β , γ or σ). These learning parameters consisted of:

- η , the learning rate;
- β , the trade-off between exploitation of what has been learned and exploration of new actions;

- γ , the discount factor that determines the importance of future rewards. A factor of 0 will make the agent "myopic" (or short-sighted) by only considering current rewards, while a factor approaching 1 will make it strive for a long-term high reward. This parameter does not exist in path integration. Instead σ , the distance estimation's uncertainty after each move was monitored. Indeed at each step taken, the agent estimates its current position with an error and this error increases with the amount of steps taken by a factor, σ .

We tested different meta-parameter sets of the algorithms. They were slightly different for the reinforcement learning models and for the path integration. Indeed our aim was to detect the best sets of parameters possible and the values in which the two family of models fits bests the mice's behaviour slightly differed.

For the two reinforcement learning models we tested:

η : [0.001, 0.005, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1];

β : [1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 100, 150, 200];

γ : [0.1, 0.3, 0.5, 0.7, 0.9].

For the path integration model we tested:

η : [0.001, 0.003, 0.005, 0.008, 0.01, 0.03, 0.05, 0.08, 0.1, 0.2, 0.4, 0.6, 0.8, 1];

β : [1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 100, 150, 200];

σ : [0.01, 0.03, 0.05, 0.1, 0.15].

This resulted in 980 sets of parameters tested per model.

The learning model simulations were tested on the whole population of mice that were initially included in the late stage group (n=30) and which performed an identical amount of training (3 days and one session on day 4, 52 trials in total). This mice population was composed of mice that reached the late stage learning criterion in 3, 4 or 5 days and mice that did not reach it within 5 days but still improved their performances (see black curves in Figure 49 b).

Data analysis

To test the adequacy of the models to the behavioural data, we evaluated two parameters: the escape latency and the number of visited alleys (it equalled three when the path was direct).

The escape latency of the agents was obtained by converting the number of steps into seconds using the scaling factor of 1.05 sec/step.

The number of visited alleys by the mice was calculated as described previously using NAT (see (Jarlier *et al.*, 2013)). Briefly, when a mouse or an agent crossed an intersection, it was considered to change alley. However in some cases mice or agents turned back into an alley. Such an event can either be considered as visiting an additional alley (doing a U-turn) or just staying in the same alley (having slightly drifted towards the intersection). In the triple y-maze, to distinguish these events, the intersection zones were divided into three equal sub-zones during the analysis. If a mouse crossed at least two sub-zones before returning to the alley then it was considered it had done a U-turn and going back into the same alley was counted as an additional alley visited. We did not discretized the virtual triple Y-maze intersection into three subzones thus we quantified the proportion of U-turns amongst all intersection crossing events for the 30 mice used in the analysis and applied this proportion (42%) to the amount of times an agent did a U-turn.

To compare the simulated data to the behavioural data, we applied Mann-Whitney and Kolmogorov-Smirnov nonparametric tests to compare distributions for the escape latency and visited alleys. For each of the 52 trials tested, the population of simulated agents was compared to the population of mice. Each trial with non-significantly different populations was marked as one. Thus a score of 52/52 for a given parameter with a given test meant that the population distributions were identical across the entire learning. The scores for both tests on both parameters were multiplied and expressed as a percentage to build simulation results

matrices.

The previous analysis tested the group similarity at each trial. We also tested if the models could replicate the mice's inter-individual variability by taking advantage of the late learning stage criterion. For each model tested, the set of parameters yielding the highest similarity score was replicated 20 times. For each replication, we calculated the number of agents reaching the success criterion of 75% on the “third day” (i.e. from trial 33 to trial 48) and 100% on the 4 successive trials (trial 49 to 52).

The models were programmed in Python using the numpy library, which was also used for the analyses.

2.4. Statistics

Statistical analyses were run using Statistica 10.0 (Statsoft) for the Fos imaging analysis (except when otherwise mentioned) and Python for the computational study. Normality was tested using the Shapiro-Wilk test for normality. When the data was normal, parametric tests were used (t-test) but if not or when the group had less than five observations, non-parametric tests were used (Kruskal-Wallis, Mann-Whitney U, Spearman, Kolmogorov-Smirnov). All analyses considered a value of $p < 0.05$ significant.

3. Results

Widespread activations underlie early stage learning and become more specific during the late stage of sequence-based navigation learning

Fifteen mice out of thirty reached the criterion of late stage learning for the Fos imaging analysis which consisted in doing over 75% correct trials during one training day within three to five days and 4 correct trials the following day. They had comparable performances on the first day ($p > 0.05$ for all Kruskal-Wallis comparisons on distance or swimming speed, see Supplementary Table 1 for details) (Figure 47a, left) as well as on their respective last full training day and last session ($p > 0.05$ for all Kruskal-Wallis comparisons on distance or swimming speed, see Supp. Table 1 for details) (Figure 47a, right).

Compared to the late stage mice's first session (three, four and five learning days' mice grouped), the early stage mice swam at a similar swimming speed (unpaired t-test, $t_{28} = -1.25$, $p = 0.22$) but travelled a shorter distance to find the platform (unpaired t-test, $t_{28} = -4.99$, $p < 0.01$) (Figure 47a, left).

To evaluate *c-fos* expression related to the non-mnemonic aspects of the testing procedure, swimming control mice were paired to early ($n=15$) or late ($n=14$) stage mice and swam in two alleys of the triple Y-maze without a platform for the same duration as their paired mouse. To compare directly all groups, Fos densities were expressed as a percentage relative to the late stage swimming control mice.

No differences were found between left and right hemispheres, for any region, in any group (Mann-Whitney for all structures, left versus right, $p > 0.05$).

No differences were found between the early stage mice and their paired swimming controls for all the structures counted (*post-hoc* Mann-Whitney for all structures, $p > 0.05$; Supplementary Figure 1a, Supplementary Table 2 for details).

Compared to late stage swimming control mice, early stage mice displayed significant Fos density increases in most cortices (primary auditory (Au1), prelimbic (PrL), infralimbic (IL), cingulate 1 and 2 (Cg1, Cg2), granular retrosplenial (RSG), parietal (Par), posterior parietal (PostPar), medial entorhinal (MEC)), in the dorsal and ventral striatum (dorsomedial (DMS), dorsolateral (DLS), accumbens core (AcbC), accumbens shell (AcbS)), in the ventral tegmental area (VTA), in the dorsal and ventral CA1 and CA3 (dCA1, vCA1, dCA3, vCA3), in the ventral dentate gyrus (vDG) and in the cerebellar cortex (lobules IV/V, VI, VII, IX, X, hemispheric lobule VI (HVI), Crus I, Crus II) (Figure 47b).

In the late stage group, significant increases in Fos density were found in the PrL, IL, Cg2, RSG, Par and PostPar cortices, in the DMS, the dCA1, dCA3, vCA3, Lob VI, Crus I, Lob VII, fastigial (Fast N) and interpositus (IntP N) deep nuclei. Activations in the deep nuclei were specific to this group (Figure 47b).

Thirteen structures were activated both in the early and the late stage groups amongst which six had higher Fos densities in the early stage group (PrL, IL, DMS, Lob VI, Crus I, Lob VII). The other seven structures had similar levels of Fos densities in both stages (Cg2, RSG, Par, PostPar, dCA1 dCA3, vCA3).

Mice in the different groups travelled different distances at different swimming speed (e.g. Figure 47a). To test whether the differences in Fos densities were due to either factor, we performed a covariance analysis (ANCOVA) using mice group as a categorical factor and travelled distance (or swimming speed) as a continuous factor on Fos densities. This analysis revealed no effect of distance or swimming speed on Fos densities in any structures (for all structures, distance or speed effect on fos: $p > 0.05$, see Supplementary Table 3). Thus the Fos density increases observed could not be explained by differences in travelled distance or swimming speed.

These results suggest that both early and late stages involved activations in the areas of the cortex, the striatum, the hippocampus and the cerebellum. However while the early stage was characterized by widespread activations, the late stage showed a more restricted number of activations.

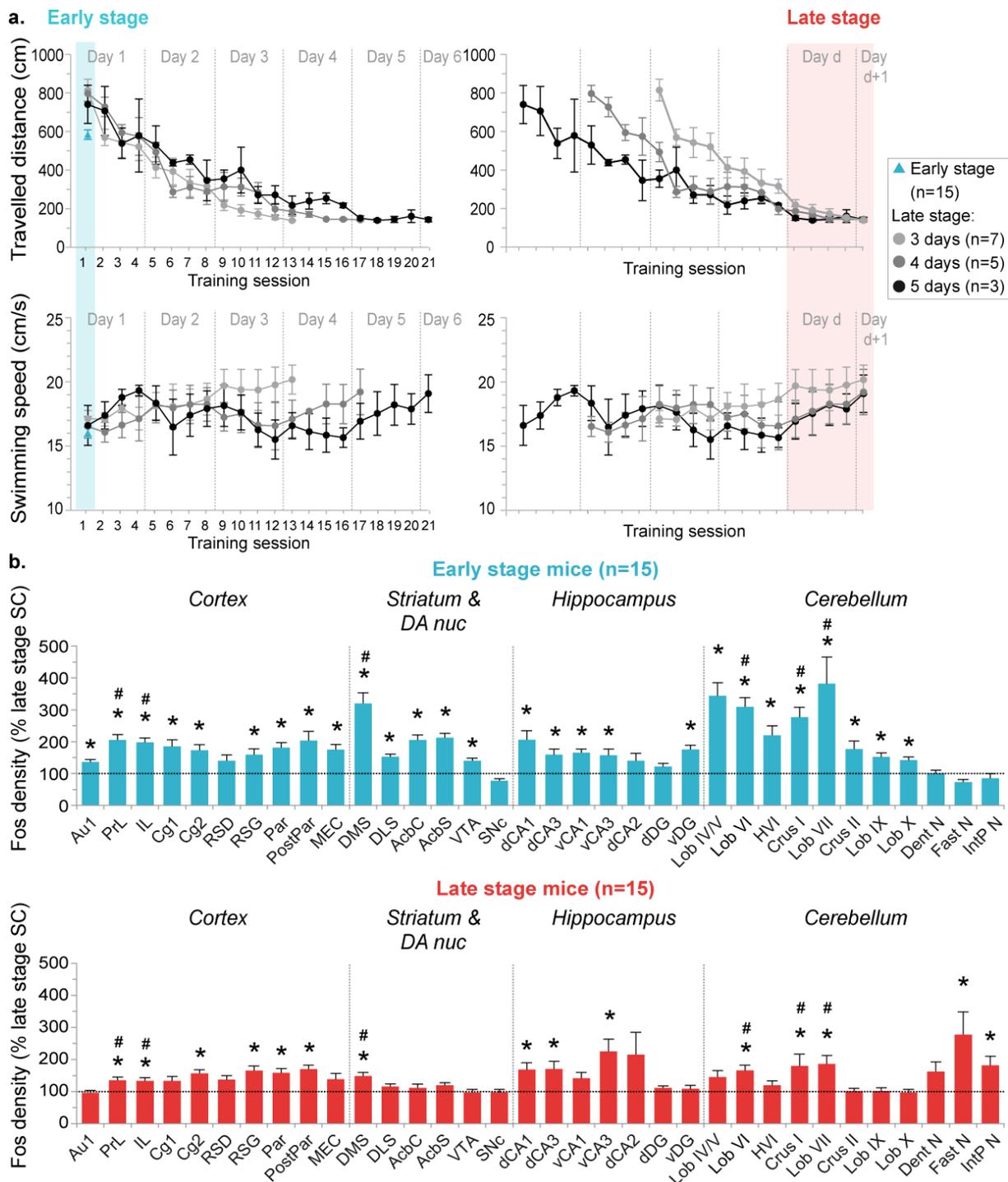


Figure 47: Identification of the structures involved in early and late stages of sequence-based navigation. **(a) Behavioural performances of early and late stage mice.** Travelled distance (top) and swimming speed (bottom) are presented for the early (blue in the left panels) and late stage groups. Mice in the late stage groups either learned in 3, 4 or 5 training days (grey shades). The curves are either aligned on the first day (left) or on the respective last day of the late stage mice (right). During the first session the three groups of late stage mice travelled a similar but higher distance compared to the early stage mice but swam at the same speed. Note that the late stage mice had comparable performances on their respective last full training day, when reaching the late stage learning criterion. **(b) Normalized Fos densities in early (top) and late (bottom) stage mice.** The dotted line indicates the level of the late stage swimming control mice (late stage SC). Compared to the late swimming control mice, most structures were activated in the early stage mice. Fewer structures were activated in the late stage group, but two were specific to this group (Fast and IntP nuclei). Data represent mean \pm s.e.m. * $p < 0.05$ Mann Whitney comparisons with swimming controls, # $p < 0.05$ Mann Whitney comparisons Early versus Late stage when both are significantly activated.

Functional networks change across learning stages

To investigate the potential interactions between the structures engaged in each learning phase, we analyzed inter-regional correlations to identify brain regions where Fos expression co-varies across mice.

Correlation matrices were generated by computing correlations between structures across subjects for each condition (Figure 48a).

In order to corroborate the absence of difference in Fos density between early stage mice and early stage swimming control mice, we tested if their matrices were similar. We performed a permutation test across the 30 early stage and early stage swimming control mice which revealed that there was no significant difference between the matrices of the two groups, consistent with the absence of significant differences in Fos densities between them. Indeed the sum of differences between their matrices was inferior to the 95th percentile of the resampled distribution (p level of 0.05, one-tailed test) (Supplementary Figure 1b). Whereas, the sum of differences between the late stage mice and late stage swimming control mice matrices was superior to the 95th percentile of their resampled distribution (Supplementary Figure 1c).

Network graphs were then generated for the late stage swimming control, the early stage and the late stage conditions considering only the strongest correlations (Spearman's $\rho \geq 0.64$, corresponding to a two-tailed significance level of $p < 0.01$) (Figure 48b). There were few significant negative correlations in the matrices but we focused on only positive correlations for the network analysis. To confirm that the main features observed at p level inferior to 0.01 are maintained across different thresholds, additional networks were generated using either less ($\rho \geq 0.51$, corresponding to a two-tailed significance level of $p < 0.05$) or more ($\rho \geq 0.73$, corresponding to a two-tailed significance level of $p < 0.002$) conservative thresholds (Supplementary Figure 2).

The structure of these network graphs varied across conditions. The late stage swimming control mice had the fewest significant correlations involving cerebellar-cortical, cerebellar-striatal, intra-cortical and striato-cortical correlated pairs. During the early stage, most of the correlations were within the striatal and cortical structures and two correlations linked the dCA1 to the parietal cortices. The most striking differences between the late stage graph network and the other two were the appearance of correlations involving the dCA1 and

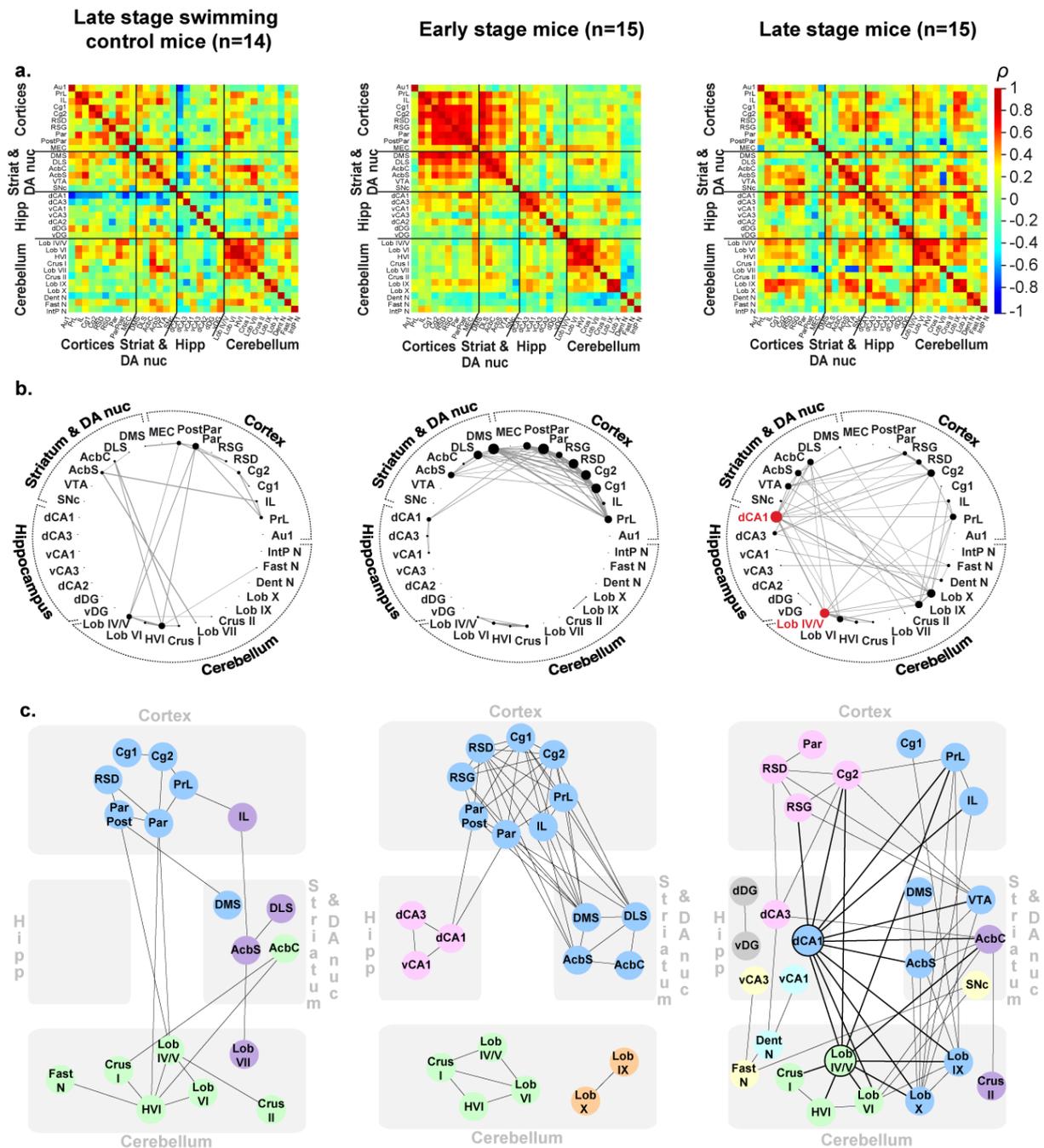


Figure 48: Functional networks of sequence-based navigation. (a) Matrices showing inter-regional correlations for Fos expression for late stage swimming controls (left), early stage (middle) and late stage (right) mice. Axes correspond to brain regions. Colours reflect correlation strength (scale, right). (b) Network graphs were generated by considering only the strongest correlations (Spearman's $\rho \geq 0.64$, corresponding to a two-tailed significance level of $p < 0.01$). Regions are grouped by major brain subdivision and node size is proportional to the number of connections (degree) while the thickness of the connection is proportional to correlation strength. The edges (or connections) represent super-threshold inter-regional correlations. The hubs are highlighted in red (late stage). No hub was detected in the late stage swimming control and early stage groups' network. (c) Markov clustering algorithm was applied to organize brain structures into discrete modules based on their common inter-connections. The structures are placed relative to their major anatomical subdivisions and are colour-coded according to the cluster they belonged to. The connections presented are the significant correlations shown in the network graphs. The hubs and their connections are highlighted in black. The late stage swimming control group's network was composed of three clusters mostly segregated within major anatomical subdivisions. The early stage group's network was divided in four clusters with a major cortico-striatal component. For the late stage, the network was composed of seven clusters with a major cluster involving areas of the four brain subdivisions.

cerebellar cortices with all the other regions.

No hub was identified for the late stage swimming control mice and the early stage mice networks. For the late stage group, the dCA1 and lob IV/V were both highly-connected nodes ranked above the 80th percentile of degree and betweenness measures in each of the low, moderate and high confidence networks. This suggests that these two regions have the most interactions within the network and that they may be important for controlling the flow of information (Rubinov & Sporns, 2010) (highlighted in red in Figure 48b and in black with their connections Figure 48c).

We then applied the Markov clustering algorithm to organize the structures into discrete modules based on their common inter-connections (Figure 48c).

This analysis identified three clusters for the late stage swimming control group, two mostly segregated within major anatomical subdivisions (cortex and cerebellum) and one involving the IL cortex, the DLS, AcbS and Lob VII. Four clusters were identified in the early stage group with a major cortico-striatal component, one hippocampal cluster and two cerebellar ones. The late stage group network was divided into seven clusters with one major inter-regional component involving on the hubs, the dCA1, with the prefrontal cortex areas (IL, PrL, Cg1), medial areas of the striatum (DMS and AcbS), the VTA and lob IX and X of the cerebellum. Another cluster involved the dCA3 with the retrosplenial cortices (dysgranular and granular (RSD, RSG), the parietal cortex and area 2 of the cingulate cortex. Two clusters involved the ventral hippocampus and the Fast N and Dent N of the cerebellum.

The three networks had a common cerebellar cluster composed of the lobule IV/V, Lob VI, HVI and Crus I. This cluster had few or no correlations with other clusters in the late stage swimming control and early stage groups respectively. In the late stage group, it exhibited an increased amount of significant correlations with hippocampal, cortical and striatal regions, through the lobules IV/V, making in at another hub region, and VI.

Path integration and reinforcement models explain group dynamics but only model-free reinforcement learning with memory reproduces individual variability

The learning model simulations aimed at fitting the whole population of mice ($n=30$) which did the triple y-maze task during an identical amount of training time (3 days and one session on day 4, corresponding to 52 trials). For each model tested, 30 agents went through 52 trials in a virtual triple y-maze (Figure 45e) at given values of the learning parameters (η ; β ; γ or σ for path integration). The ability of the model to fit the experimental data was accomplished by quantifying the amount of trials where the population of agents and mice were similar for two behavioural parameters (latency and number of visited alleys), using two non-parametric tests. The amount of similar trials for each test on both parameters were multiplied and expressed as a percentage to build simulation results matrices (Figure 49 a).

Model-based reinforcement learning, which relied on building a representation of the locations in the maze linked through the action leading from one to another, yielded poor similarity compared to the mice's behaviour (Figure 49 a, top). The set of parameters with the closest fit had a similarity score of 44% and agents did not learn the sequence (Figure 49 b, top). This model was however able to generate some individual variability, indeed 1.6 ± 0.2 agents reached the late stage learning criterion out of 20 replications of the best fitting set of parameters (Figure 49 c, top). In this version of the model, if an agent did a U-turn in a corridor and went back towards an intersection, it considered it to be a new maze part as there are no environmental cues to identify and recognize intersections. We also tested a version of the algorithm where agents detected they had retraced their steps and thus did not consider the intersections they returned to as a new area. This resulted also in a poor reproduction of the behavioral results (Supplementary Figure 3a, top), with the best set of parameters at a similarity score of 13% (Supplementary Figure 3b, top) and without any agents reaching the late stage learning criterion (Supplementary Figure 3c, top).

Model-free reinforcement learning relied on associating a given state of the environment (dead-end, corridor or intersection), the stimulus, to the most rewarding action. As there are no external cues in the environment, two successive intersections are indistinguishable. Indeed running this model leads to poor learning: the best parameter set gave a 54% similarity score and no agents reaching the late learning stage criterion

(Supplementary Figure 3a,b,c, bottom). Adding a short-term memory component of the three previous actions to the definition of the stimulus allowed distinguishing two consecutive intersections according to their order along a travelled path. This led to improved performance of the agents (Figure 49 a, middle). The best fit of parameters had a similarity score of 96% (Figure 49 b, middle), with only the number of visited alleys significantly different for the first trial, detected by both tests. When replicated 20 times, 4.5 ± 0.2 agents reached the late learning stage criterion (Figure 49 c, middle). This was significantly higher than with the model-based RL model (Mann-Whitney U, $p=0$).

In path integration, agents used travelled distance to evaluate the position of the goal relative to the starting position to then calculate the displacement vector from the starting position to the reward. For this model there is no discount factor (γ) but an error associated to the estimation of position (σ). With this model a set of parameter gave a similarity score of 80% (Figure 49 a, bottom). This set of parameter provided a good fit of the latency parameter (52/52 for each test) (Figure 49 b, bottom). However this model did not replicate individual variability: indeed, no agents reached the late learning stage criterion across the 20 replications (Figure 49 b, bottom).

We also represented the 10% of sets of parameters giving the highest similarity scores for all models in a graph representing the product of the scores obtained in each test for latency on the y axis and visited alleys on the x axis (Supplementary Figure 4). This showed that model-free RL with memory was the only model that had high scores in both parameters, latency and visited alleys.

Thus only model-free reinforcement learning model with memory reproduced the group learning dynamics in the triple Y-maze as well as the variability in learning rate amongst individuals.

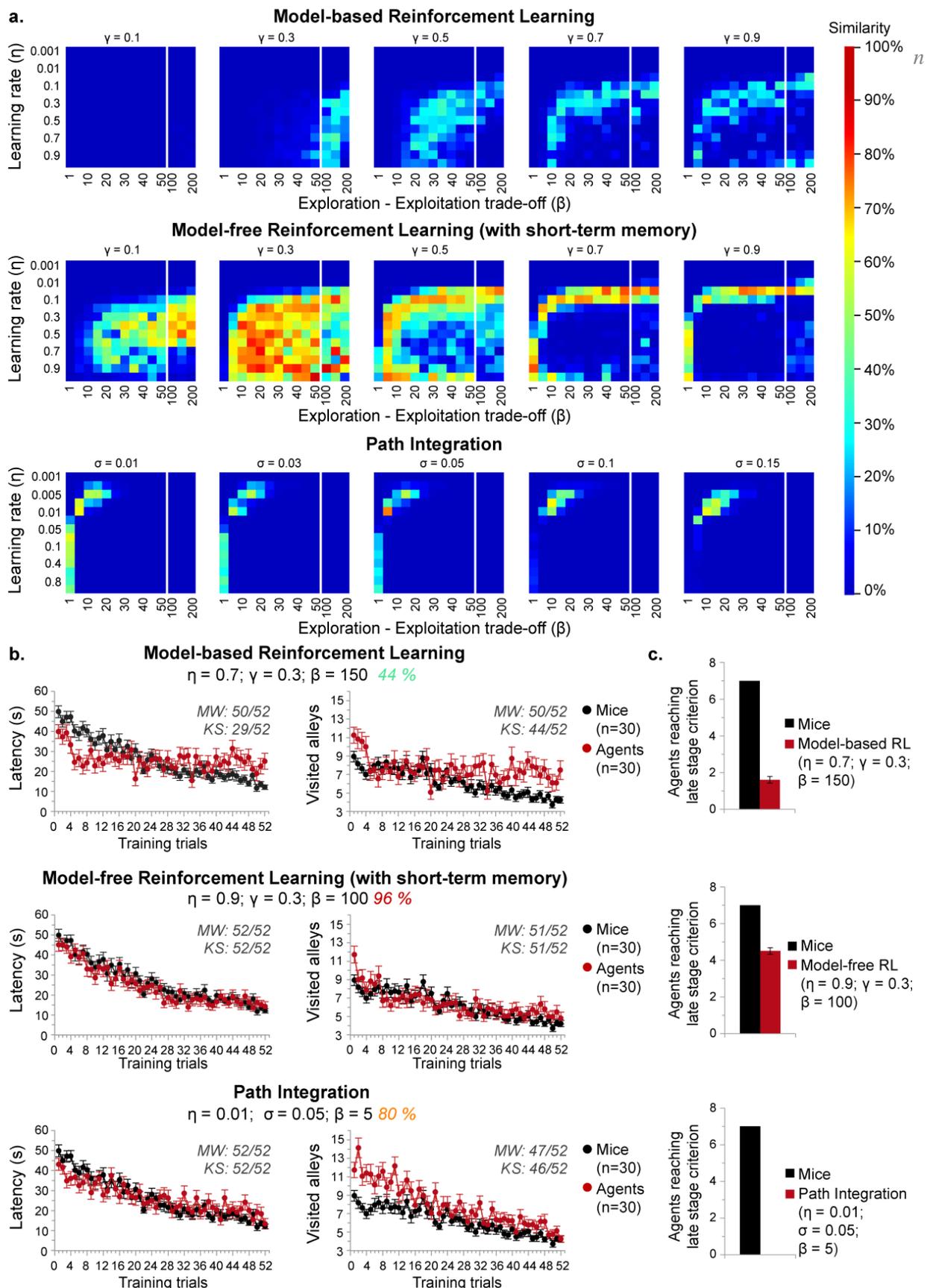


Figure 50: Only model-free reinforcement learning with memory reproduces group dynamics and individual variability. (a) Similarity scores obtained for the sets of parameters tested for each model are presented in matrices. The colour code indicates the similarity score. The learning rate (η) varies across the y axis, the exploration-exploitation trade-off (β) varies across the x axis and the discount factor (γ), or distance error (σ) for path integration, is fixed for each matrix. (b) Examples of the best fitting parameter sets for the different models are presented. Latency and visited alleys are plotted for the agents and the mice. For each parameter tested, the similarity scores obtained either with Mann-Whitney (MW) or Kolmogorov-Smirnov (KS) tests are given. The general score obtained for a given set of parameters is obtained by multiplying the different scores and expressed as a percentage in the same colour code as for the matrix. (c) Quantification of agents reaching late learning stage criterion for the set of parameters giving the best similarity score. Data represent mean \pm s.e.m.

4. Discussion

We investigated the neural circuits and the learning algorithm of sequence-based navigation in mice. The training took place in a triple Y-maze to learn a path of two turns in the absence of environmental cues. We used Fos imaging and graph theoretical approaches to describe the functional networks underlying the early and late learning stages of sequence-based navigation. The early learning stage engaged cortical, striatal, hippocampal and cerebellar regions. A major cortico-striatal cluster highly mutually correlated characterized the early stage network. Once the sequence of turns was well learned, fewer structures were activated but their network organization drastically changed: this network was marked by the appearance of multiple functional correlations involving dorsal hippocampal regions and cerebellar cortices with the cortical and striatal regions. Finally, our computational simulations showed that only a model-free reinforcement learning model, to which we added a memory component to the definition of the stimuli, could reliably reproduce the whole learning dynamics of mice.

In this discussion I will consider aspects closely related to the results presented in this paper. The hypothesis about the processes involved in the late learning stage, i.e. when the sequence is learned, will be discussed in details in the general discussion of this thesis, together with the computational model and the other studies performed on sequence-based navigation.

Fos activations observed in early and late learning sequence-based navigation stages

c-fos expression is known to be sensitive to stress (Tischmeyer & Grimm, 1999). A first experience in a water-maze may generate stress in mice. In order to limit *c-fos* expression related to discovering features of the task, the early stage mice and their controls performed a pre-training session in a two-alley corridor. Following this pre-training, early stage mice demonstrated an efficient search of the platform. Compared to the first session of the late stage mice, which did not have a pre-training session, the early stage mice travelled a shorter distance to reach the platform, despite swimming at a similar speed. The beneficial role of the pre-training session observed on mice's behaviour presumably allowed minimizing the contribution of swimming novelty in the early stage groups.

The comparison of Fos densities and correlation matrices between the early stage mice

and their paired swimming controls revealed no significant differences. What distinguished these groups was that: 1) the early stage group swam in the whole maze whereas the control mice returned to the corridor as in the pre-training session; 2) the configuration of the environment was different (number of alleys, intersections and presence of a platform). However these differences were not reflected in Fos densities and density correlations. We examined whether this could be due to a ceiling effect in *c-fos* expression, i.e. if Fos densities had reached a maximal level that did not allow detecting further increases. In a preliminary study, we compared Fos densities in a subset of regions between mice having swum one session in the triple Y-maze with or without a pre-training session. Mice that had not done a pre-training session had higher densities (data not shown), suggesting that we had not reached a maximum level in the early stage mice. The similar Fos densities between the early stage mice and their paired swimming controls suggested that we were observing a process common to both groups. Even though they had different purposes (i.e. sequence learning vs swimming controls), it is likely that at this early stage both groups were discovering task features (such as structure of the maze, task rule...), thus inducing equivalent Fos expression patterns.

To identify the structures specifically activated in the early stage, we thus compared these groups to the late stage swimming control mice, which had been swimming up to 6 days in the same environment. Their Fos expression was expected to control for Fos expression due to motor activity and general experimental set-up-related Fos expression but to allow detecting Fos expression related to novelty detection.

Amongst the structures activated during the early phase, the increased Fos density in the dorsal hippocampus is consistent with studies showing an increased Fos expression when rodents explore a new environment (Guzowski *et al.*, 1999; Guzowski *et al.*, 2001; Bourgeois *et al.*, 2012). This activity could reflect topographical information processing which has been shown to take place as early as the first trials in an environment (Alvernhe *et al.*, 2012).

Increased activations in cerebellar cortices compared to the swimming controls could relate to the sensory processing subtended by the cerebellum and participating in hippocampal place cell activity during open-field exploration (Rochefort *et al.*, 2011).

Medial entorhinal, parietal and retrosplenial cortices have been shown to perform navigation-related information processing with respectively grid cell and border cell activity (Fyhn *et al.*, 2004; Hafting *et al.*, 2005; Savelli *et al.*, 2008), egocentric motion cell activity (Whitlock *et al.*, 2012) and egocentric to allocentric reference frame transitions and *vice versa*

(Burgess *et al.*, 2001a; Byrne *et al.*, 2007; Vann *et al.*, 2009). Immediate-early gene and lesion studies have suggested that the granular retrosplenial cortex has a greater involvement in internally directed navigation whereas the dysgranular retrosplenial cortex seems more important for visually guided navigation (Vann & Aggleton, 2005; Pothuizen *et al.*, 2009). Only the granular region was significantly activated in the early stage (also in the late stage) compared to the swimming controls. The absence of environmental cues relevant for creating an allocentric representation of space may explain the absence of activation in dysgranular region.

The involvement of the different regions belonging to the reward circuit (VTA, nucleus accumbens and medial prefrontal cortex, including the prelimbic, infralimbic and cingulate region) (Haber & Knutson, 2009) has been previously shown during exploration of a novel environment (Wirtshafter, 2005; Bourgeois *et al.*, 2012). fMRI data in human have also implicated the substantia nigra/VTA system (Wittmann *et al.*, 2007; Krebs *et al.*, 2009), the nucleus accumbens (Krebs *et al.*, 2009) and the prefrontal cortex (Daffner *et al.*, 2000) (for review (Ranganath & Rainer, 2003)) in novelty exploration. It has been proposed that the reward system treats novelty as rewarding to promote exploration (Krebs *et al.*, 2009).

The activation of auditory cortex in the early stage was not expected. Indeed the white noise played in the room from evenly distributed loud speakers insured that sounds were not relevant for solving the task. This was confirmed by the absence of significant activation in the auditory cortex in the late stage group. However Arc mRNA expression, a synaptic plasticity effector immediate early gene (IEG), has recently been shown to be expressed in mice auditory cortex after having been exposed twice (with a 24h interval) to a new sound in the absence of explicit behavioural contingencies for the sound, similarly to the early stage mice (Ivanova *et al.*, 2011). Increased Fos density in the early stage mice may thus be due to the white noise.

During the late learning stage, most cortices and hippocampal regions maintained Fos densities at similar levels as during the early stage (except for the prelimbic and infralimbic which decreased slightly). In the striatum, only the dorsomedial area was significantly activated. This activation is consistent with previous work showing that sequence-based navigation learning required the dorsomedial striatum (Fouquet *et al.*, 2013), possibly by enabling goal-directed behaviour (Yin & Knowlton, 2006). In the cerebellum, the fastigial and interpositus deep nuclei were significantly activated in this stage, along with some of the cortices, namely lobule VI, VII and crus I, which however had lower densities in this stage

compared to the early stage. The specific engagement of deep nuclei with task mastery is consistent with motor sequence learning studies (Nezafat *et al.*, 2001; Doyon *et al.*, 2002).

More generally, the changes observed in structure activation across learning stages is consistent with results obtained in motor sequence learning studies in humans and theorized in several models (Hikosaka *et al.*, 2002; Doyon *et al.*, 2009; Penhune & Steele, 2012). These studies have shown that motor sequence learning can behaviourally be divided in two stages: an early stage where changes are rapid and a slow-learning stage where the task is mastered and during which movement timing, kinematics and dynamics are optimized (Karni & Sagi, 1993; Shadmehr & Brashers-Krug, 1997). Each learning stage has been associated to specific brain networks: it has been proposed that within cortico-striatal and cortico-cerebellar loops, the associative regions of these loops underlie the early stage and the motor regions of these loops underlie the late stage (Hikosaka *et al.*, 1999; Doyon & Benali, 2005; Penhune & Steele, 2012). Studies in rodents have also observed a change of networks across learning, in motor (Yin *et al.*, 2009), conditional T-maze (Thorn *et al.*, 2010) and spatial (Poirier *et al.*, 2008; Conejo *et al.*, 2010) tasks. Despite differences concerning the structures involved in each learning stages, the network dynamics across learning stages seem to be independent of the task's nature.

Whereas in human studies only the left hippocampus was involved in sequence-based navigation (Iglói *et al.*, 2010), no lateralization was observed in the mice in this study. In mice, left-right asymmetry in the hippocampus has been found in spines at CA3-CA1 synapses. According to the hemispheric origin of CA3 afferents, the CA3-CA1 synapses differ in glutamate receptor composition (Kawakami *et al.*, 2003; Shinohara *et al.*, 2008), resulting in different plasticities: left CA3 input produces more long-term potentiation at CA1 synapses than right CA3 input (Kohl *et al.*, 2011). However unilateral lesions of only left or right hippocampus in rats did not disrupt spatial memory, whereas bilateral lesion did (Poe *et al.*, 2000). The absence of left-right differences in Fos densities is consistent with the lesion study.

Fos imaging and functional connectivity analysis

Fos imaging allows doing global activity analysis to map multiple brain regions at the same time. Comparing densities between conditions allows identifying regions that are differentially activated across conditions. However evidence from physiological studies supports the idea that cognitive processes also depend on interactions among distributed neuronal populations and brain regions (Mcintosh, 1999; Bressler & Menon, 2010). Imaging-

based approaches can detect coordinated activity across distributed and spatially remote brain regions by computing interregional correlations. These allow identifying brain regions where *c-fos* expression co-varies across mice and which could therefore form functional components of a network (Wheeler *et al.*, 2013).

There are however drawbacks in the use of Fos imaging for global mapping.

Promoter-specific differences in regional and cellular expression may result in a non-uniform relationship between neural activity and *c-fos* expression across the brain. Such issues do not affect comparisons between groups performed within structures, but these regional differences in Fos signal magnitude may compromise inter-structure correlation analysis. However, it has been shown that correlation strength was not strongly influenced by Fos signal (Wheeler *et al.*, 2013). Moreover, in our study, global Fos levels were higher in the early stage group compared to the late stage group, but the amount of significant correlations at a p level of 0.01 was the same. It is thus unlikely that the networks were affected by regional difference in *c-fos* expression.

Another issue is whether networks based on different activity markers may differ from one another. In Wheeler *et al.* (Wheeler *et al.*, 2013), the authors compared networks obtained with another IEG, *Zif268/egr1*. While there were some regional differences in *Zif268/egr1* and Fos expression following fear memory recall, a difference also shown in other studies (Guzowski *et al.*, 2001; Maviel *et al.*, 2004), the patterns of inter-regional correlations derived from *zif268/egr1* vs. Fos expression were very similar (Wheeler *et al.*, 2013). The robustness of network organization across different IEGs in expression further strengthens the use of network analysis.

The functional connections in the networks reflect statistical rather than physical relationships between regions. However, some correlations reflect known anatomical connections but most importantly some correlations observed with Fos, which requires sustained neural activity to be expressed, have also been shown in electrophysiological studies. For example, in spatial tasks, coordinated activation has been shown between the hippocampus and prefrontal cortex (Jones & Wilson, 2005; Benchenane *et al.*, 2010) and also between the hippocampus and ventral striatum (Lansink *et al.*, 2009). Correlation between the hippocampus and the cerebellum (HVI region specifically) has also been observed in rabbits, in a hippocampal-dependent version of the eye blink conditioning task (Hoffmann & Berry, 2009; Wikgren *et al.*, 2010).

Thus, together with multiple site LFP recordings (Chapuis *et al.*, 2009), IEG imaging

techniques help getting a more global picture of the functioning of multiple brain regions during a given cognitive process.

Functional networks in swimming control, early and late stage mice

The correlation analysis performed on the late stage swimming control groups revealed few functional correlations, but this network shared similarities with both the early and the late stage networks.

The presence of correlations between cortical areas and the dorsomedial striatum, leading to a cortico-dorsomedial striatum cluster, was reminiscent of the cortico-striatal cluster of the early stage mice. Similarly to the early stage mice, this cluster contained cortices related to decision-making (prelimbic and cingulate) and cortices more related to spatial information processing (parietal and retrosplenial). However the number of correlations was considerably reduced.

Similarly to the late stage mice, there were correlations between cortical and cerebellar regions. Yet once again their number was reduced in the control group and they did not concern the same pairs.

The functional connectivity analysis in the early stage group revealed that together with the parietal and retrosplenial cortices, the striatal and cortical reward circuit regions belonged to the same cluster and were highly mutually inter-correlated. Interestingly, the organization of the significant correlations amongst cortical and striatal regions were reminiscent of the cortico-striatal anatomical connections (Voorn *et al.*, 2004).

The network organization of the late stage was characterized by a major involvement of hippocampal and cerebellar correlations with the rest of the network. This resulted in the identification of a cluster involving cortical, striatal, hippocampal and cerebellar regions. Illustrating the considerable involvement of hippocampal and cerebellar regions in the network, the dorsal CA1 and the lobule IV/V were both identified as hubs of the network. This suggests that these regions may play important roles in the transfer of information within the network thus influencing overall network function (Power *et al.*, 2013; Wheeler *et al.*, 2013). Consistently, impairing plasticity in the dorsal CA1 has been shown to prevent mice from learning sequence-based navigation (Rondi-Reig *et al.*, 2006).

During this phase, some structures have correlated activity despite absence of significant activation relative to controls (e.g. the lobule IV/V). This feature has previously

been observed (Wheeler *et al.*, 2013). That a given structure's activity albeit reduced in magnitude remains tightly coupled with activity in other activated regions suggests that it also plays a role, a feature which would not have been captured without functional connectivity analyses.

The lobules IV/V, VI and hemispheres HVI and Crus I were correlated to each other and always belonged to one cluster in all three behavioural groups. The Fos densities in these four regions were not the same between the three experimental groups, however their tendency to be correlated and to belong to the same cluster suggests they may subserve the same function in all three groups. In a motor sequence learning study in humans, the activity of lobules IV-V and ipsilateral lobule VI (to the hand doing the sequence) was modulated by performance during sequence learning and non-sequence learning in control conditions, suggesting the primary contribution of these areas to sensory processing and motor implementation (Orban *et al.*, 2010). Activity in the contralateral lobule VI was however strongly correlated with learning the sequence specifically, thus participating to the cognitive implementation of the sequence (Orban *et al.*, 2010). I did not separate the lobules in left or right hemispheres thus Fos density in lobule VI likely reflects both processes. This dual activity could explain the finding of a similar cerebellar cluster in all three conditions, and also its specific increase in functional connectivity when mice were performing sequence-based navigation.

The contributions of the different regions to sequence-based navigation will be further discussed in the general discussion of this thesis.

Computational analysis of sequence-based navigation learning

Three families of models were tested to see whether one, or several, could reproduce the mice's learning dynamics of sequence-based navigation. Two versions of a model-based reinforcement learning (RL) (with or without the ability to recognize intersections they went back to during a trajectory), two versions of a model-free RL model (with or without a retrospective memory defining stimuli) as well as path integration were tested. The sequential nature of this navigation, which is supported by the hippocampus (Rondi-Reig *et al.*, 2006; Fouquet *et al.*, 2013), suggested that a model-based RL underlied sequence-based navigation (Arleo & Rondi-Reig, 2007). However, none of the model-based RL model versions was able

to replicate the groups learning dynamics. In the version without memory, some agents were able to learn the sequence (Figure 49c, top) but the group dynamics could not be reproduced. The model's performances were either much better than the mice (i.e. a plateau at the best level of performances was reached by all agents within the first two days) or much worse (a plateau was attained at a poor level of performances, e.g. Figure 49b, top). Path integration models had the opposite behaviour: we found one set of parameters that could reproduce the group's behaviour, but no agents actually reached the late learning stage criterion. The group of mice modelled contained mice that had reached the learning stage criterion and some which had not. Thus the groups mean level was intermediate (black curves Figure 49). With the set of parameters that reproduced the group's behaviour in path integration, all agents performed at this mean level, i.e. increasing their performances but slowly and all at similar rates, resulting in a good group fit. Finally, the model-free RL model, to which a retrospective memory of the actions performed was added to the definition of the stimulus, was the only one to reproduce accurately both the group's dynamics and the individual variability. Moreover, a good fit was obtained across a range of parameter values, suggesting that this result was robust to variations in parameters value and was not obtained by chance. The retrospective memory load was required to differentiate parts of the maze, which are otherwise similar according to an egocentric viewpoint.

These results suggest that mice learning sequence-based navigation in the triple Y-maze did not use a representation of the organization of the maze (corresponding to a world model) nor did they use path integration to directly compute a vector towards the platform. Rather these results suggest that they used a mechanism to distinguish the intersections (here modelled as a retrospective memory load) to then learn stimulus-response associations to reach the platform.

The structures that could support this model as well as the memory of the previous actions will be discussed in the general discussion.

5. Supplementary material

Supplementary Methods

For both model-based and model-free algorithms, the sensory inputs I encoded the local shape of the maze and could take three different values $\{I, u, Y\}$, respectively corresponding to corridors, dead-ends and Y intersections.

As the triple Y-maze is part of the starmaze, a pentagon, the three angles of the Y intersections are not equal: for each Y intersection, the interior angle of the pentagon equals 108° and the two exterior angles equal 126° . We however hypothesized that mice were not able to distinguish these differences due to their poor visual acuity (Prusky *et al.*, 2000) and did not define different states for the Y-intersections depending on the alley the mice entered the intersections.

Concerning action selection, four actions were defined $\{F, L, R, U\}$, corresponding to going forward, turning left, turning right and doing a U-turn. We supposed that mice, and thus agents, already knew that bumping into walls was not an interesting behaviour; thus, during action selection, in each of the models, were considered only the actions for which openings were available.

1. Model-based algorithm

The model-based algorithm gradually built, by exploration, an internal representation of the states encountered and of the transition probabilities between states (i.e. the probabilities that in a given state, a given action will lead to another given state). The internal representation was thus a graph, in the computer science meaning of the term: a set of nodes (referring to the perceptual states) linked by arcs (the actions allowing to reach a given new state from a given starting state).

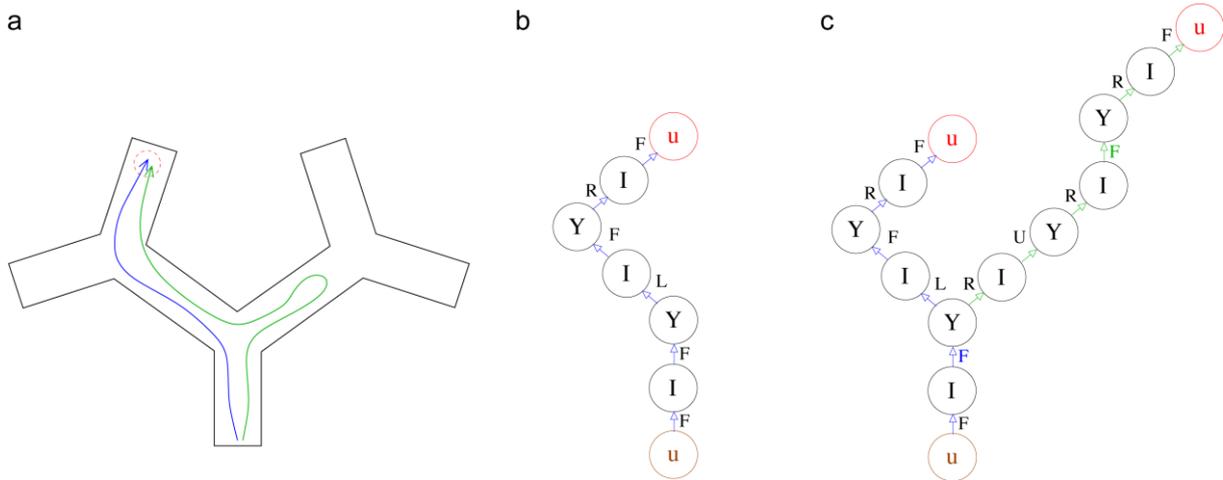


Figure 1: Model based algorithm internal representation. (a) Two trajectories experimented in the maze. (b) Internal graph built after the execution of the blue trajectory. (c) Updated graph after the execution of the green trajectory. The node in brown is the initial state, nodes in red are those where reward has been obtained ($R=1$), the colour of transitions indicates during which trajectory they were created, and is strictly illustrative.

The states were based on the sensory inputs only, they were thus ambiguous as many different positions in the maze generated the same perception. Still, the states were disambiguated by their position in the graph. For example, in the blue trajectory presented in Figure 1a, three identical corridors (I) were experienced and thus stored in the internal graph (Figure 1b), the first one was reached by choosing the F action from the initial state, the second one was reached after a F-F-L sequence of actions, and the third one with the F-F-L-F-R sequence.

Note that no backtracking memory was implemented, so that, when one agent made a U-turn, it was not aware that it may afterward go back to a previously experienced node (in Figure 1c, the green trajectory experienced after the blue one led to the addition of a new branch, with another reward node, while these two nodes corresponded to the same place in the maze). The main reason for doing so was that giving this backtracking ability would have required the agent to store the whole choice history of the current trajectory, so that when it went back to a previously encountered Y intersection, it could compute that if that Y was previously left from a R choice, then choosing L would have brought it back to the previously explored corridor, while choosing R would have led to a new branch of the graph.

When beginning the maze task, the agent considered that it always started from the same node N_0 (in brown in Figure 1). Any subsequently chosen action could either lead it to a newly experienced node, in which case a new node and a new transition had to be added to the graph, or to a previously explored node, in which case the transition only had to be updated.

When the agent left a node N_k and tried an action a_i never tried before, then a new node N_{m+1} had to be added to the m currently known nodes. If the new node contained the platform, the information that reward was available in that node was stored ($R(N_{m+1}) = 1$), otherwise $R(N_{m+1})$ was set to 0. A new transition was also created:

$$T(N_k, a_i, N_{m+1}) = \eta$$

Otherwise, the transition probability that from node N_k , action a_i led to node N_{m+1} was strengthened as follows:

$$T(N_k, a_i, N_{m+1}) \leftarrow T(N_k, a_i, N_{m+1}) + \eta(1 - T(N_k, a_i, N_{m+1}))$$

The parameter η was thus the learning rate of the transitions.

Using the current representation of the task (the set of nodes N and the set of transitions T), the agent could evaluate the value of choosing a given action in the current state. It was done by propagating the reward information in the graph to attribute to each state a value V depending on its distance to the rewarded states, using a constant discount factor γ . This propagation, known as value iteration, consisted in repeating the following operation over all the nodes, until convergence:

$$V(N) \leftarrow \max \left(R(N), V(N), \max_i (\gamma T(N, a_i, N') V(N')) \right)$$

Action selection was performed by computing for the current node N_k the value $Q(N_k, a_i)$ of each action a_i , which was either 0 if the action had never been tried, or $\gamma T(N, a_i, N') V(N')$, with N' the node which was attained when choosing a_i . The final selection was then made by drawing in the probability distribution defined as a softmax of the Q-values:

$$P(N_k, a_i) = \frac{e^{\beta Q(N_k, a_i)}}{\sum_j e^{\beta Q(N_k, a_j)}}$$

This model was thus characterized by three parameters:

1. η the learning rate of the transitions,
2. γ the discount factor of the value iteration process,
3. β the exploration/exploitation trade-off of the softmax action selection.

2. Model-free algorithm

The model-free algorithm used was the standard *actor-critic*, from the TD-learning family. Its only specificity was to consider states S resulting from the concatenation of the sensory input I , with a memory of the n past performed actions:

$$S^t = (I^t, a^{t-1}, \dots, a^{t-n})$$

with $I^i \in \{I, u, Y\}$ and $a^i \in \{F, L, R, U\}$.

The critic component of the algorithm learnt to evaluate the value $V(S^t)$ of a given state S^t , while the actor learnt to attribute the value $p(S^t, a)$ of choosing action a in state S^t . All V and p were initialized to 0.1. The V and p values were then updated using the reward prediction error δ , where r^t is the reward delivered at time t :

$$\delta^t = r^t + \gamma V(s^{t+1}) - V(s^t)$$

in the following manner:

$$\begin{aligned} V(s^t) &\leftarrow V(s^t) + \eta \delta^t \\ p(s^t, a^t) &\leftarrow p(s^t, a^t) + \eta \delta^t \end{aligned}$$

Action selection was performed by drawing in the distribution resulting from a softmax applied to $p(s, a)$:

$$P(s, a_i) = \frac{e^{\beta p(s, a_i)}}{\sum_j e^{\beta p(s, a_j)}}$$

This model was thus characterized by four parameters:

1. n , the size of the action memory,
2. γ the discount factor on future reward value,
3. η the learning rate of the actor and critic,
4. β the exploration/exploitation trade-off of the softmax action selection.

3. Path integration

The path integration maintained at every time step t an estimation of the position $P^t(Pos)$ of the agent during its displacements with regards to its departure point. It also maintained an internal estimation of the position of the goal $P(Goal)$ which was updated every time the goal was encountered. Using these two distributions, a distribution of the directions $P^t(Dir)$ leading most probably to the goal was computed, and used to select the next action.

$P^t(Pos)$ was modelled as a gaussian 2D distribution, centered on the current position of the agent in the environment. To model the accumulation of errors intrinsic to path integration processes, its standard deviation increased at each time step:

$$P^t(Pos) = N(\mu = (x(t), y(t)), \sigma = \sigma_0 t)$$

$P(Goal)$ was initially a uniform distribution over the 2D space, which was updated as

follows every time the goal was attained, using the current estimation of the position $P^t(Pos)$:

$$P(Goal) \leftarrow (1 - \eta)P(Goal) + \eta P^t(Pos)$$

Finally, for any direction α , $P^t(Dir = \alpha)$ was:

$$P^t(Dir = \alpha) = \frac{\sum_{(Pos, Goal) \in D^\alpha} P^t(Pos) \times P(Goal)}{\sum_{(Pos, Goal)} P^t(Pos) \times P(Goal)}$$

with

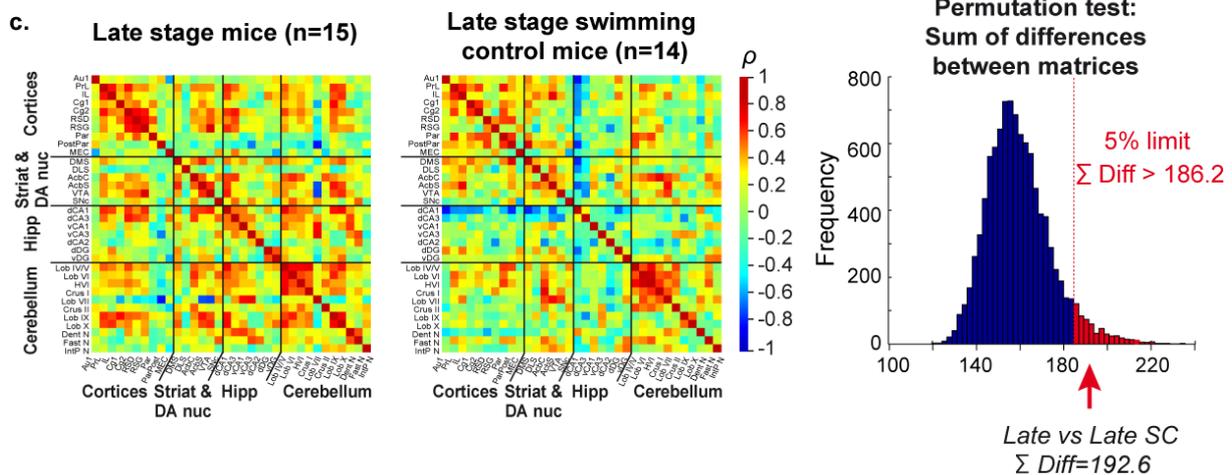
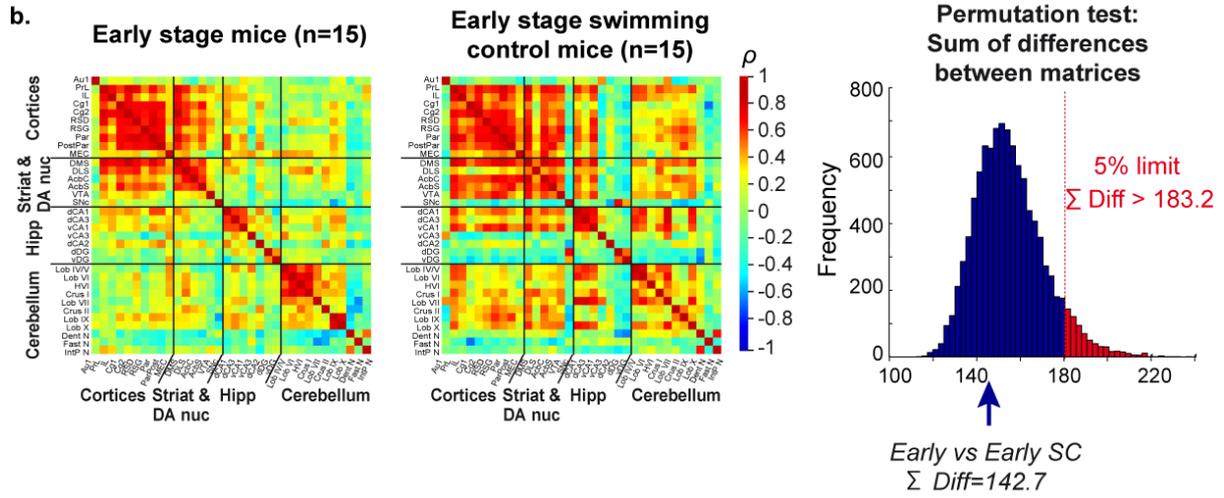
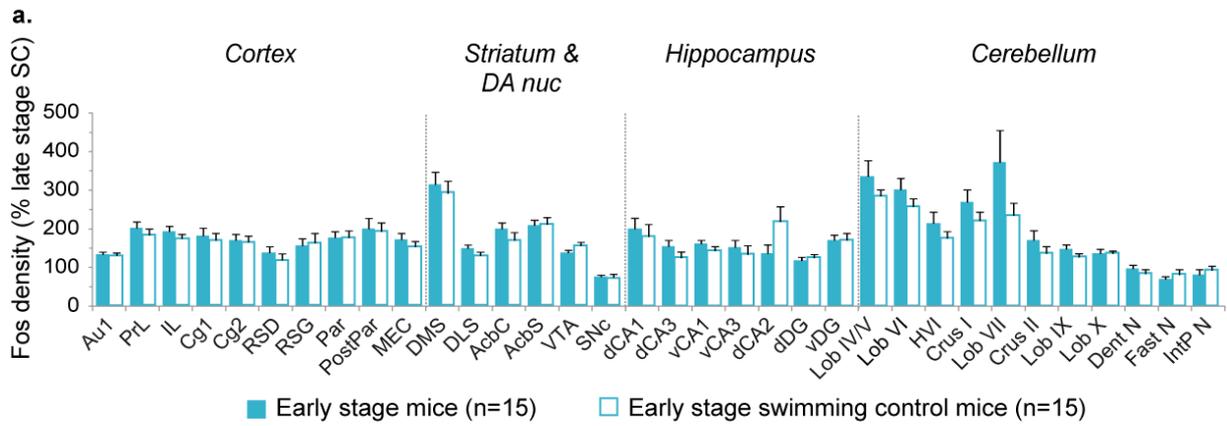
$$D^\alpha = \{(Pos, Goal) | \text{atan2}(Goal - Pos) = \alpha\}$$

Action selection was performed by drawing in the distribution resulting from a softmax applied to $P^t(Dir)$:

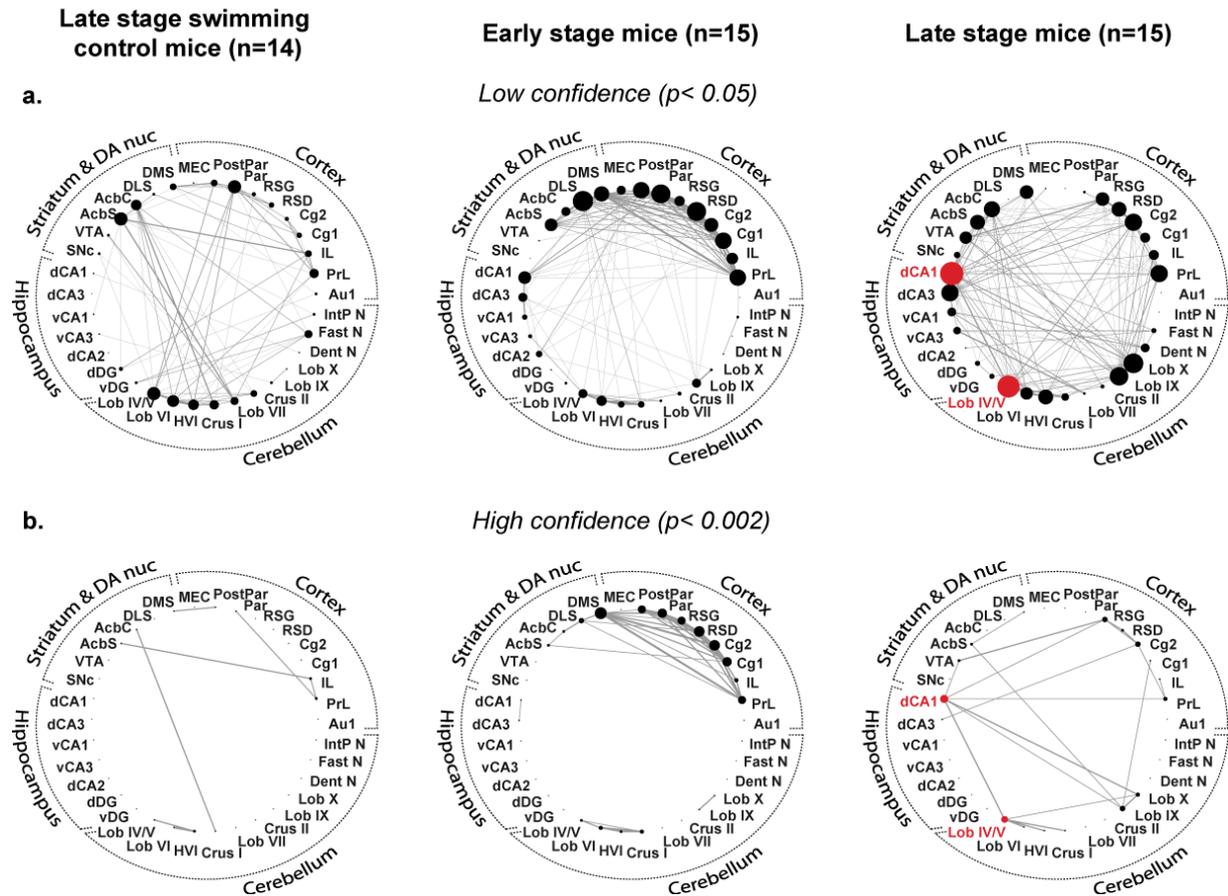
$$P^t(a_i) = \frac{e^{\beta P^t(Dir=a_i)}}{\sum_j e^{\beta P^t(Dir=a_j)}}$$

This model was thus characterized by three parameters:

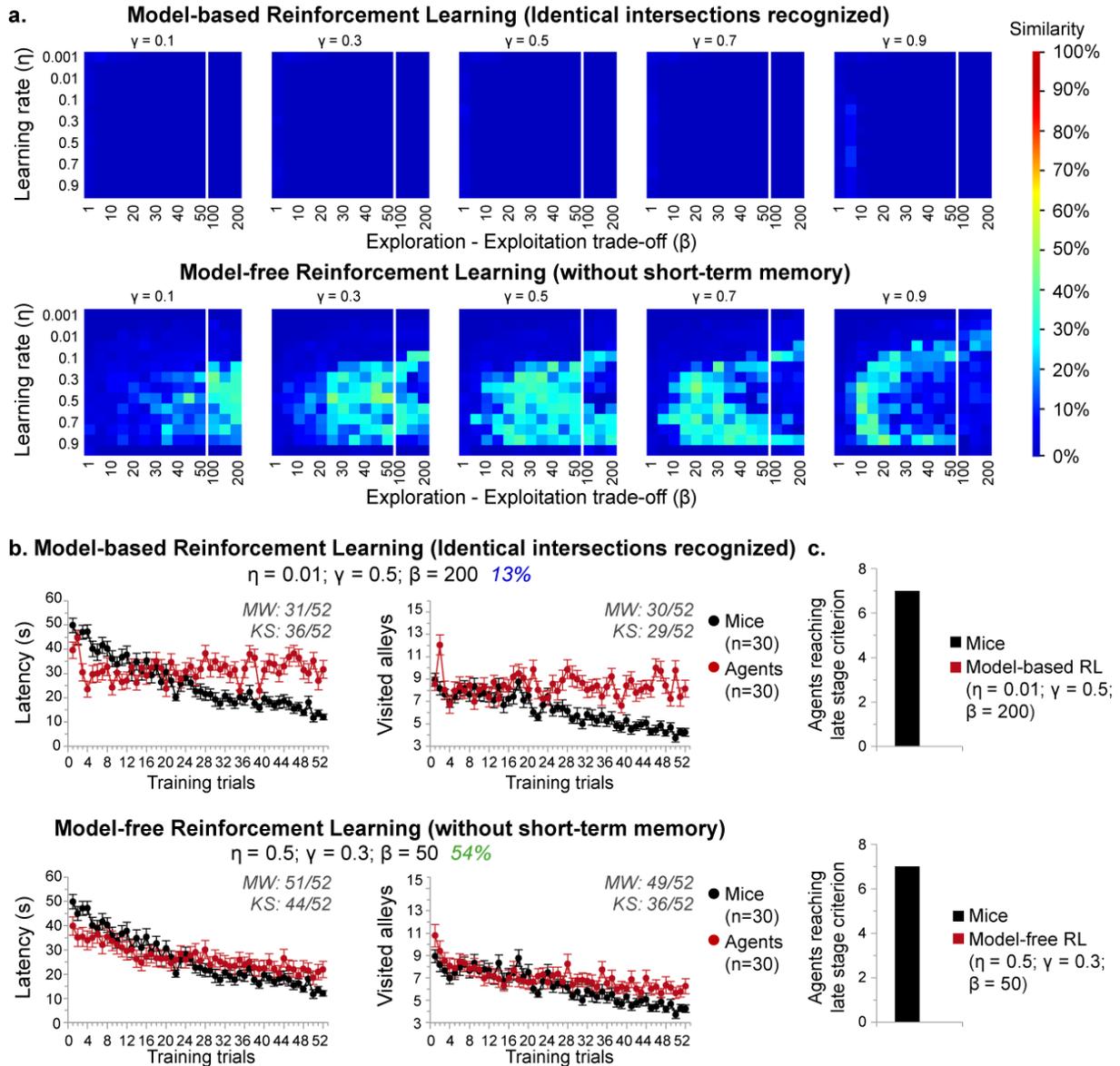
1. σ_0 , which characterizes error accumulation in position estimation,
2. η the learning rate of the goal position estimation,
3. β the exploration/exploitation trade-off of the softmax action selection.



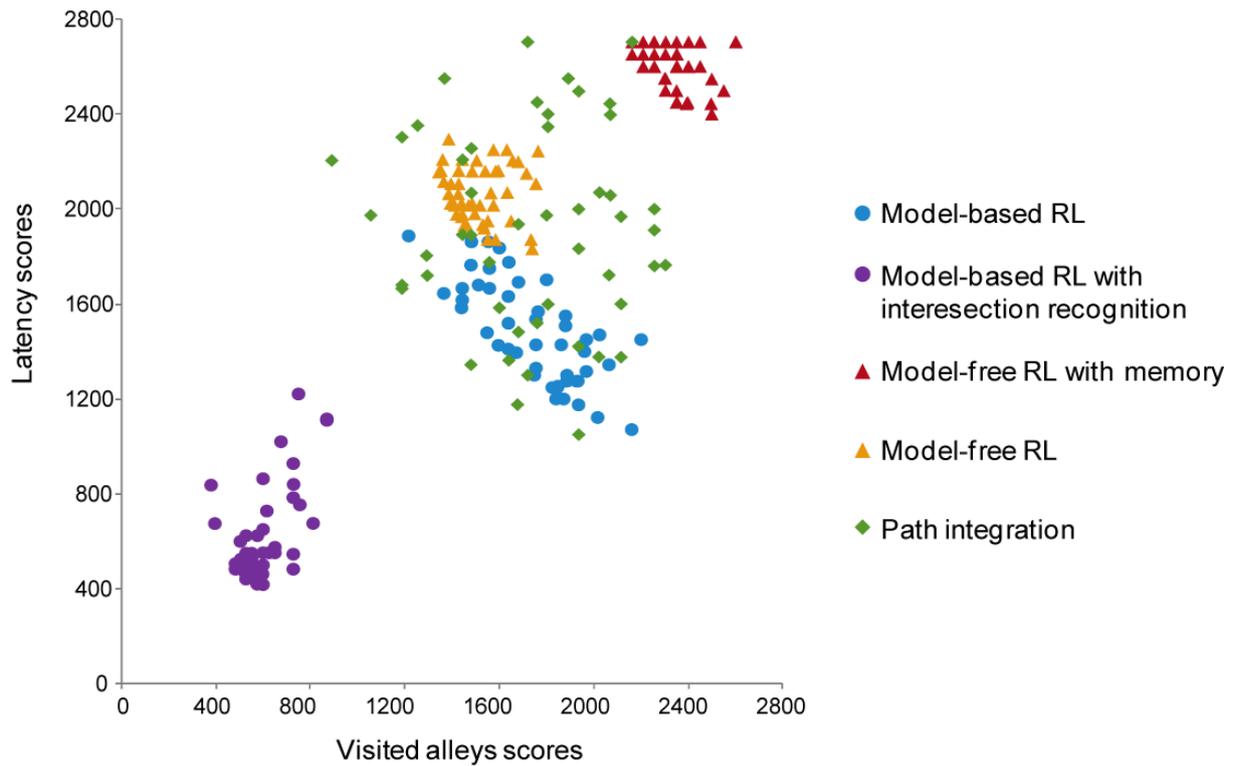
Supplementary Figure 1: Early stage and early stage control mice analysis. (a) Fos densities for early stage and early stage swimming control mice. No differences were observed in Fos densities between the early stage mice and their swimming controls, despite swimming in two different shaped mazes, with or without a platform (respectively). (b) **Permutation test on early stage mice.** Within the 30 early stage mice and their swimming controls, two groups of 15 subjects were resampled 10000 times and the correlation matrices were calculated each time. For each permutation, the sum of differences between the two resampled correlation matrices was calculated. The 95th percentile was calculated by ranking the 10000 resampled sums of differences. The sum of differences between the early and early swimming control stage matrices was 142.7, inferior to the 95th percentile of resampled pairs of matrices (corresponding to a one-tailed significance level of $p > 0.05$) thus the two matrices were not significantly different. (c) **Permutation test on late stage mice.** For the late and late stage swimming controls, the sum of difference between the two original matrices was superior to the 95th percentile of 10000 resampled pairs of matrices thus the two matrices were significantly different.



Supplementary Figure 2: Low and high confidence networks of spatio-temporal sequence learning. Network graphs were generated by thresholding inter-regional Fos correlations in mice using either a low confidence threshold of $r \geq 0.53$ (corresponding to a two-tailed significance level of $p < 0.05$ for $n=14$, $p < 0.04$ for $n=15$) (A) or a high confidence threshold of $r \geq 0.75$ (corresponding to a two-tailed significance level of $p < 0.002$ for $n=14$, $p < 0.0012$ for $n=15$) (B). Regions are grouped by major brain subdivision and node size is proportional to the number of connections (degree) while the width of the connection is proportional to correlation strength. The hubs are highlighted in light red (late stage swimming controls) or red (late stage).



Supplementary Figure 3: Analysis for model-based reinforcement learning with no recognition of intersection and model free reinforcement learning without memory. (a) Similarity scores obtained for the sets of parameters tested for each model are presented in matrices. The colour code indicates the similarity score. The learning rate (η) varies across the y axis, the exploration-exploitation trade-off (β) varies across the x axis and the discount factor (γ), or distance error (σ) for path integration, is fixed for each matrix. (b) Examples of the best fitting parameter sets for the different models are presented. Latency and visited alleys are plotted for the agents and the mice. For each parameter tested, the similarity scores obtained either with Mann-Whitney (MW) or Kolmogorov-Smirnov (KS) tests are given. The general score obtained for a given set of parameters is obtained by multiplying the different scores and expressed as a percentage in the same colour code as for the matrix. (c) Quantification of agents reaching late learning stage criterion for the set of parameters giving the best similarity score. Data represent mean \pm s.e.m.



Supplementary Figure 4: Best 10% sets of parameters for each model. Each parameter set is plotted with the product of the scores obtained with the two non-parametric tests (Mann-Whitney and Kolmogorov-Smirnov) for visited alleys on the x-axis and for latency on the y-axis. If both scores were at the maximum, 52, their product equals 2704. Model-based reinforcement learning with interesection recognition reproduced badly latency and number of visited alleys of the mice. Path integration and model-free reinforcement learning better reproduced the latency than the number of visited alleys. The contrary was observed for model-based reinforcement learning. Only model-free reinforcement learning with a memory of the last events reproduced well both latency and number of visited alleys of the mice.

		Kruskall-Wallis on late stage mice learning in 3 (n=7), 4 (n=5) or 5 (n=3) days	
		Travelled distance	Swimming speed
First training day	First session	p=0,770	p=0,934
	Second session	p=0,124	p=0,437
	Third session	p=0,910	p=0,310
	Fourth session	p=0,845	p=0,490
Last training day (day d)	First session	p=0,526	p=0,617
	Second session	p=0,256	p=0,580
	Third session	p=0,702	p=0,754
	Fourth session	p=0,871	p=0,754
Session before sacrifice (day $d+1$)		p=0,991	p=0,845

Supplementary Table 1: Behavioral parameters of the late stage group. Travelled distance and swimming speed were compared between the mice learning in 3, 4 or 5 training days on the 4 sessions of day d when they achieved over 75% success rate and during the session on the following day before being sacrificed (day $d+1$). Whether mice learned the sequence in 3, 4 or 5 days, there was no difference in distance and speed when their level of task mastery was equivalent.

Structures	Kruskal-Wallis on Early, Early SC, Late and Late SC	Mann-Whitney U-tests			
		Early vs Early SC	Early vs Late SC	Late vs Late SC	Early vs Late
	p	p	p	p	p
Au1	0,019	0,934	0,008	0,020	0,534
PrL	0	0,507	0,000	0,005	0,008
IL	0	0,407	0,000	0,017	0,001
Cg1	0,004	0,772	0,002	0,077	0,106
Cg2	0,002	0,803	0,005	0,001	0,561
RSD	0,084				
RSG	0,026	0,934	0,012	0,002	0,619
Par	0	0,934	0,000	0,001	0,407
PostPar	0,001	0,879	0,003	0,000	0,678
MEC	0,001	0,384	0,000	0,198	0,107
DMS	0	0,648	0,000	0,000	0,000
DLS	0	0,213	0,000	0,156	0,008
AcbC	0	0,213	0,000	0,810	0,000
AcbS	0	0,803	0,000	0,183	0,000
VTA	0	0,115	0,004	0,616	0,002
SNc	0,27				
dCA1	0,007	0,534	0,001	0,014	0,263
dCA3	0,022	0,245	0,005	0,012	1,000
vCA1	0,001	0,245	0,000	0,093	0,062
vCA3	0,003	0,097	0,020	0,002	0,407
dCA2	0,086				
dDG	0,116				
vDG	0	0,590	0,000	0,810	0,001
Lob IV/V	0	0,340	0,000	0,111	0,000
Lob VI	0	0,199	0,000	0,002	0,000
HVI	0	0,300	0,001	0,445	0,005
Crus I	0	0,263	0,000	0,042	0,016
Lob VII	0	0,221	0,000	0,035	0,039
Crus II	0,015	0,281	0,014	0,913	0,011
Lob IX	0,005	0,300	0,005	0,981	0,017
Lob X	0,001	0,967	0,004	0,844	0,013
Dent N	0,106				
Fast N	0,001	0,678	0,198	0,015	0,000
Interpos N	0,002	0,213	0,419	0,005	0,001

Supplementary Table 2: Detailed results of Fos densities comparison across groups. P levels inferior to 0.05 are highlighted in red.

ANCOVA analysis Effect of mean travelled distance on Fos densities, with group type as co-factor		
Structures	F	p
Au1	2,93	0,093
PrL	0,06	0,802
IL	0,12	0,728
Cg1	0,47	0,496
Cg2	0,02	0,898
RSD	0,92	0,342
RSG	0,00	0,954
Par	0,01	0,905
PostPar	1,17	0,285
MEC	1,29	0,261
DMS	0,16	0,688
DLS	2,19	0,145
AcbC	0,29	0,590
AcbS	0,04	0,834
VTA	0,08	0,776
SNc	0,10	0,754
dCA1	1,72	0,196
dCA3	0,32	0,571
vCA1	0,00	0,982
vCA3	0,02	0,883
dCA2	0,04	0,849
dDG	0,09	0,762
vDG	0,00	0,963
Lob IV/V	0,01	0,930
Lob VI	0,01	0,933
HVI	0,17	0,685
Crus I	0,00	0,946
Lob VII	1,61	0,211
Crus II	0,09	0,759
Lob IX	2,50	0,120
Lob X	0,39	0,533
Dent N	0,04	0,837
Fast N	0,01	0,910
Interpos N	0,45	0,505

Supplementary Table 3: Detailed results of the ANCOVA analysis run to test the effect of travelled distance on Fos densities. Early, Early SC, late and late SC mice were grouped in this analysis, using the group type as a co-factor. Here are indicated the effect of distance on Fos densities without the group type effect. P levels inferior to 0.05 are highlighted in red.

***GENERAL
DISCUSSION***

My PhD has been focused on sequence-based navigation. Using Fos imaging, lesion studies, network analysis and computational learning, I have contributed to characterizing the way a path composed of a sequence of turns is learned. In this discussion, I shall review the early and recent studies on sequence-based navigation along with my results.

1. Hippocampus and sequence-based navigation

When a subject learns a path composed of a sequence of turns, the use of sequence-based navigation in the star-maze task is revealed by changing the departure point and observing that the subject repeats the sequence of movements, even if these movements are now performed in different places relative to the surrounding environment (Rondi-Reig *et al.*, 2006; Igloi *et al.*, 2009). Thus sequence-based navigation does not rely on the use of a spatial map of the environment. Even though its detection is similar to the detection of a stimulus-response association in a cross-maze task, being based on the reproduction of a sequence of movements (Tolman *et al.*, 1946; Packard & McGaugh, 1996), it specifically relies on the ability to distinguish *multiple locations spatially distinct* and to organize them temporally to perform the correct sequence of turns (Rondi-Reig *et al.*, 2006; Igloi *et al.*, 2009).

Sequence-based navigation was initially developed with regard to the relational theory of the **hippocampus** in the organization of information (Eichenbaum, 1999) to test whether the memorization of a **sequence of turns** involved the hippocampus. Rondi-Reig *et al.* showed that sequence-based navigation in mice required an intact hippocampus, whereas learning one stimulus-response association for a simple egocentric strategy did not (Rondi-Reig *et al.*, 2006). The same mice (NR1-KO) were also impaired in a “forced sequential egocentric version” of the task where mice were taught a path composed of two turns without environmental cues (Rondi-Reig *et al.*, 2006). These results confirmed the role of the hippocampus in relational learning, but they also put forward the specific nature of sequence-based navigation as being different from a single stimulus-response association by requiring the hippocampus, contrary to the results obtained in a cross-maze task (Packard & McGaugh, 1996). It was proposed that the hippocampus, and more specifically NMDAR-dependent mechanisms in the **dorsal CA1** area of the hippocampus, would be necessary for organizing temporally the three turns along the path (Rondi-Reig *et al.*, 2006).

This role of the hippocampus in temporal order memory is consistent with lesion experiments which showed that the dorsal CA1 was necessary for learning the temporal order

of objects (Hoge & Kesner, 2007; Hunsaker *et al.*, 2008) and spatial locations (Hunsaker *et al.*, 2008), as well as with electrophysiology recordings of CA1 place cells demonstrating that they encode retrospective and prospective information (Frank *et al.*, 2000; Ferbinteanu & Shapiro, 2003) as well as sequence representation during replay events (Lee & Wilson, 2002).

Using this task in virtual reality with **humans**, functional imaging studies also revealed an activation of the hippocampus when subjects were using sequence-based navigation (Iglói *et al.*, 2010). Interestingly, it was specifically the **left hippocampus** which was activated whereas the right one was activated when subjects used the map-based allocentric strategy.

In human, studies have revealed distinct roles for left and right hippocampi in spatial memory. Imaging studies have demonstrated that the right hippocampus in humans plays a more substantial role in spatial navigation (see for review (Burgess *et al.*, 2002)). For example, the right hippocampus is preferentially activated when an internal representation of the environment is needed, but not when navigation can be achieved by following a trail (Hartley *et al.*, 2003). By contrast, when task demands are changed to require the spatial contextual retrieval of episodic memory, it is the left hippocampus which shows greater relative activation (Burgess *et al.*, 2001b). Further the left hippocampus is involved while mentally navigating along a previously learnt route (Ghaem *et al.*, 1997) and in detecting sequence novelty (Kumaran & Maguire, 2007). The imaging results are also consistent with a study conducted on left and right medial temporal lobe damaged patients. This study reported that left medial temporal lobe patients were more impaired on context-dependent episodic memory tasks whereas right medial temporal lobe patients were more impaired in topographical memory (Spiers *et al.*, 2001).

Iglói *et al.*'s findings fit the distinction between right and left hippocampi, with the right hippocampus involved in the associations of spatial stimuli to create an allocentric representation of space and the left hippocampus involved in spatiotemporal associations between multiple events to constitute an episodic memory (Iglói *et al.*, 2010).

2. Model-free reinforcement learning with memory and sequence-based navigation

The involvement of the hippocampus in sequence-based navigation was consistent with the proposed learning processes underlying “route learning” (O'Keefe & Nadel, 1978;

Redish, 1999; Arleo & Rondi-Reig, 2007). Indeed these authors have proposed that routes are learned as a chain of stimulus-response-stimulus associations which allow the navigator to predict the next stimulus based on the current stimulus-response association. Such learning can be modelled by a model-based reinforcement learning algorithm where a *model of the world* is built by organizing the different parts of the maze in the hippocampus (for review see (van der Meer *et al.*, 2012)).

We directly tested the hypothesis that a model-based reinforcement learning model could replicate mice's behaviour learning sequence-based navigation, but it failed to do so. Interestingly, a **model-free reinforcement learning model** was able to replicate both the group's learning dynamics and the individual variability observed in the mice. However a classical model-free algorithm, with the state being defined as the current egocentric perception of the maze (a corridor, an intersection, a dead-end) was associated to a particular action, failed to reproduce the mice's behaviour in our task. In such conditions, the agents improved their performance but could not learn the sequence of turns as the different intersections are identical with regards to an egocentric perception. However adding a mechanism to distinguish the intersections, here the **memory of the last actions performed**, allowed a model-free reinforcement learning system to replicate the mice's behaviour. The amount of actions to be remembered must be sufficient to distinguish the intersections when performing the correct sequence. When being at the second intersection of the path, this memory covered the actions performed as from the previous intersection. Thus the first intersection was defined as "a Y-intersection + *gone straight* movements" and the second as "a Y-intersection + *gone straight- turned left-gone straight* movements". Once the intersections were defined with this memory, learning independent stimulus-response associations explained best the mice's behaviour.

These results suggest that to learn a sequence of two turns without cues in the triple Y-maze, mice do not need to have a representation of the topographical organization of the maze (corresponding to a *world model*). They do not need to remember how each parts of the maze are related one another. What they do need to remember is, at each moment, the last few actions which they have just performed. This retrospective memory load is sufficient to differentiate parts of the maze which are otherwise similar according to an egocentric viewpoint.

These results have several consequences:

1) They bring information concerning the **type of information** the mice use to perform the task: the mice do not seem to compute a vector of the whole trajectory towards the platform by using travelled distance and they do not use a map-like representation of the environment build with a chain of maze parts linked to each other by given actions. They rather use a retrospective memory load of the last actions performed, associated to the current egocentric perceptions of the maze part.

2) They question the **role of the hippocampus in sequence-based navigation**. Indeed, one of the neural bases associated with *world models* is the hippocampus. It is thought to be involved in learning and planning in a model or graph of possible transitions between states, no matter if these states are spatial or not (van der Meer *et al.*, 2012), as proposed in the relational theory of the hippocampus (Eichenbaum, 1999). Its' essential role revealed by knock-out studies (Rondi-Reig *et al.*, 2006) or lesion studies (Fouquet *et al.*, 2013) may however be explained within the framework of the model-free reinforcement learning model with a memory of the previous actions. Interestingly, Rondi-Reig *et al.* had initially proposed that the hippocampus was required to “*organize temporally the three independent stimulus–response behaviours required at each intersection*” (Rondi-Reig *et al.*, 2006). However rather than providing the link between three independent stimulus-response associations, the model suggests that the hippocampus supplies the memory of the last events which allows differentiating the different maze parts to then learn independent stimulus-response associations.

The **CA3** has been proposed to store sequences of events, which can here be a series of actions (Lisman *et al.*, 2005). It has been shown to play an important role in the encoding of new spatial information within short-term memory with a duration of seconds and minutes in tasks that require rapid encoding, novelty detection, one-trial short-term memory, and one-trial cued recall primarily for spatial information (reviewed in (Kesner, 2013)). These tasks require the acquisition of arbitrary and relational associations and are assumed to operate within an auto-associative network function of the CA3 region (Treves & Rolls, 1994; Rolls & Kesner, 2006a). The CA3 also supports sequential processing of information in cooperation **with the CA1** (Kesner, 2013). The cooperation of the CA3 and the CA1 in sequence-based navigation has recently been shown: electrophysiological recordings performed in mice doing the starmaze task have brought insight into the hippocampal neural dynamics when performing sequence-based or map-based navigation (Cabral *et al.*, 2014). During the probe

trial where the departure was rotated, when mice used the map-based strategy, CA1 place cells fired in the same location as in training trials, revealing their anchoring on external landmarks. But when they used the sequence-based strategy, the place cells preserved the firing sequence observed during training trials but that sequence was expressed at spatial locations which were rotated compared to the training trial and the rotation corresponded to the rotation induced by changing the departure arm (Figure 50). Thus when using the sequence-based strategy, place cells fired in an egocentric reference frame. Interestingly, a given cell could fire in an allocentric reference when using the map-based strategy or in an egocentric reference frame when using the sequence-based strategy (see cells 1 and 2 in Figure 50).

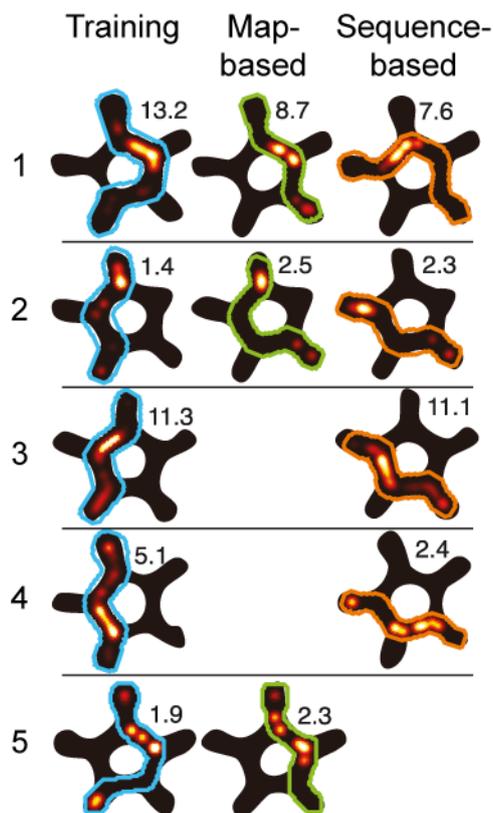


Figure 50: Place cell behaviour during map-based and sequence-based probe trials. Left: example place cells in training (mouse trajectory outlined in cyan), map-based strategy (green outlines), and sequence-based strategy (orange outlines) trials. The peak firing rate is indicated next to each display. Gaps correspond to sessions where that particular strategy was not expressed. *Adapted from* (Cabral *et al.*, 2014).

Map-based or sequence-based strategy use was also accompanied by different patterns of **oscillations**. In the hippocampal formation, gamma rhythms are thought to modulate the interaction between structures: low-frequency (23-40 Hz) and high-frequency (55-95 Hz) gamma oscillations mediate coherence between CA1 and, respectively, CA3 and the medial

entorhinal cortex (Bragin *et al.*, 1995; Colgin *et al.*, 2009). By quantifying the ratio between high-frequency and low-frequency gamma, the authors showed that the use of the map-based strategy was associated with a greater involvement of high-frequency gamma whereas the sequence-based strategy was associated with a greater involvement of low-frequency gamma (Cabral *et al.*, 2014). The change in input dominance reflects a more direct input of landmark information in map-based navigation through the entorhinal cortex-CA1 connection whereas CA3 input is more dominant in the CA1 during sequence-based navigation.

Cabral *et al.* proposed that the shifted place cell firing during sequence-based strategy trials and the dominance of CA3 input may reflect the retrieval of **memorized sequences of cell assemblies** (Pastalkova *et al.*, 2008; MacDonald *et al.*, 2011), possibly stored in CA3, and paced by self-motion information or by local landmarks (e.g., maze intersections) that segment the trajectory (Cabral *et al.*, 2014). It has indeed been shown that in a multi-intersection “hairpin” maze, CA1 activity was reset at each intersection, so that adjacent arms traversed sequentially were represented similarly whereas CA3 activity was not (Royer *et al.*, 2010; Mizuseki *et al.*, 2012), suggesting that, under those conditions, CA3’s activity reflected differences in the sequence of events. This sequence information could correspond to the memory of the last movements modelled in the model-free reinforcement learning model.

Moreover, **time cells** in the **CA1**, which have been shown to code for time and/or distance in working memory tasks (MacDonald *et al.*, 2011; Kraus *et al.*, 2013), could also provide a substrate for distinguishing two intersections which cannot otherwise be distinguished by their allocentric position in the maze. Indeed, as the maze has no external cues, a place cell coding for one intersection would probably signal any intersection (Spiers *et al.*, 2013). Time cells could code differently similar intersections, based on the elapsed time and/or distance from the departure. They have been shown to be active within time ranges up to 15 seconds and distances up to 800 cm (Kraus *et al.*, 2013) – mice performed the correct sequence in approximately 7 seconds and less than 200 cm. Even though our path integration model suggests that distance information is not used to learn the whole trajectory to the platform, this does not exclude the use of short distance information, equivalent to a small amount of actions, to define and distinguish different parts of the maze. On the other hand, time cells have been recorded in conditions where animals were running on a treadmill or a wheel (Pastalkova *et al.*, 2008; MacDonald *et al.*, 2011; Kraus *et al.*, 2013), consequently the effect of different sequences of preceding actions has not been tested on time cells coding.

The CA1 place cells recorded by Cabral et al. when performing the sequence-based strategy could be a direct evidence of intersection coding depending on the intersection's order in the sequence (Cabral *et al.*, 2014). They, as such, could be categorized as time cells in the sequence-based strategy, as time cells have been shown to have classical place fields additionally to their “time cell” property (Kraus *et al.*, 2013).

Another support to the role of the hippocampus in defining the different intersections through the memory of the last actions performed can be found in the activation dynamics of the hippocampus when performing the trajectory.

The observed hippocampal place cells' activity which, at decision points, sweep forward from the actual location of the subject, first down one path, then down the other (Johnson & Redish, 2007; Pfeiffer & Foster, 2013) has been proposed to reflect graph search in the *world model* (van der Meer *et al.*, 2012; Dolan & Dayan, 2013). Besides, in their study dissecting navigation in a virtual reproduction of London, Spiers & Maguire reported transient activation of the hippocampus specifically when the taxi drivers were initially planning their route (Spiers & Maguire, 2006). Thus in model-based reinforcement learning, the hippocampus seems only transiently active when looking at BOLD imaging, transient activation during which the graph is searched to find the trajectory as shown with place cells¹.

On the other hand, in our model-free model with a memory of the last actions, if the hippocampus supports this memory function, it should then be assumed to be active whilst performing the trajectory. Indeed this memory function is essential along the whole trajectory to always encode the last actions and then use this information specifically when at the intersections.

In Igloi et al.'s study, BOLD activation were only analysed in the departure alley, to directly compare map-based and sequence-based strategies (Iglói *et al.*, 2010). However additional analyses have revealed that in the map-based strategy, the hippocampus was not active in the following alleys whereas it was in the sequence-based navigation (unpublished data, communicated by Dr Kinga Igloi). These results are in favour of the hippocampus being the substrate of the memory of actions necessary to identify the intersections.

¹ The BOLD imaging contrasts were performed between the several navigational process and when the taxi drivers were coasting, i.e. driving without having in any thoughts, (Spiers & Maguire, 2006) thus revealing hippocampal activity which signalled more than the current location. This does not exclude the activity of place cells, which were probably active and signalling position in coasting as well as in active navigation epochs.

In Spiers et al. study, the left hippocampus was activated (Spiers & Maguire, 2006), similarly to Igloi et al.'s study. However, the activation was transient, in contrast to Igloi et al.'s study. The left activation in Spiers et al. suggests that taxi drivers were using a sequential representation of their trajectory (first left, then right,...) and if activation dynamics can give insights into the computational processes involved, this suggests that the taxi drivers were building this sequence using a model of the world through model-based reinforcement learning. This comparison suggests that depending on the complexity of an environment (number of cues, intersections, possible routes...) the computational process of sequence-based may change.

3) Finally, the identification of model-free reinforcement learning model as the one underlying sequence-based navigation **questions the dichotomized association between action-outcome - goal-directed learning – dorsomedial striatum with model-based reinforcement learning on the one hand, and stimulus-response – habitual learning – dorsolateral striatum with model-free reinforcement learning on the other**. Indeed the computational model suggests that a model-free reinforcement learning model is involved but the Fos analysis and the lesion experiment show an involvement of the dorsomedial striatum (Fouquet *et al.*, 2013).

How can we explain this apparent discrepancy? A solution is by looking closer at the two reinforcement learning models. A model-based reinforcement learning model is quickly adaptable to any change in the context, for example changing the position of the reward or devaluating it. Indeed the *world model* directly represents action-outcome contingencies and can modify them directly. On the other hand a model-free reinforcement learning models requires further extensive training for the change in reward to propagate through the independent stimulus-response associations (Khamassi & Humphries, 2012). The two models were thus proposed to respectively parallel goal-directed behaviour, in which the animal is able to modify its responses to changes in outcome, mediated by the dorsomedial striatum, and habitual behaviour, in which the animal does not respond to changes in outcome (it perseveres with its previous action), mediated by the dorsolateral striatum (Dickinson, 1985; Balleine, 2005; Yin & Knowlton, 2006). However the goal-directed or habitual nature of the behaviour is tested once the task is learned, not during learning as we have done. Moreover a model-free reinforcement learning system is not totally impermeable to goal or outcome information. It indeed *uses* goal information to create and reinforce the association between a state and an action. Indeed the temporal difference signal actually represents the difference

between expected and *obtained* outcome (Sutton & Barto, 1998). Consistently, an imaging study in humans showed a correlation between activity in the caudate (equivalent to the dorsomedial striatum) and temporal difference error in an aversive conditioning task (Seymour *et al.*, 2004). The explicit representation of the consequences of one's actions through action-outcome associations in the dorsomedial striatum could participate in building stimulus-response associations in the model-free reinforcement learning system. Similarly, the hippocampus, which is classically associated with model-based learning (van der Meer *et al.*, 2012), can also contribute to model-free reinforcement learning. Indeed model-free reinforcement learning can be performed by associating a place, defined by a place cell's place field, to a given action (Trullier *et al.*, 1997). This type of learning was prominent in early models of hippocampus-dependent navigation (Burgess *et al.*, 1994; Arleo & Gerstner, 2000; Foster *et al.*, 2000).

I thus propose here that in the field of reinforcement learning the involvement of a structure is not strictly restricted to a model-based or a model-free system. Rather model-based and model-free systems require diverse information and this requirement can change with increasing task knowledge. Accordingly the transition of activity observed from the dorsomedial striatum to the dorsolateral striatum in the cued T-maze task (Thorn *et al.*, 2010) (page 56) does not necessarily parallel a transition from a model-based to a model-free learning system. Rather, this transition could reflect the importance of outcome information provided by the dorsomedial striatum in creating the stimulus-response associations possibly stored in the dorsolateral striatum. With extensive training and stable stimulus-response associations, the dorsolateral striatum could then solely express the stimulus-response association (Thorn *et al.*, 2010). The amount of training could depend on the complexity of the stimulus-response associations to learn. In Thorn *et al.* (Thorn *et al.*, 2010) rats performed 40 trials a day and had to perform over 72.5% success in 10 out of 11 consecutive daily sessions, thus overtraining lasted at least 10 days. Consequently, a prediction of this is that in the triple Y-maze, I should reveal an involvement of the dorsolateral striatum with further training. However I observe an increased Fos density in the dorsolateral striatum in the early learning stage but not in the late stage. Accordingly, in the virtual reality version of the task, sequence-based navigation was only associated to caudate activations (equivalent to the dorsomedial striatum) but not putamen activations (equivalent to the dorsolateral striatum) (Iglói *et al.*, 2010). Therefore the stimulus-response associations in sequence-based navigation may not be at all "stored" in the dorsolateral striatum. Two recent studies have also questioned

the dependence of stimulus-response learning on the dorsolateral striatum (Botreau & Gisquet-Verrier, 2010; De Leonibus *et al.*, 2011). Both studies used the cross-maze task and showed that lesioning the dorsolateral striatum did not prevent rats from learning the stimulus-response strategy. The infralimbic area of the prefrontal cortex has also been shown to be necessary in acquisition and expression of stimulus-response associations (Coutureau & Killcross, 2003; Smith *et al.*, 2012). It could thus be another site for supporting model-free reinforcement learning and storing stimulus-response associations. Interestingly, there are no known projections from the infralimbic to the dorsolateral striatum whereas there are projections from the infralimbic to the dorsomedial and ventral striatum (Vertes, 2004). These anatomical connections could further support a role of the dorsomedial striatum in model-free reinforcement learning.

3. Network underlying sequence-based navigation

The Fos imaging analysis of the early and late learning stages of sequence-based navigation revealed a **reorganisation of the underlying network**, as observed in other task learning studies (e.g. (Doyon & Benali, 2005; Poirier *et al.*, 2008; Yin *et al.*, 2009; Conejo *et al.*, 2010)).

The **early stage** network reflects multiple processes: the mice are discovering the maze and they are trying to identify a way to get out of it (which corresponds to learning the rule of the task).

During this stage, most of the structures had increased c-fos expression and analyzing the correlations of c-fos expression between the structures revealed that most of the significant correlations in the network were between cortical and striatal regions, which were identified as belonging to one cluster.

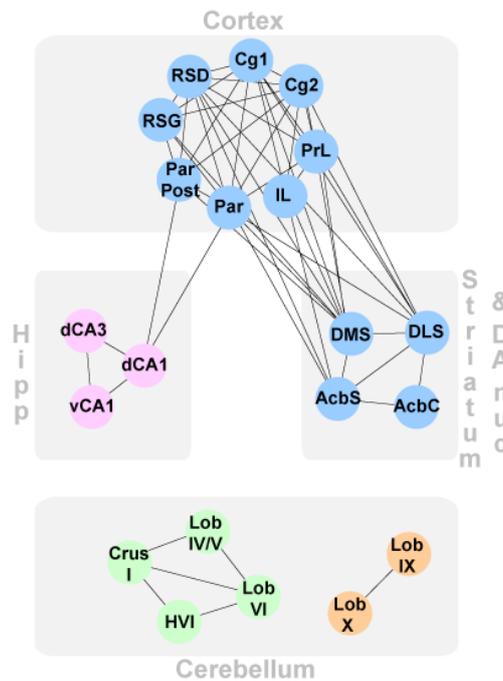


Figure 51: Network of the early learning stage in sequence-based navigation. The structures are placed relative to their major anatomical subdivisions and are colour-coded according to the cluster they belonged to. The connections presented are the significant correlations shown in the network graphs.

This cortico-striatal cluster contained the prefrontal, parietal and retrosplenial cortices and dorsal (medial and lateral) and ventral striatum (Figure 51). The cortical regions involved were regions known to be involved in navigation-related information processing such as reference frame manipulations and egocentric motion coding (retrosplenial and parietal cortices) (Vann *et al.*, 2009; Harvey *et al.*, 2012; Whitlock *et al.*, 2012) and regions involved in goal coding, decision making and motivation maintenance (prelimbic, infralimbic and cingulate cortices and dorsal and ventral striatum) (Hok *et al.*, 2005) (Cowen *et al.*, 2012; Euston *et al.*, 2012).

The hippocampal regions (dorsal CA1, dorsal CA3 and ventral CA1) formed another cluster mutually correlated. This cluster was related to the major cortico-striatal cluster through correlations between the dorsal CA1 and the parietal cortices (Figure 51). The increased Fos expression in the dorsal hippocampus may reflect processing associated to the exploration of a new environment (Amin *et al.*, 2006; Alvernhe *et al.*, 2012; Bourgeois *et al.*, 2012). The ventral hippocampus has been shown to be involved in the early stages of water maze learning as its lesion impaired performance during the first trials but did not prevent learning the location of the platform (Ruediger *et al.*, 2012). The authors proposed that the ventral hippocampus was involved in learning consistent goal-context relationships (Ruediger

et al., 2012), which is consistent with their broader place fields (Maurer *et al.*, 2005; Kjelstrup *et al.*, 2008) which are thought to convey information about the whole environment (Andersen *et al.*, 2006).

The cerebellar cortices, which also had increased Fos densities, were grouped in two purely cerebellar clusters, without any significant correlations with other regions (Figure 51). One of them contained the lobules IX and X, and the other cerebellar cluster was composed of the lobules IV/V and VI, Crus I and HVI (both hemispheres of the lobule VI). I will further detail the contribution of these regions in the following pages when commenting the late stage network, to fully discuss their contributions to sequence-based navigation.

Interestingly, the organization of the significant correlations amongst cortical, striatal and hippocampal regions closely matched anatomical pathways (Gruber & McDonald, 2012) (Figure 51).

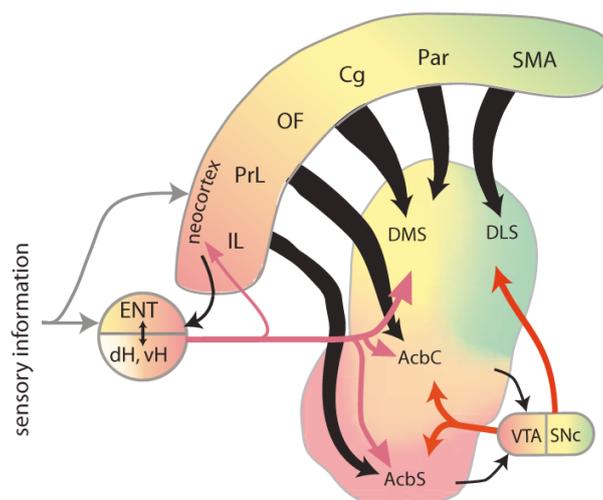


Figure 52: Diagram illustrating connectivity of cortex, striatum, hippocampus and dopaminergic nuclei in rodent. The colour gradient approximates the gradient of afferent projections to the striatum (Voorn *et al.*, 2004). Tapered arrows indicate highly convergent input. Note that the ventral hippocampus has direct projections (in pink) outside of the hippocampal formation, whereas the dorsal hippocampus does not. Projections from dopamine neurons in the VTA and SNc are shown in red. Abbreviations: IL, infralimbic; PrL, prelimbic; OF, orbitofrontal; Cg, cingulate, Par, parietal; SMA, sensorimotor; DLS, dorsolateral striatum; DMS, dorsomedial striatum; AcbC, core of the nucleus accumbens; AcbS, shell of the nucleus accumbens; VTA, ventral tegmental area; SNc, substantia nigra pars compacta; dH, dorsal hippocampus; vH, ventral hippocampus; ENT, entorhinal cortex. *Adapted from* (Gruber & McDonald, 2012).

This suggest that during the early stage of sequence-based navigation learning, the structures involved in navigation and decision-making are activated compared to swimming control mice (identified through Fos expression) and their activity is organized through the

major anatomical connections (identified through correlation analysis). Alongside the cerebellar cortices are activated but their activity is not correlated non-cerebellar regions.

With learning, fewer structures showed an increased activity compared to the swimming control mice. However there were as many significant correlations in **the late stage** as in the early learning stage, but they involved more structures than during the early stage (Figure 53). Thus the correlations amongst structures reorganized when performing sequence-based navigation.

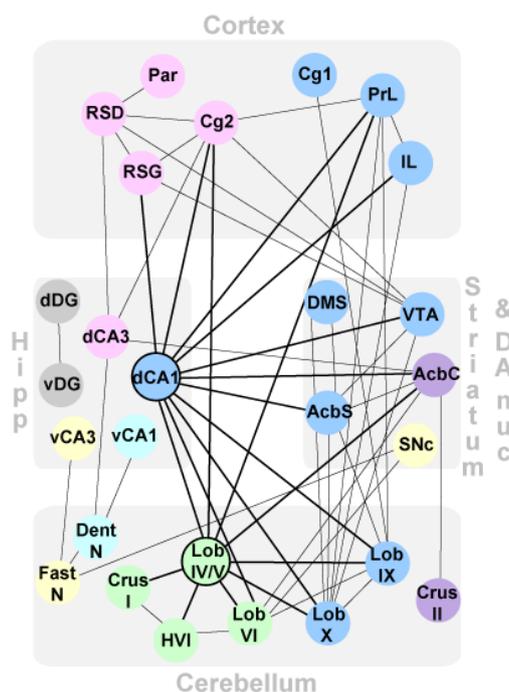


Figure 53: Network of the late learning stage in sequence-based navigation. The structures are placed relative to their major anatomical subdivisions and are colour-coded according to the cluster they belonged to. The connections presented are the significant correlations shown in the network graphs.

The regions which underwent the most changes in functional connectivity between early and late learning stages were the cerebellar cortices and dorsal hippocampus.

The late stage network also contained the **cerebellar cluster composed of the lobules IV/V, VI, Crus I and HVI** (both hemispheres of the lobule VI) (Figure 53). This cluster was actually found in all three conditions: early and late learning stages and late stage swimming control mice, despite different Fos densities between the conditions. This suggests a common role in the three conditions.

The lobule IV/V belongs to the anterior cerebellum, which is classically associated to motor functions (Apps & Hawkes, 2009) to which it participates through cerebro-cerebellar loops connecting the anterior region of the cerebellum to motor cortical areas (Bostan *et al.*, 2013). The lobule VI and its hemispheres belong to the posterior cerebellum (Manni & Petrosini, 2004), rather associated to non-motor cerebral regions (Strick *et al.*, 2009). The lobule VI and its hemispheres have been shown to be functionally coupled with associative regions (prefrontal, posterior parietal, superior and middle temporal association areas, cingulate gyrus and retrosplenial cortex) in resting-state functional connectivity studies (Krienen & Buckner, 2009) and are activated in humans in a variety of non-motor processes, including working memory, language generation and mental rotation tasks (Stoodley *et al.*, 2012). In rabbits the HVI region has been shown to have synchronized theta oscillations with the hippocampus during a hippocampal-dependent version of the eye blink conditioning task (Hoffmann & Berry, 2009; Wikgren *et al.*, 2010). Anatomically, in the rat the lobule VI has recently been shown to belong to a cerebro-cerebellar loop with the cingulate cortex, through the fastigial nucleus (Galgiani, 2013). Thus this cluster contains a combination of cerebellar areas associated to motor and cognitive cerebral regions.

Due to its cytoarchitectonic homogeneous structure, it has been proposed that the same computational principles apply to both the motor-related and non-motor-related areas of the cerebellum. A proposed function is that it supports the adaptive plasticity needed for the emergence of skilled behaviour. This general idea has been detailed in models of motor control, which contain three basic elements: (a) internal models that either predict the sensory input that should occur as a consequence of a motor output (forward models) or that predict the movements necessary to achieve a goal (inverse models), (b) a comparison process that detects errors in predicted versus actual outcomes, and (c) a learning process that uses error information to adaptively modify internal models so that movement execution can be fast and accurate (Ito, 2005b; Strick *et al.*, 2009). The role of the cerebellum in the internal representations underlying motor control can also apply to internal representations underlying cognitive functions: cerebellar processing may help to adaptively modify internal representations so that the desired goals of cognition can be achieved in a skilled, and error-free, manner (Ito, 2008; Strick *et al.*, 2009).

Some of the known afferents to the lobule IV-V, lobule VI and its hemispheres are respectively known to be proprioceptive information from the neck (Manzoni *et al.*, 1999), visual input (Snider & Stowell, 1944) and whisker input (Shambes *et al.*, 1978). These regions could perform **self-motion information processing to participate to the mental**

representation of space (Rocheffort *et al.*, 2013).

The activation of these regions, lobule IV-V, lobule VI, HVI and Crus I, during the early stage could reflect increased sensory information processing provided by self-motion and contributing to the creation of the mental representation of space (Rocheffort *et al.*, 2011). The similar correlations within the cluster across the three experimental groups could reflect a maintained processing of sensory information to continuously update the internal representation of space (through error detection between predicted versus actual outcomes). In the late learning stage specifically, this cluster had many correlations with striatal, hippocampal and cortical areas, especially through the lobule IV/V, making it a hub in the network. This suggests that when performing a goal-directed trajectory, this cluster interacted with the structures involved in learning the accurate sequence. The correlated activity of this cluster with cortical, hippocampal and striatal regions could reflect its involvement in generating an optimized trajectory to the goal (Burguière *et al.*, 2005). The connection between the lobule VI and cingulate cortex (Galgiani, 2013) could allow the direct interaction of this cluster with navigation-related cognitive regions.

In the virtual reality starmaze, recent analysis have shown that concomitantly to the left hippocampus, the prefrontal cortex and the left cerebellum Crus I area are activated and the activations of these three structures are correlated ((Iglói *et al.*, 2014), in review). Moreover, the correlation between Crus I and left hippocampus correlated with the tendency of the subjects to use sequence-based navigation (Iglói *et al.*, 2014). The left cerebellum Crus I in humans has been proposed to anatomically correspond to the hemispheric region of the lobule VII, termed Crus II in rodents (Apps & Hawkes, 2009). However these regions have been subject to many changes across species: the hemispheres which project to the prefrontal cortex in primates have considerably expanded with the expansion of the prefrontal cortex (Balsters *et al.*, 2010). This could explain the anatomical discrepancies. We can however propose here a functional equivalence between the mice and human Crus I regions, as they are both activated when performing sequence-based navigation and are both part of a correlated network involving prefrontal and hippocampal regions.

Two other cerebellar cortical regions underwent drastic changes in functional connectivity: the **lobules IX and X**. The clustering analysis performed on the Fos densities at the late learning stage revealed that these two structures belonged to a major inter-regional cluster with the **dorsal CA1, the prelimbic, infralimbic and cingulate area 1 cortices, the**

dorsomedial striatum, the accumbens shell and the ventral tegmental area (Figure 53).

The prefrontal, striatal and dopaminergic areas of this cluster all belong to an anatomical loop involved in reward-guided learning and decision-making (Ashby *et al.*, 2010; Ito & Doya, 2011; Khamassi & Humphries, 2012; van der Meer *et al.*, 2012) and could therefore, together with the dorsal CA1, be the neural substrate underlying the model-free reinforcement learning model with the memory of the last events.

As mentioned earlier, the infralimbic thought to be involved in habitual behaviour, could store the stimulus-response associations (Killcross & Coutureau, 2003). The shell of the nucleus accumbens and ventral tegmental are thought to belong to the same anatomical loop as the dorsomedial striatum and medial prefrontal cortex (Gruber & McDonald, 2012). Through its dopaminergic input to the striatal and cortical areas, the ventral tegmental area could participate in learning the stimulus-response associations by signalling prediction errors (e.g. (Penner & Mizumori, 2012; van der Meer *et al.*, 2012)). The proposed role of the nucleus accumbens in producing a sequence of sensori-motor actions to the goal as suggested by (Poucet *et al.*, 2004) could be explained through its role within the reinforcement learning and decision-making framework. Due to its major dopaminergic input as well as limbic (hippocampal and prefrontal inputs) and motor inputs, it is thought to participate in model-based and model-free learning by providing a value signal of the reward (Roesch *et al.*, 2009) (reviewed in (van Der Meer & Redish, 2011)). In this sense it could act like the “critic” in the actor-critic architecture of the model-free reinforcement learning system (Bornstein & Daw, 2011). Thus, rather than computing the sequence of actions to the goal, it could provide the signal to learn this sequence.

Within this cluster, the dorsal CA1 could provide the information necessary to distinguish the intersections, through the memory of the last actions performed at any point of the trajectory provided through cell assemblies in the dorsal CA3 (Royer *et al.*, 2010; Mizuseki *et al.*, 2012; Kesner, 2013) and/or CA1 time or place cells (MacDonald *et al.*, 2011; Kraus *et al.*, 2013; Cabral *et al.*, 2014). The dorsal CA1’s Fos expression was correlated with many other structures, also out of its cluster, making it the second hub of the network analysed and confirming its paramount role in sequence-based navigation (Rondi-Reig *et al.*, 2006). Supporting the functional connectivity observed with the dorsal CA1, there are known functional relationships between the prefrontal cortex, the ventral striatum and the hippocampus (O'Donnell & Grace, 1995; Laroche *et al.*, 2000) and between the hippocampus and the cerebellum (Hoffmann & Berry, 2009; Wikgren *et al.*, 2010).

Finally, the lobules IX and X could contribute to this network by providing information concerning the parts of the maze. These lobules combine semicircular and otolith organs inputs (Yakusheva *et al.*, 2007) (Angelaki *et al.*, 2010) as well as visual information (Glickstein *et al.*, 1994). The computations these lobules perform allow translating these separate information of head movements and external visual information in a unified representation. This could be especially important for mice to accurately identify intersections in the maze whilst they are swimming. The significant correlations between these regions and the other cerebral regions observed only in the late stage suggest that the visuo-vestibular information processing performed by lobule IX and X may be of particular importance when performing the learned trajectory.

Another cluster contained the **dorsal CA3** and cortices more related to **navigational aspects: the parietal and retrosplenial cortices** (Figure 53). This cluster also contained the **cingulate cortex, area 2**.

Through its inputs from primary sensory cortex (Calton & Taube, 2009) as well as the cerebellum (Giannetti & Molinari, 2002), the parietal cortex is thought to convey environmental and self-motion information to the hippocampal formation (Calton & Taube, 2009; Save & Poucet, 2009). This information, mostly provided in an egocentric reference frame, can first be processed to an allocentric reference frame by the retrosplenial cortex to participate in the hippocampal coding of the environment (Vann *et al.*, 2009). Interestingly the dorsal CA3 belongs to this cluster, possibly involved in associating the short sequence of actions and places traversed to provide the memory necessary to distinguishing the intersections (Cabral *et al.*, 2014) (see (Kesner, 2013) for review). The granular retrosplenial cortex, mostly involved in internally directed navigation (Vann & Aggleton, 2005; Pothuizen *et al.*, 2009), is activated in the late stage and has correlated activity with the dorsal CA1 as well as belonging to the same cluster as the dorsal CA3. It could receive the path information from the dorsal CA1, the output of the hippocampus, and then funnel it back to the parietal cortex to allow it to organize the sequence of actions, this time in an egocentric reference frame (Harvey *et al.*, 2012; Whitlock *et al.*, 2012). This sequence could then be send by the parietal to the secondary motor cortex to carry out the actions (Harvey *et al.*, 2012).

The cingulate cortex has been divided in a dorsal (1) and a ventral (2) area, a separation which parallels the dysgranular and granular separation in the retrosplenial cortex, in the same antero-posterior axis as the cingulate. The recordings identifying neural correlates involved in maintaining a course of action in the face of countervailing forces rather than

deciding which course of action to pursue (Cowen *et al.*, 2012; Holec *et al.*, 2014) have not distinguished the two zones, nor have the lesion studies as they are small (Walton *et al.*, 2002; Walton *et al.*, 2003; Rudebeck *et al.*, 2006). If both regions are not functionally distinct regarding the cingulate cortex's role in maintaining motivation to reach the goal along a trajectory, it is interesting to see that the cingulate cortex participates in the two clusters, one containing regions rather involved in actually learning the sequence of turns and the other one more involved in processing the navigational information necessary to perform the path.

During the late stage, the medial entorhinal cortex did not show an increased Fos density compared to the control mice, nor did its Fos density correlate with any other region counted. This is consistent with the results obtained in the electrophysiological study in the starmaze where inputs from the dorsal CA3 dominated inputs from the medial entorhinal cortex (Cabral *et al.*, 2014). The activity of the dorsal CA3 and dorsal CA1 were correlated ($\rho=0.61$) but at a p-level between 0.05 and 0.01. Even if the correlation between the Fos densities of these two regions was weak during the late stage, the considerable anatomical connections between the two regions insures a transfer of information. Their affiliation to two separate clusters highlights their different roles in learning the sequence. The dorsal CA3, known to encode spatial information within short-term memory (Kesner, 2013), can assume its function by interacting with navigation-related cortices. This information can then be used by the dorsal CA1 to differentiate the intersection, revealed by the place cell activity in a sequence-based reference frame (Cabral *et al.*, 2014), and thus participate in learning the whole sequence through interactions with the prefrontal cortices and striatal regions (O'Donnell & Grace, 1995; Laroche *et al.*, 2000).

In conclusion, during sequence-based navigation, the structures involved in decision-making and navigation are activated compared to swimming control mice (identified through Fos expression) and their activity is organized through the major anatomical connections (identified through correlation analysis). With learning, fewer structures show increased activity compared to swimming control mice but more structures are engaged in the network through correlated variation in their activity. The regions involved in the sequence-based navigation early and late learning stages as well as their correlations are summed in Figure 54. This figure also presents the putative functions of these regions based on the literature and the computational study.

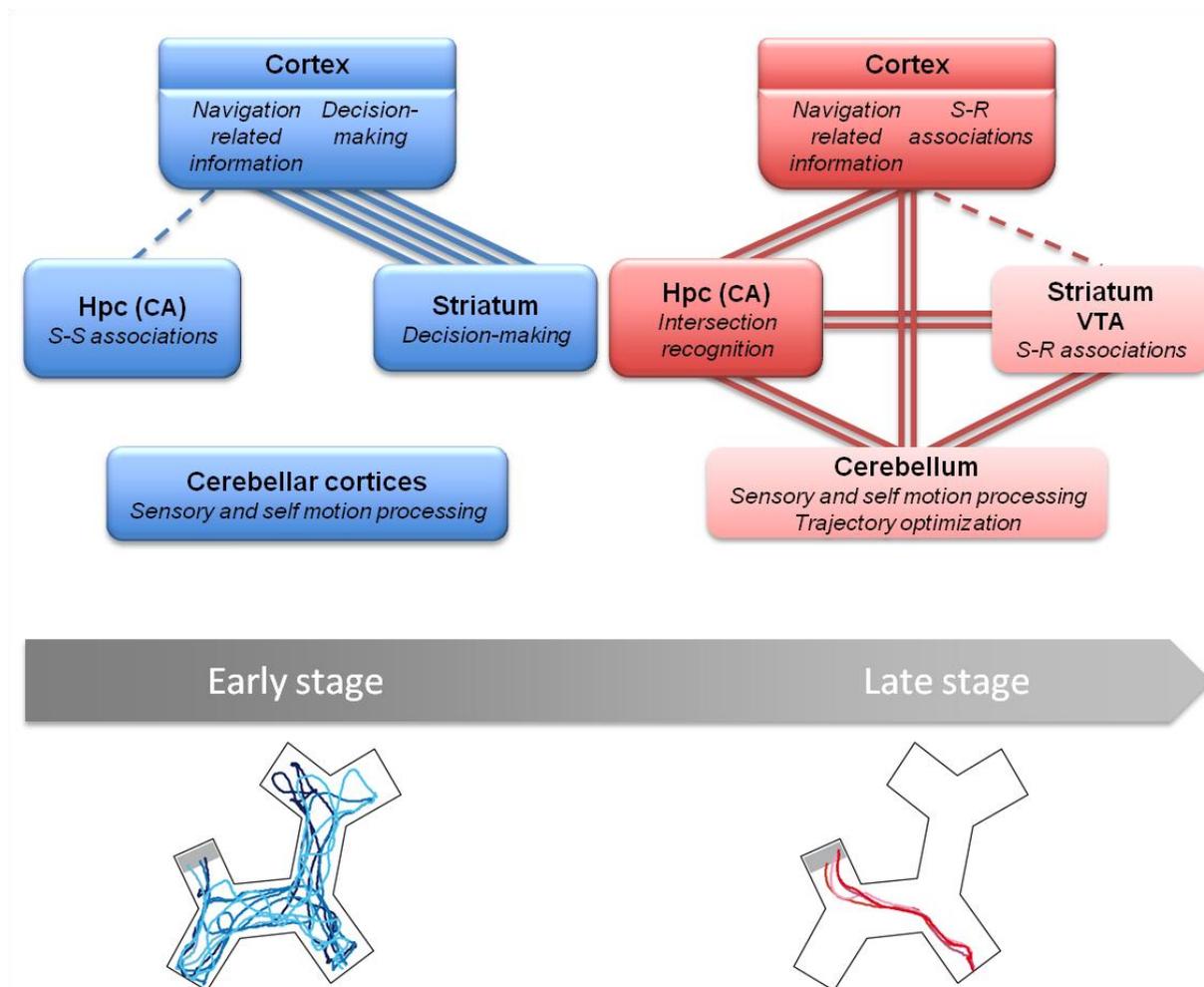


Figure 54: Networks and processes underlying early and late stage sequence-based navigation. The main anatomical subdivisions are presented in boxes as well the putative function they could underlie in each stage, based on the literature and the computational model. The intensity of the colouring is proportional to the overall Fos density in the region (e.g. during the early stage, all striatal areas had increased Fos densities, whereas during the late stage, only the dorsomedial striatum had increased Fos density). The links represent the amount of significant correlations: dashed lines are for a small number of correlations (<4), solid lines are for over 4 significant correlations. Below are shown two sessions of a mouse belonging to the early stage group (left) and a mouse having reached the late learning stage criterion (right). Four trials are performed per session, in blue (left) or red shades (right). These are the only trials the mice performed the day they were sacrificed for Fos imaging. Abbreviations: Hcp, hippocampus; CA, Cornu Ammonis; VTA, Ventral tegmental area.

Finally, compared to the proposed models of motor sequence learning studies, the network obtained in the late stage of sequence-based navigation shares similarity with the fast learning stage of motor sequence learning. This fast learning stage is characterized by an involvement of associative regions of the striatum (including the dorsomedial and ventral regions), cerebellum (such as the lobule VI), the prefrontal and parietal cortices (Hikosaka *et al.*, 2002; Doyon *et al.*, 2009; Penhune & Steele, 2012). Doyon *et al.* (Doyon *et al.*, 2009) also proposed that this fast learning stage is characterized by a shift of activation from the cerebellar cortex to the deep nuclei, which what I also observed in the Fos activation analysis.

However this contrast with the definition of the fast stage in which considerable improvement in performance can be seen within a single training session (Doyon *et al.*, 2009). Indeed late learning stage mice had stable performance over two days (5 sessions of 4 trials each). This suggests that the network of the slow learning phase differs between motor sequence learning and sequence-based navigation. Motor sequence learning tasks usually involve performing a movement in response to a readily identifiable cue. It is likely that sequence-based navigation requires further cognitive processing to differentiate cues and manipulate navigation-related activity that must be up-kept even during the slow learning phases.

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