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Disentangling the Content and the state of consciousness : from the theory to a practical proposition with the heart brain-interaction

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Démêler contenu et état de conscience : de la théorie à une proposition pratique avec l'interaction cœur-cerveau.

Disentangling the Content and the state of consciousness: from the theory to a practical proposition with the heart brain-interaction.

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Abstract/ Résumé

Le diagnostic de conscience chez les patients neurolésés a un impact majeur sur la prise en charge diagnostique, thérapeutique et pronostique. Ainsi, le médecin essaie de déterminer dans quel état de conscience ou niveau de conscience se trouve le patient, mais n'accède pas à ce que le patient pense, au contenu de sa conscience. L'étude de l'état de conscience et du contenu conscient chez ces patients est donc un défi majeur. Cette thèse vise à tenter de démêler le contenu et l'état de conscience chez les patients atteints de lésions cérébrales. Dans une première partie, nous proposons une représentation graphique simple (un espace 2d) qui peut être utile pour contraster les caractéristiques de l'activité cérébrale dans deux dimensions selon le contenu conscient et l'état conscient. Dans une deuxième partie, nous avons exploré de manière prospective la valeur pronostique d'une signature EEG de conscience -l'effet global, marqueur de contenu conscient- pour prédire le pronostic d'état de conscience dans une large cohorte de patients avec une lésion cérébrale. Dans une troisième partie, nous explorons la relation entre les états/contenu de conscience et un paradigme incarné de la cognition. Nous montrons que les fluctuations de la fréquence cardiaque dépendent de l'attention top-down portée au stimulus et peuvent représenter une mesure simple pour évaluer l'état et le contenu de la conscience chez les patients.

The diagnosis of consciousness in brain-injured patients has a major impact on diagnostic, therapeutic and prognostic management. Thus, the physician tries to determine what state of consciousness or level of consciousness the patient is in, but does not have access to what the patient is thinking, the conscious content. The study of the state of consciousness and the conscious content in these patients is therefore a major challenge. This thesis aims to attempt to disentangle the content and state of consciousness in brain-damaged patients. In a first part, we propose a simple graphical representation (a 2d space) that can be useful to contrast the characteristics of brain activity in two dimensions according to conscious content and conscious state. In a second part, We prospectively explored the prognostic value of an EEG signature of consciousness -the global effect, a marker of conscious content- for predicting the prognosis of conscious state in a large cohort of patients with brain injury. In a third part, we explore the relationship between states/content of consciousness and the embodied paradigm to cognition. We show that fluctuations in heart rate depend on top-down attention to the stimulus, predict memory performance and may represent a simple measure to assess conscious state and conscious content in patients.

Contents

Contents	5
I General introduction	7
1 From consciousness of patients to neural correlate of consciousness	8
1.1 Medical statement in intensive care	8
1.2 Definitions of consciousness	9
1.3 Neural correlate of consciousness (NCC)	11
2 Application of a theory of consciousness and cerebral investigation of patients with disorder of consciousness	18
2.1 A theory of consciousness: the Global Workspace Theory . .	19
2.2 Behavioral assessment	21
2.3 EEG	24
2.4 Functional imagery	33
2.5 Tractography MRI	34
3 Brain body interaction	37
3.1 Brain-heart interaction	38
II Content-State Dimensions characterize different	

types of neural correlates of consciousness 46

III Auditory event-related ‘Global effect’ predicts recovery of overt consciousness 79

IV Conscious processing of narrative stimuli synchronizes heart rate between individuals 93

V Discussion 131

3.2 Summary of the main results 132

3.3 The importance of contrast for a more accurate study of conscious states and contents 133

3.4 The study of content and state: a theoretical breakthrough . . 134

3.5 Content and state of consciousness in the prognosis of neurological patients 136

3.6 A new window to study not only the content but also the state of consciousness. 137

VI Conclusion and perspectives 138

References 141

Part I

General introduction

Chapter 1

From consciousness of patients to neural correlate of consciousness

1.1 Medical statement in intensive care

In the Intensive Care Unit (ICU), the clinical state of patients requires organ support (such as mechanical ventilation, dialysis...) to allow the survival of the patient. When such support is provided, evaluating if the patient could be weaned off these assistance becomes a daily issue. For organs such as the heart, lungs, or kidneys, it is necessary to find markers showing whether their function is recovered. For instance, we can evaluate the cardiac function with echocardiography, the lung function with blood gases, or the kidney function with the level of creatinine in the blood serum. Even though these markers refer to well-known organs, on which literature is abundant, they are still often debated.

But the question of brain function recovery is even more complex. First, there is no specific organ support for the brain and in severe cases, a patient with a brain lesion suffers from a disorder of consciousness, which may require specific support - for example, mechanical ventilation to avoid aspi-

ration pneumonia or respiratory injury. When we take care of these patients, the recovery of consciousness is the primary preoccupation to consider being discharged from ICU. An efficient definition of consciousness is essential when we are interested in the emergence of consciousness and the prognosis of these patients. Consciousness recovery in these patients tends to follow a fixed sequence: when they exit from coma, they are first able to open their eyes. Then further progress to the minimally conscious state which allows them to follow their own image in a mirror or a simple instruction. Final recovery is reached when they can communicate with a more or less important handicap. Not all patients go through all these stages, but it is a framework that guides our practice in patients with brain lesions.

Thus, the medical doctor tries to determine what state of consciousness or level of consciousness the patient is in, but does not access what the patient is thinking, the content of consciousness. Sometimes the state of consciousness diagnosed with the behavioral examination is not in agreement with the real conscious content of the patient. Since the diagnosis of consciousness has a major impact on diagnostic, therapeutic, and prognostic management, the study of the state of consciousness and conscious content in these patients is a major challenge.

The study of consciousness no longer becomes a philosophical challenge but an experimental one. We are looking for objective cerebral phenomena for subjective phenomena signatures of consciousness signatures of measurable phenomena that indicate to us that the person is conscious.

This thesis aims to try disentangling the content and the state of consciousness in patients with brain lesions.

1.2 Definitions of consciousness

The definition of consciousness has been long discussed by philosophers, as it does not relate to simple physical evidence. The term consciousness is particularly difficult to define since it constantly re-uses the concept of consciousness to define itself. Defining the concept of consciousness in the healthy subject is a colossal task. Traditionally, consciousness is defined with conceptual opposition between phenomenal consciousness (P-consciousness) and access consciousness.

P-consciousness is defined as a quality of a sensitive experience (like the red of apple and what it does). This experience is unique, not describable, subjective, ineffable [42]. Many thought experiments: “What is it Like to Be a Bat?”, Thomas Nagel 1974 [89] – Marie and the color vision, Jackson 1982 [61] capture the concept of phenomenal consciousness. In these examples, humans, unlike bats, will never know how it feels to use echo-localization, or Marie, a neurobiologist who knows everything about color vision but who lives in a black and white room will not know what it’s like to see red. Chalmers [23] defines the philosophical issue of consciousness in two major problems: the easy problem and the difficult problem. The easy problem tries to explain the behavior and cognitive function of the conscious state and the difficult problem, translating what it feels like to be me, what it feels like to have emotions, feelings, sensitive, visual or auditory experiences.

The conscious access theory includes the reportability criterion in the definition of consciousness: subject must describe or report by word, behavior, or non-verbal his content of consciousness (for example: “I’ve seen the apple, I have consciousness that the apple exists”). The conscious information is, at the time, accessible to all cognitive functions (memorization, to drive the future behavior...). This definition is easy to use in research as long as we accept that the subject’s introspectiveness and report are consistent.

Researchers defending the theory of P-consciousness believe that the objective description of our states of consciousness by a neural system, could not include the subjective dimension of consciousness. Thus all tentatives to get a unique theory for the consciousness would collide in an “explanatory gap” [75]. Nevertheless, in the absence of an empirical proposal to differentiate between conscious access and P-consciousness, the intuitions concerning the concepts of objective and subjective often must be revised and it is possible that when we will explain all the behavior and cognitive function of conscious state, there will be nothing left to explain [38].

Without getting into the debate, we need an operational definition of consciousness to study patients with disorders of consciousness. We will call consciousness: the conscious access. We will distinguish the state of consciousness and the conscious content. “Being conscious” (transitive) being related to state of consciousness (ex: sleep, general anesthesia, vegetative state...), and “being conscious of something” referring to conscious content. In this way, for patients with a disorder of consciousness, the issue is to report their conscious content. To explore this, the neurological exam allows

correlating indirect signs: vegetative responses, like hypertension or acceleration of cardiac rate when the stimulation is painful, or an electrophysiological response while a cognitive stimulus is presented. It is delicate to qualify these signs as an automatic response or a really conscious response. The problem is therefore two-fold. The objective is to know the conscious content of patients by observing if they are able to integrate the information that is presented to them, and on the other hand to study their state of consciousness: are they conscious or not?

The observation of these patients and the founding work on the different topographies of brain lesions [99], lead us to consider that there are prerequisites for the emergence of consciousness. Indeed, we know that lesions of some brain structures (i.e brainstem, thalamic in particular) can lead to the state of coma, especially if the brain lesion is very extensive.

1.3 Neural correlate of consciousness (NCC)

The advent of neuroimaging in XXe allows studying neural correlate of consciousness, the processes that occur in the brain circuit during a particular conscious experience. The difference between the neural correlate of consciousness (NCC) and the factors essential for the consciousness which don't contribute directly to its contents can be difficult to analyze. These factors, known as background conditions, represent the factors allowing the emergency of consciousness, but do not participate directly in the conscious content.

Basis of neural correlate of consciousness

Neuroimaging has also made it possible to define the prerequisites leading to the emergence of consciousness: wakefulness, a thalamocortical treatment of the information and an attentional amplification with an access to a large brain network distributed across the entire extent of the brain.

The arousal circuits have been described through several clinical and experimental observations. During the spanish flu pandemic (1918-1925), the researcher Constantin Von Economo [125] observed that some patients showed neurological signs and specific behaviors: some were comatose and others restless and insomniac. Studying the brain dissection of patients, he found that comatose patients had lesions in posterior hypothalamus and the insomniac

patients had lesions in anterior hypothalamus. The link between Spanish flu and lethargic encephalitis is debated but Von Economo is the first to postulate that the “center of wakefulness” was located in the hypothalamus.

Later, Giuseppe Moruzzi et Horace Magoun (1949) [84] proposed two models in cats: an isolated encephala with a low medullary level transection and an isolated brain with pons transection. Wakefulness wasn't affected by medullary transection but drowsiness developed after pons transection. They named this structure formation reticularis. However, the stimulation of this formation reticularis aroused the cat and the electrical simulation modulated the EEG with cortical waves more frequent and smaller in amplitude. They then formulated the existence of ascending reticular activating systems with ascendants systems emerging from the reticulated formation and projects to the cortex. The reticulating ascending activating formation is a system contained in the brainstem, composed of numerous activating nuclei (basal Meynert nucleus (acetylcholine), locus coeruleus (noradrenaline), black substance and ventral tegmental area (dopamine), medial raphe nuclei (serotonin)) allowing a rich interoceptive and exteroceptive integration via the formation of a reticulo-thalamo-cortical pathway and a reticulo-hypothalamo-cortical pathway. This integration of sensitive information and arousal is automatic and ascending (it goes from the anatomical brain structures placed the lowest to the highest). Nevertheless, clinical observations show us that if vigilance is necessary for the emergence of consciousness, it is not sufficient.

The second requirement is the possibility of having thalamocortical treatment. This was demonstrated by blindsight in 1974 by Weiskrantz [129]: the patient GY had complete blindness in the left visual field (suffering from right V1 lesion), but he was able, forced to make a choice, to discriminate facial emotions, presented in the left visual field, at a level of performance higher than chance demonstrating that there was a subcortical pathway representing sensitive information in a non-conscious condition. Tractography sequences from MRI shows [16] that the white matter tracts between the lateral geniculate nucleus and V1 appear to show some degeneration, while the tracts between lateral geniculate nucleus and MT+/V5 do not differ from controls.

The third prerequisite is attentional amplification and access to a distributed cerebral network, that is to say that local unconscious information does not become conscious until the moment when by an attentional phenomenon, it is disseminated to a vast distributed brain network predominantly in the anterior cingulate cortex, the prefrontal cortex and lower parietal. This

vast brain network requires slow, reentrant and descending loops but also an internal space for synthesizing, maintaining and sharing information. There is therefore not a single structure responsible for consciousness, but indeed structures whose level of activation determines the possibility of consciousness.

Neural correlate of state and content

From these elements, we try to define the neural correlates of consciousness state (NCCs) and the neural correlates of conscious content (NCCc).

Neurology provides a better understanding of the concepts of content and state of consciousness. The neural correlates of consciousness are the minimal neural processes that must occur in the brain for a particular conscious experience to occur. We dissociate the brain activity associated with specific conscious content and the brain activity associated with different states of consciousness independently of content.

The neural correlate of conscious or unconscious state seems to be easier to define. It corresponds to the notion of level of consciousness. When we speak of level of consciousness, we instinctively think of wakefulness and sleep, but there are also many other pathological or altered states of consciousness: epilepsy, patients with brain damage and consciousness disorders, general anesthesia, the use of certain drugs. A more representative description of the clinical states-of-consciousness is done in a two-dimensional space including wakefulness and awareness [72] (see figure 1.1). Nevertheless, this conception is very schematic because we consider that a person is conscious when he or she has a subjective point of view, and this subjective point of view seems difficult to grade and to place on the axis of a figure. In the same way, the state of consciousness graded on a single axis is probably useful in clinical practice but cannot be used to construct a theory of consciousness [12]: indeed studying sleep or general anesthesia or patient with disorder of consciousness on the unique axis don't make sense. Here we prefer to study minimal contrasts between states of consciousness: for example, for patients with consciousness disorders compare patients in a vegetative state and patients in a minimal state of consciousness or in sleep, compare subjects in deep sleep and Rapid Eye Movement (REM) sleep. From a neurophysiological point of view, the state of consciousness is defined by a minimal state of brain activity that allows awareness. The brain does not necessarily need ex-

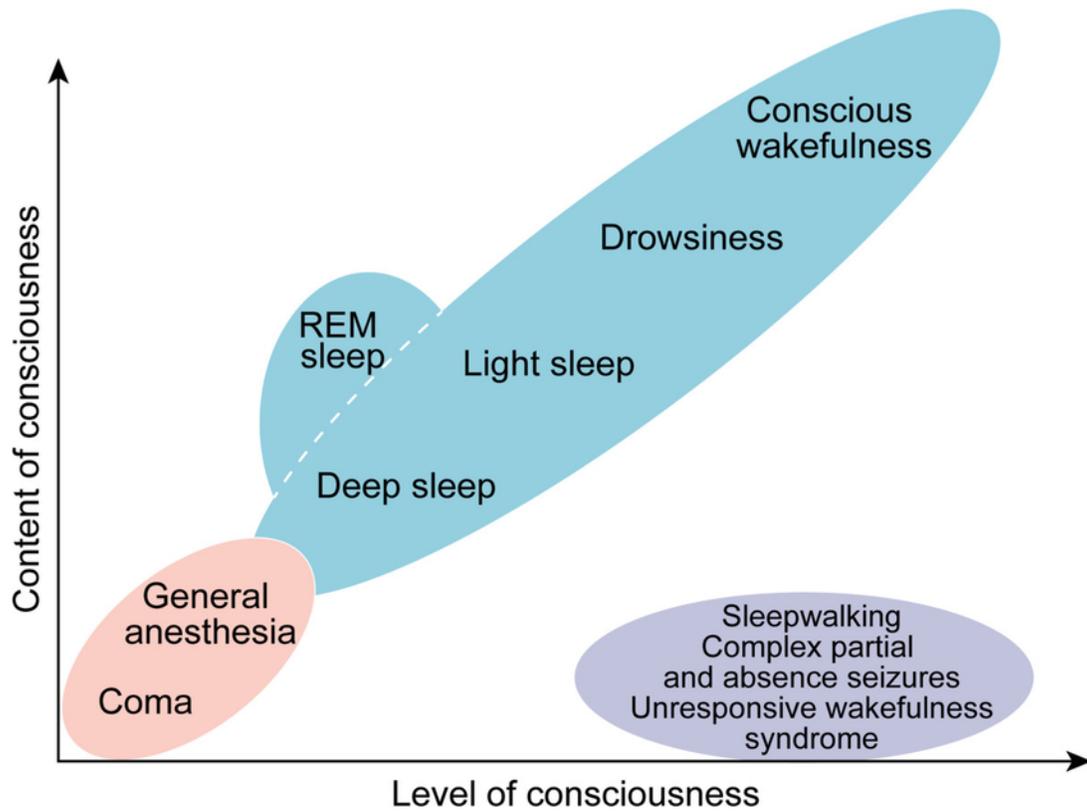


Figure 1.1: Representation of the different states of consciousness (awareness according to wakefulness).

In blue, representation of the states of sleep, in pink of the states without awareness and without wakefulness and in purple of intermediate pathological state.

From Laureys 2005 [72]

ternal input to generate brain activity, the brain is constantly traversed by a complex configuration of activities, this activity is related to functional brain connectivity, i.e. spontaneous activity synchronized between groups of neurons. It has been shown that this spontaneous activity can predict the content of consciousness in sleep but also that this spontaneous activity is maintained even during deep general anesthesia [36, 10]. It seems, however, that functional connectivity is rather constrained by anatomy in non-conscious states and much richer connectivity in conscious states. States of consciousness are thus the result of spontaneous and dynamic brain activity, preparing the emergence of consciousness.

The neural correlates of consciousness of content are usually the neural processes that occur in a specific experiment. NCC are normally studied by comparing conditions where specific conscious contents (perception of sound or image...) are present or absent in the same state of consciousness. For several decades, threshold visual/auditive paradigms, masking paradigms or paradigms of perceptual suppression have been developed through ERP, evoked oscillatory activity or evoked connectivity in order to study the neural correlates of consciousness of content. These experiments are based on the subjective relationship of the subject when he or she claims to have seen/heard or not seen/heard a stimulus. This access consciousness is also conditioned by attention.

Some authors have tried to escape the constraint of conscious access by developing paradigms of non-access with, for example, paradigms of binocular rivalry with stimuli moving in opposite directions [107]. The subject cannot see the two stimuli at the same time but necessarily in alternation. An optokinetic nystagmus (the eye slowly moves in the direction of the stimulus and then performs a rapid corrective saccade in the opposite direction) is sought and is correlated with conscious processing of the direction of the target in the studies. The research for correlates of neural correlates of consciousness of content contrasts conscious versus unconscious situations with different brain imaging techniques.

However, this result is in no way an exoneration of the level of consciousness. It is undeniable that level and conscious content are closely linked. The presence of cerebral signature of consciousness content can distinguish the different states of consciousness for instance in the DOC patient [44], but it is not obvious that the level of consciousness can be classified solely on the basis of the classification of conscious content and vice versa.

NCC research challenges

Identifying the neural substrates of consciousness raises a theoretical challenge to the meaning of the neural correlate of consciousness: is the goal to find the correlates between brain activity and conscious content or the correlates of states of consciousness?

It turns out that most of the time, we are not testing the conscious state but rather the content of consciousness. When, for example, there are contrasting tests where targets are seen or not seen, the subject is already conscious and we do not explain why this subject is conscious but we describe the brain activity associated with a content (in this case, seen or not seen) when we know that the subject is already conscious.

Chalmers [24] defines an arbitrary NCC as a region of the brain correlating with a given conscious state or content. For him, the research for these NCC helps us little to better understand consciousness. A completely arbitrary NCC should be interpreted outside of a theory of consciousness because it is not able to predict or extrapolate beyond the experience in which it was tested. However, Chalmers agrees that most often, the NCCs are not totally arbitrary because they are interpreted within the framework of a theory of consciousness (ex: frontoparietal activity for the broadcast of information in the conscious access [80] or in posterior hot spots in integrative information theory [68]). Through these theories of consciousness, it is often difficult to separate the state of consciousness from the conscious content.

Some studies focused on this task. Bachmann [9] proposes a 3D-axis representation of consciousness: the x-axis corresponding to conscious content, the y-axis to the state of consciousness, and the z-axis to the subjective level of consciousness. Aru [4] presents a neurobiological view to a neuropsychological phenomenon, he hypothesizes that the thalamo-cortical loops for the state of consciousness and cortico-cortical loops for the conscious content intersect and depend on the level of activity of the pyramidal neurons of the cortical layer 5. Noreika [95], in an unpublished paper, shows that behavioral and neural markers in EEG of conscious content depend on the conscious state during sleep phase transition. A recent review [60] proposes in view of these elements, a distinction between states and contents of consciousness, probably a satisfactory outcome for NCC is to treat states and contents together [11, 59].

Perspective: article 1

In the first part of this thesis, it seems important to study in the same framework conscious content and conscious state. We propose a simple framework (a 2d space) that can be useful to contrast brain activity features in both NCC dimensions at the same time, and to characterise different types of NCC according to the location in the proposed 2d space.

We provide two experimental examples with EEG markers that we dispose in a 2-dimensional space and we attempt to explain the implications for content and conscious states according to their position in space.

Chapter 2

Application of a theory of consciousness and cerebral investigation of patients with disorder of consciousness

Patients with disorders of consciousness constitute a major medical, ethical and scientific challenge. Indeed, as we are facing an increasing progress in invasive resuscitation techniques, making us able to support the most severe organ failures, we do have deep concerns about prognosis of these brain-injured patients. The exploration of patients suffering from disorders of consciousness is motivated by two major goals. First, because we believe it can improve the diagnosis of consciousness in these patients and even predict the return to consciousness. Second, it offers a model to test theories of consciousness and to better understand the neural bases underlying consciousness [35].

In this way of clinical and translational research, clinical examination is

essential in the evaluation of patients with consciousness disorder, but it is also possible, with electrophysiology techniques, functional or metabolic imaging, to find neurophysiological signatures of state of consciousness or, of the conscious treatment of auditory or visual stimuli in these patients. The morphologic neuroimager is also important to track the consciousness networks. These various examinations allow us to assess the state of consciousness and to try to predict the neurological evolution.

2.1 A theory of consciousness: the Global Workspace Theory

Several theories of consciousness have been developed, we expose here the theory of global workspace as a theory of conscious access.

The basis of the theory was described by Baars [7], it is a psychological concept which postulates that perceptual contents (localized processor) become conscious when they are widely distributed throughout the brain (see figure 2.1). Unlike other theories [124] (like Information integration theory), this theory is binary, meaning that you are conscious or you are not. There is no transient state.

Anatomically, Baars described the reticulo-thalamic system as the main structure forming the workspace but he does not differentiate the content of the level of consciousness (the reticulo-thalamic system rather pertaining to the level of consciousness).

Jean-Pierre Changeux and Stanislas Dehaene integrated these ideas into it a neuro-anatomical base comprising the pyramidal neurons of the cerebral cortex which have long axons capable of connecting distant cortical areas to each other. This model is in a way a "neural circuit" of conscious workspace.

The ignition concept is added, it is characterized by suddenness, coherence, and exclusive activation of a subset of neurons in the workspace coding for the current conscious content, along with the rest of the neurons in the workspace potentially inhibited. This can be triggered by sensory stimuli but also at rest. As this fMRI work [36] shows, even at rest, the brain goes through states of spontaneous activity.

However, this is not a localizing theory, several hubs must play an important role: the prefrontal cortex and its high density of neurons, the dorsolateral

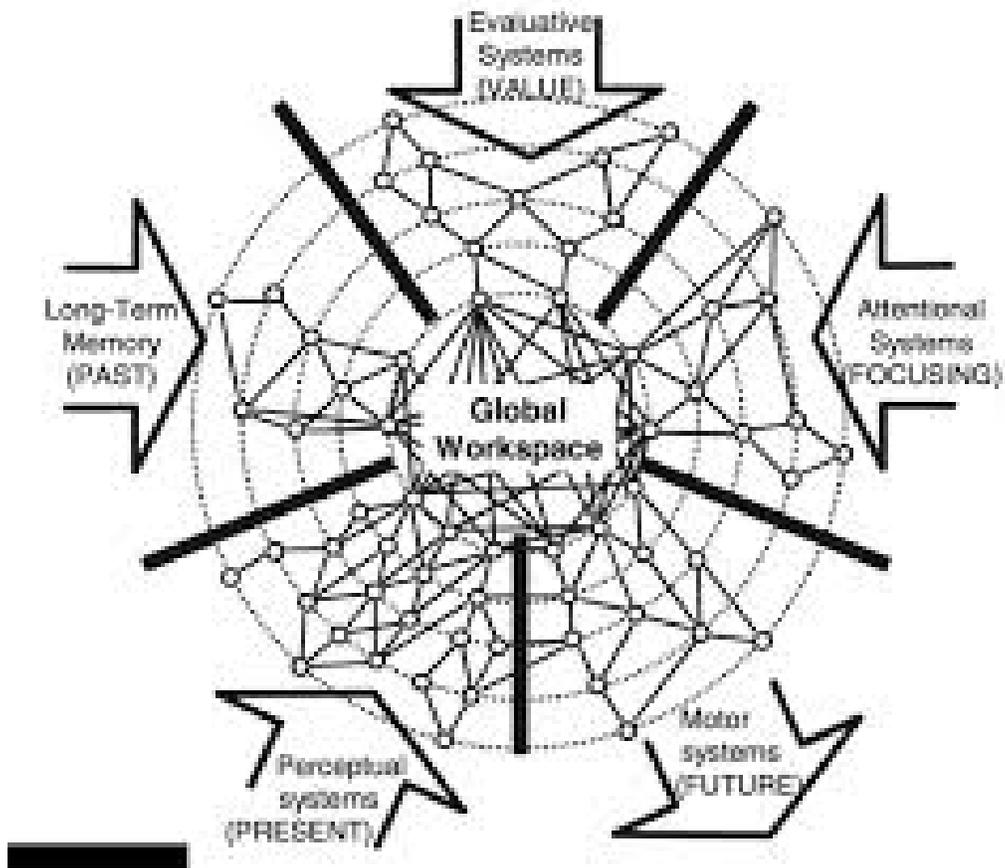


Figure 2.1: **Schematic illustration of Global Workspace Theory.**

Local processor with long-distance diffusion that has reached the global workspace. This theory also involves working memory, sensitive inputs, attention, a system of evaluation and reporting (according to Dehaene 1998 [34]).

prefrontal cortex and the lower parietal cortex or the cingulate cortex.

The global workspace can be illustrated by new data that highlights brain activity contrasts, between conscious or non-conscious content as well as between conscious or non-conscious states. All these experiments show that there is a divergence towards 200-300ms post stimuli. In this way of research, finding a potential neurophysiological marker became a new challenge. A vast debate is still going on to find this marker. Indeed, the first 200 ms seem to correspond to an unconscious post-stimuli processing in many experimental modalities, whether auditory, visual or tactile [50, 19, 101]. In a visual modality, for example, images are presented very quickly to a subject so that some images are seen and others not. In magneto-encephalography, it is possible to dissect the vision temporality of these images [78]. The first 150 ms all the images have the same parallel processing, from around 150 ms, the neuronal responses are amplified in the ventral visual areas; around 350ms, only the images reported subsequently give rise to late all-or-nothing activations in the visual and parietal areas. Other experiences have undergone the same temporality of conscious access [79, 114] (see figure 2.2).

Similarly, in evoked potentials, awareness of a stimulus correlates with a “late positive” component at the peak, called P300 [35, 14]. Interestingly, this wave disappears in cases of inattention or while sleeping [123].

It seems that in order to apply this theory to patients with disorders of consciousness, there is a double theoretical necessity. To become conscious of the information, it is necessary both that (1) the conscious workspace is in an appropriate state (state of awareness) (2) that the selected information is broadcasted to the conscious workspace.

2.2 Behavioral assessment

The patients with disorders of consciousness can evolve in various ways and often exhibit fluctuations in wakefulness and consciousness. These clinical presentations include coma, vegetative state (VS), minimally conscious state (MCS) and normal state of consciousness with more or less marked cognitive disabilities.

Coma most often results from severe brain damage (anoxia after cardiac arrest, brain trauma, cerebral hemorrhage, stroke). It corresponds to a state of total loss of consciousness, with closed eyes, there is no sleep wake cycle

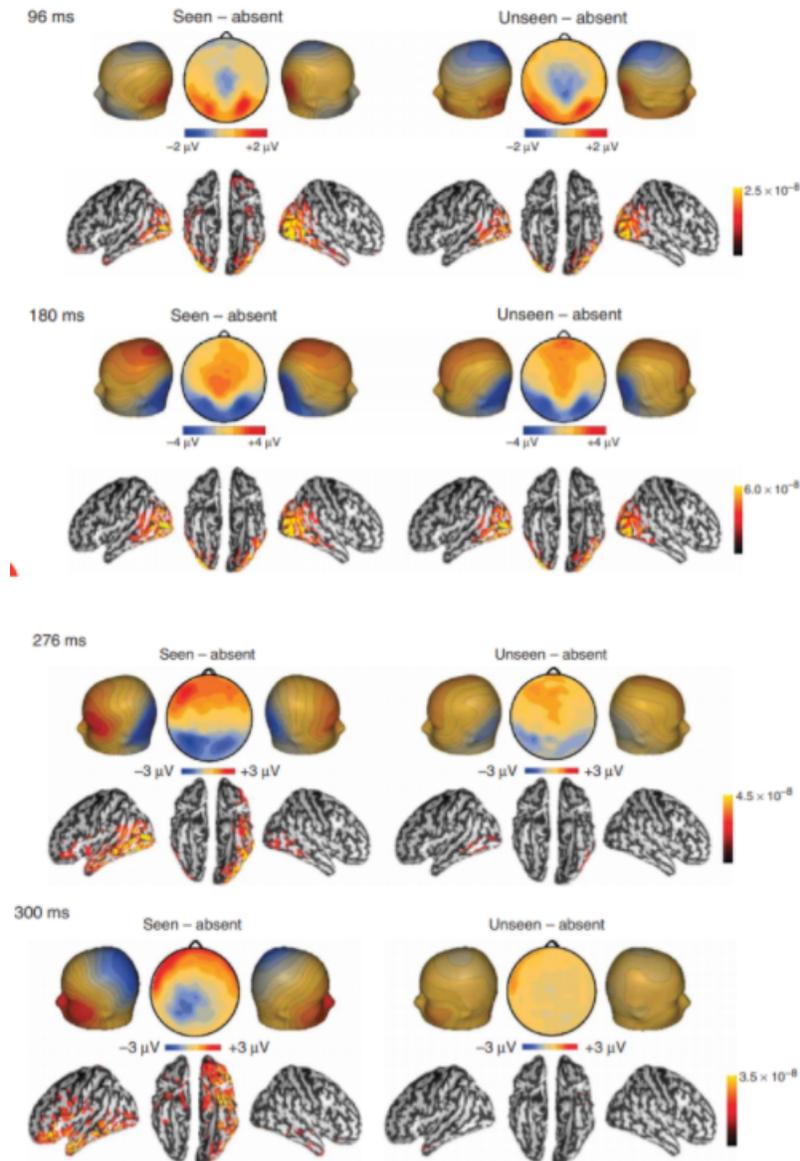


Figure 2.2: **Time course of scalp event-related potentials evoked by an identical visual stimulus, presented during the attentional blink.**

Early events (P1 and N1) were strictly identical, but the N2 event was amplified and the P3 events (P3a and P3b) were present essentially only during conscious perception. From Sergent 2005 [115].

anymore [63]. If these patients are allowed to evolve for several weeks by compensating for organ failures, in particular respiratory organs, the patients become vegetative most of the time, they reach a state of awareness with open eyes, spontaneous oculomotor movements, postural reflexes (tone of the whole body) as well as reflex movements of the limbs. Patients are then awake, but they are not aware of their environment and themselves. They can then stay in this state or continue to evolve towards a minimal state of consciousness. The minimal state of consciousness [53] is defined as a state of awakening with more or less conscious phases of information processing. It is illustrated by richer behaviors than the reflexes observed in vegetative states, such as an eye pursuit at the vision of a mirror and its own reflection, a response to a motor command, a localization of nociceptive stimulations (for example painful). These responses are sustained, but often fluctuate throughout the day.

A

JFK COMA RECOVERY SCALE - REVISED ©2004																	
Record Form																	
This form should only be used in association with the "CRS-R ADMINISTRATION AND SCORING GUIDELINES" which provide instructions for standardized administration of the scale.																	
Patient:		Diagnosis:					Etiology:										
Date of Onset:		Date of Admission:															
Date		Week															
		ADM	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
AUDITORY FUNCTION SCALE																	
4 - Consistent Movement to Command *																	
3 - Reproducible Movement to Command *																	
2 - Localization to Sound																	
1 - Auditory Startle																	
0 - None																	
VISUAL FUNCTION SCALE																	
5 - Object Recognition *																	
4 - Object Localization: Reaching *																	
3 - Visual Pursuit *																	
2 - Fixation *																	
1 - Visual Startle																	
0 - None																	
MOTOR FUNCTION SCALE																	
6 - Functional Object Use †																	
5 - Automatic Motor Response *																	
4 - Object Manipulation *																	
3 - Localization to Noxious Stimulation *																	
2 - Flexion Withdrawal																	
1 - Abnormal Posturing																	
0 - None/Flaccid																	
OROMOTOR/VERBAL FUNCTION SCALE																	
3 - Intelligible Verbalization *																	
2 - Vocalization/Oral Movement																	
1 - Oral Reflexive Movement																	
0 - None																	
COMMUNICATION SCALE																	
2 - Functional: Accurate †																	
1 - Non-Functional: Intentional *																	
0 - None																	
AROUSAL SCALE																	
3 - Attention																	
2 - Eye Opening w/o Stimulation																	
1 - Eye Opening with Stimulation																	
0 - Unarousable																	
TOTAL SCORE																	

B

Response	Glasgow coma scale	Pediatric Glasgow coma scale	Score
Eye opening	Spontaneous	Spontaneous	4
	To command	To sound	3
	To pain	To pain	2
	None	None	1
Verbal response	Oriented	Age-appropriate vocalization/interaction	5
	Confused	Cries spontaneously	4
	Inappropriate words	Cries to pain	3
	Incomprehensible sounds	Moans to pain	2
Motor response	None	None	1
	Obeys commands	Spontaneous movements	6
	Localizes pain	Localizes pain	5
	Withdraws	Withdraws to pain	4
	Abnormal flexion	Decorticate posture	3
	Abnormal extension	Decerebrate posture	2
None	None	1	

C

EYE RESPONSE

- 4 = Eyelids open or opened, tracking or blinking to command
- 3 = Eyelids open but not tracking
- 2 = Eyelids closed but opens to loud voice
- 1 = Eyelids closed but opens to pain
- 0 = Eyelids remain closed with pain stimuli

MOTOR RESPONSE

- 4 = Thumbs up, fist, or peace sign
- 3 = Localizing to pain
- 2 = Flexion response to pain
- 1 = Extension response
- 0 = No response to pain or generalized Myoclonus status

BRAINSTEM REFLEXES

- 4 = Pupil and corneal reflexes present
- 3 = One pupil wide and fixed
- 2 = Pupil or corneal reflexes absent
- 1 = Pupil and corneal reflexes absent
- 0 = Absent pupil, corneal, or cough reflex

RESPIRATION

- 4 = Regular breathing pattern
- 3 = Cheyne-Stokes breathing pattern
- 2 = Irregular breathing
- 1 = Triggers ventilator or breathes above ventilator rate
- 0 = Apneic or breathes at ventilator rate

Figure 2.3: Clinical score to evaluate the state of consciousness.

A: CRS-R, B: Glasgow score, C: FOUR Score

These states are to be distinguished from the locked-in-syndrome which corresponds to a lesion of the brainstem without disturbance of awareness or consciousness, but to a complete paralysis of the whole body except the vertical oculomotor movements. The clinical examination of these patients is delicate and the differences in state are sometimes tenuous for teams with limited experience. The question is always to know if the motor behavior is absent because the patient is unconscious (not aware of his environment) or if he cannot execute the command. The clinician is therefore helped by scores allowing diagnostic help. Many tools in intensive care monitor the brain but the difficulty is capturing the transition and the different state of consciousness.

The most used score is the Glasgow Score [123], but unfortunately it only partially captures the different state of consciousness, does not allow the assessment of intubated patients and does not use the brainstem reflexes. This score was initially created to predict the outcome in the acute phase of patients after severe brain trauma. It is a scale from 3 to 15 comprising three items: motor / verbal / eye movement (see figure 2.3).

The FOUR (Full Outline of Unresponsiveness) score includes 4 items: eye response / motor response / trunk reflex and breathing (see figure 2.3). It makes it possible to evaluate patients under mechanical ventilation, better identifies patients in locked-in-syndrome and vegetative states with a better correlation to the prognosis [131]. In this thesis, we use CRS-R [52] (Coma Recovery Scale-Revised). It is the most sensitive scale concerning patients with disorder of consciousness[51].CRS-R scoring ranges from 0 to 23. It includes 6 subscales: auditory, visual, motor, verbal, communication, arousal level. It is very detailed, reproducible, but takes a long time to practice (see figure 2.3). It has shown that it can correct the diagnosis in nearly 40% of patients when applied rigorously [113]. The multiplication of this clinical exam improves the diagnosis of consciousness [128]. Other interesting signs have been developed such as the habituation of the auditory startle reflex [58]. This sign shows the preservation of brain-scale fronto-parietal networks and distinguishes patients in vegetative state and minimally conscious state.

2.3 EEG

The EEG records the electrical activity that is generated by the temporal and spatial summation of postsynaptic depolarizations of the pyramidal neurons

of the neocortex. The EEG has the advantage of being an inexpensive, non-invasive and standardized examination [93].

EEG in clinical practice

The primary interest of the EEG in DOC patients in the acute phase is to diagnose a complication impairing consciousness recovery [29]. This is interesting when the detection of these anomalies can have a therapeutic impact. Most of the time, the examination lasts about 30 minutes but some intensive care units have continuous monitoring. The main complications are 1) epilepsy and in particular non-convulsive seizures or non-convulsive status epilepticus [25], 2) the presence of encephalopathy, whether metabolic, septic, drug-induced or toxic.

Secondly, the EEG is also a valuable help in the prognosis of cerebral lesions [29]. It is, for example, well coded in the management of post-cardiac arrest and, together with other markers (clinical, biomarker, brain imagery), allows the worst prognosis to be detected [109]. The study of these EEGs consists in analyzing background activity and reactivity. For background activity, the amplitude and frequency of brain activity is studied. Decreased amplitude and frequency, depressed background activity, burst suppression sequences in the absence of sedation are elements of poor prognosis [27]. The study of reactivity is more controversial [1] and in particular the lack of reactivity in the early days with the outcome at 6 months, this analysis needs more standardization of stimulation and interpretation methods [5].

The clinical EEG study is based on visual inspection and is often poorly standardized with a very high inter operator variation. From this observation, the idea was to develop quantitative and automatic tools, this approach has already shown a real added value in addition to a well conducted clinical examination [118, 43].

Extracting consciousness related features from the EEG

These different quantified measurements from the EEG can be classified into 3 types: spectral analysis derived from Fourier frequency analysis, measurements derived from information theory based on the complexity of the signal, and finally a functional connectivity measurement that studies the long-distance connections between brain areas through the exchange of information between EEG electrodes.

Spectral and frequency domain Spectral analysis is a well-established method for the analysis of EEG signals. There are 5 basic bands frequencies:

1. Alpha: frequencies between 8 and 13 Hz and an amplitude between 25 and 100 mV. We find this rhythm with a bilateral occipital predominance which most often extends to the anterior regions [92]. They are collected mainly when the subject closes the eyes. Opening the eyes makes the alpha rhythm disappear while keeping the rhythms fast [13].
2. Beta: fast frequencies, higher than 12 Hz (and generally lower than 45 Hz). They are of low amplitude (5 to 15 mV) and especially visible on the fronto-parietal regions. They correspond to the rhythm that is recorded in an awake subject, during information processing but also during REM sleep [90].
3. Gamma: fast frequencies above 30 Hz. We can detect them all over the scalp. Research is interested in the field of perceptual construction, cognitive functions and consciousness [81].
4. Delta: up to 4 Hz frequency and 100 to 200 microvolts of amplitude, normal for very young children, they can characterize some brain lesions. We find them in deep sleep.
5. Theta: frequencies between 4.5 and 8 Hz, from 50 to 100 microvolts of amplitude. We observe them mainly in children, adolescents and young adults. It's a rhythm associated with limbic activity, linked to the memorization of information [130]. They sometimes reflect a cortical or sub-cortical suffering in some pathologies.

In a previous study [118], it was shown that the measurement of spectral power in the alpha band and theta band could discriminate VS patients from MCS. The power of normalized alpha increases significantly from the patient VS to the conscious patient. Mathematically, the power spectral density is estimated by the Welch method. The power in a given band is calculated as the integral of the spectral power density then it is linearized using a logarithmic scale. The estimation of the spectral power density can be biased because of the eye movements or the impedance of the electrodes, which are specific to the subject and the session. To solve this problem, the normalized power is calculated by dividing the power in each band by the total energy in the trial. It is expressed in dB and therefore represents a percentage of power.

Parameters derived from theory of information Information theory is a probabilistic theory whose purpose is to quantify the content of information in a signal. This theory is applied to the EEG signal.

Complexity of Kolmogorov Chaitin We apply the complexity of Kolmogorov Chaitin to the EEG signal. Complexity is the easiest way to code a signal. In other words, it measures the degree of redundancy of a signal and to what extent this signal can be compressed [31]. For example, the good quality recording of an opera will have a very high complexity, since it will have to be broken down into several signals comprising a lot of information and the quality of the recording will depend on the difficulty in compressing the recording. On the other hand, a message comprising only “A” will have a low complexity, containing little information, and easily compressible.

In our case, the complexity of the signal is represented by the size of the smallest computer program that can be made to define this signal. In this theory, it is impossible to find an algorithm capable of measuring this complexity. The lower limit is therefore estimated by applying lossless compression, that is to say a compression which restores after decompression a series of bits strictly identical to the original. The degree of compression is then compared to the basic signal. We use here an open source compressor: gzip. It uses a compression algorithm, a method called Deflate including the LZ77 algorithm and Huffman coding [132]. The first is based on dictionary compression by transforming the sequence into 32 symbols, then we replace the recurring sequences by the position and the length of the occurrences in a sliding window. The second is based on the construction of a tree where we assign to each redundant sequence, a weight. Thus, after having calculated the number of occurrences of a sequence, the more redundant the sequence the more a small number of bits is allocated to code it. Compression by gzip is therefore based on signal redundancy. We then compare the size of the compression compared to the initial file. The more compressed the file, the less information it contains.

Permutation entropy Permutation entropy (PE) was developed by Bandt and Pompe (Bandt and Pompe, 2002). The basic principle of this method is the transformation of the time signal into a sequence of symbols before estimating entropy. The complete description is given in Sitt, Brain,

201416 The transformation is made by considering consecutive sub-vectors of the signal of size n , $n=3$ here, and a parameter defining a broad frequency-specific. After the symbolic transform, the probability of each symbol is estimated, and PE is computed by applying Shannon's entropy formula to the probability distribution of the symbols.

Functional connectivity

Weighted symbolic mutual information (wSMI) The purpose of this new measure, wSMI [67], is to assess long-distance connectivity. The wSMI is a measure based on the prediction of the theory of the global workspace and of experiments concerning the conscious perception of subliminal stimuli. Indeed, several studies⁶³ have shown a late use of the fronto parietal network and above all an increase in the sharing of information between brain areas. In a previous study [118], the wSMI showed that it was an efficient marker for discriminating VS patients from MCS patients (see figure 2.4). The principle of calculation of the wSMI is summarized in the figure 2.5.

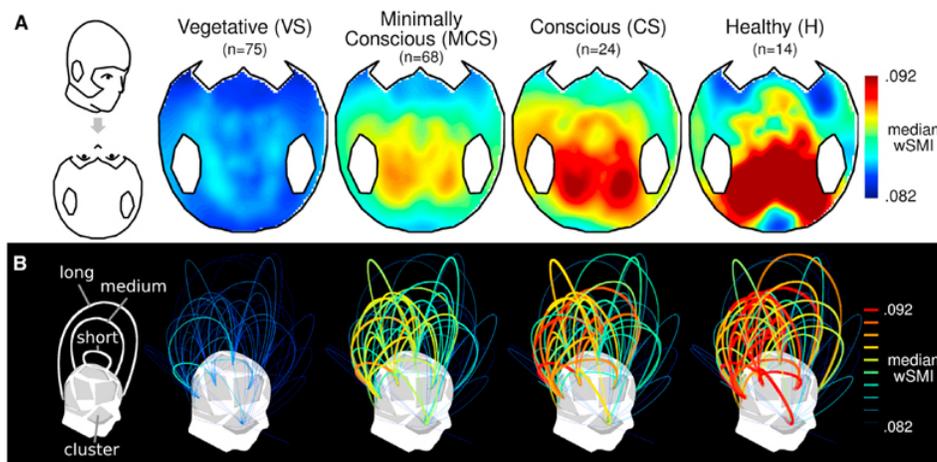


Figure 2.4: **Representation of wSMI by patients group**

A) The average WSMI by patient group shows that wSMI discriminates VS and MCS patients. B) Line color represent the mean wSMI shared by the brain area. there are more long-distance connections between brain areas for healthy subjects and conscious patients than for MCS or VS patients. From King, 2013 [67]

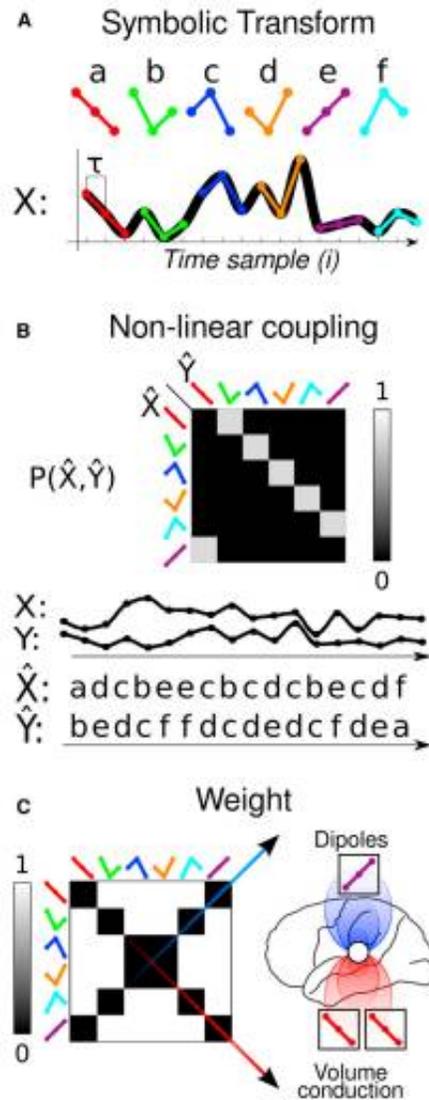


Figure 2.5: Calculation principle of wSMI.

A) The EEG signal is transformed into a sequence of 6 symbolic figures. B) Each pair of electrodes are considered to compute the probabilities corresponding to the conjunction of symbolic elements. C) The probability value is weighted to ignore conjunction of identical or opposite symbols. From King 2013 [67]

The EEG signal is transformed into a sequence of 6 symbolic figures then the permutation entropy (PE) given by this formula is calculated:

$$PE(x) = - \sum_{m=1}^M p_m(x) \log(p_m(x))$$

where X is a system with M states. In our case, the EEG signal is restricted to 6 states. We then take each pair of electrodes and observe the conjunction of symbolic elements. Mutual information measures the quantity of information distributed on average by a realization of X over the probabilities of realization of Y. Here, symbolic mutual information (SMI) is used.

$$SMI(X, Y) = \frac{1}{\log(k!)} \sum_{x \in X} \sum_{y \in Y} p(x, y) \log \frac{p(x, y)}{p(x)p(y)}$$

where x and y are the symbols present in the signal, p(x,y) is the joint correspondence of the co-occurrences of the symbols in the signal, p(x) and p(y) are the probabilities of each symbol respectively in each signal and k! the number of symbols. The SMI is weighted to ignore conjunctions of identical or opposite symbols that may come from a common source of artifacts. Weighted symbolic reciprocal information (wSMI):

$$wSMI(X, Y) = \frac{1}{\log(k!)} \sum_{x \in X} \sum_{y \in Y} w(x, y) p(x, y) \log \frac{p(x, y)}{p(x)p(y)}$$

If there is a conjunction of identical or opposite symbols, w(x,y)=0 otherwise w(x,y)=1. The connectivity measurement is obtained by taking the median value of all pairs of electrodes.

Local Global Paradigm The Potentials Evoked (PE) consist in measuring the brain responses to specific sensory stimuli, in this case, auditory stimulation to study cognitive processing. The founding article describing the paradigm was published in 2009 [14]. It is a protocol inspired by the odd-ball paradigm, allowing to discriminate between a conscious treatment and an unconscious treatment. We define 4 types of auditory series, called epochs. The epochs are either composed of 5 identical sounds: AAAAA or BBBBB, or composed of 4 identical sounds and 1 deviating sound: AAAAB or BBBBA. A block is made up of 100 epochs with two levels:

1. - A violation of the local regularity: After 4 identical sounds when the fifth sound is different, there is a violation of the local regularity. These

epochs are called "Local Deviant" (LD). If the 5 sounds are identical, it is a "Local Standard" (LS).

- A violation of the global regularity: In a sequence, the most frequent epochs (80%) represent the rule, it is about the "Global Standard" (GS) while the rare epochs (20%) represent the violation of the rule and are called the "Global deviant" (GD). Each epoch is defined in terms of Global and Local. The blocks take place as summarized in figure 2.6.

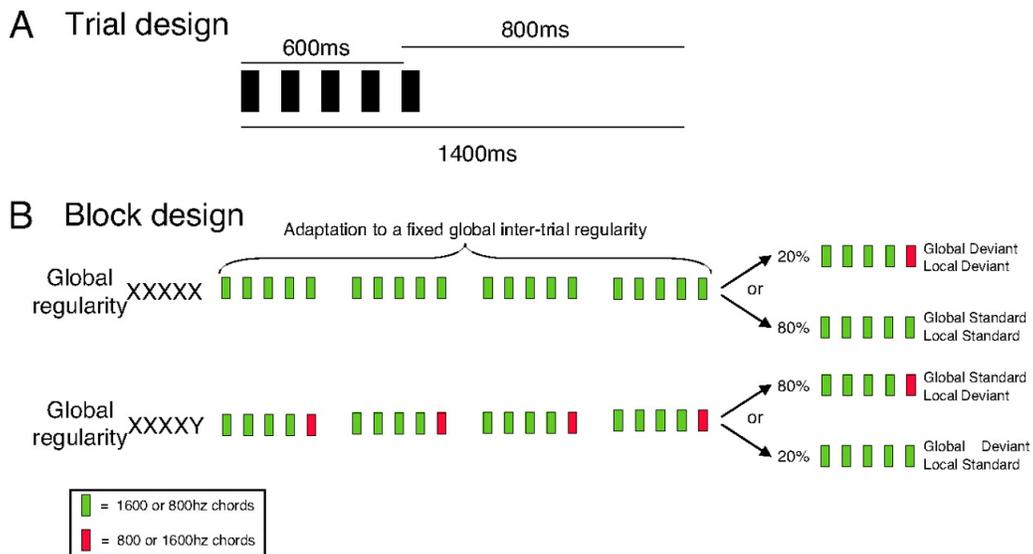


Figure 2.6: **Description of the global deviant/standard and local deviant/standard.**

The global standard matches the rule. The first four epochs are identical. The fifth epoch is different or not from the four others, it represents the GD when this fifth epoch is different from the first epochs, and represents the GS when it is identical to the first. Within an epoch, if the five sounds are identical, it is a LS, otherwise it is aLD. GD = Global Deviant, GS = Global Standard, LD = Local Deviant, LS = Local Standard. According to Bekinchtein 2009 [14].

More precisely, the sequence of 5 sounds lasts 600 ms. The duration of each sound is 50 ms with an interval between sounds of 100 ms. 600 ms corresponds to the start of the 5th sound. The analysis of the evoked potentials is done from 600 ms, it makes it possible to study the response to deviance according to the methods: Local and Global and to discriminate between the unconscious treatment of novelty and the conscious treatment of

novelty. The duration following the presentation of the 5 sounds is variable (from 750 to 1050 ms) to avoid the habituation phenomenon, consisting in the gradual decrease in the intensity of the response. In total, an epoch lasts from 1350 to 1650ms (figure 2.7).

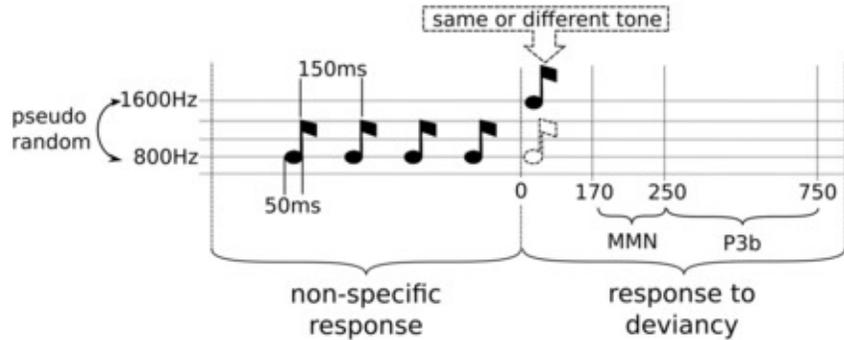


Figure 2.7: **Local global paradigm.**

The duration of each sound is 50 ms with an interval between sounds of 100 ms. The fifth sound is the same or different. When the fifth sound is different, there is a violation of local regularity. In EEG, the mismatch negativity (MMN) is a negative wave around 170 to 250 ms after the onset of the fifth sound, which signals the automatic detection of the novelty. In a sequence of several repetitions of these five sounds, the violation of this regularity, is represented in the brain by the P3b waveform around 300ms. From sitt 2014 [118]

Using the auditive stimulation described above, we can extract different evoked related responses (ERPs):

1. Mismatch negativity (MMN) The mismatch negativity is a negative wave around 130 to 200 ms post-stimulation which signals the automatic detection of the novelty, it predominates in the frontal and temporal regions of the cortex64. It is obtained by subtracting the event-related response to the standard event from the response to the deviant event. It is automatic, because it does not require attentional resources, it can be obtained without a task or even during tasks distracting from the stimulus. It is found in sleep [121, 108], during general anesthesia [117] and in some patients with disturbances of consciousness. Concerning patients with consciousness disorders, and more particularly patients in coma, several studies [64, 46] have shown that the presence of MMN could predict a

return to consciousness with a specificity of 80 to 100 %. On the other hand, the absence of MMN does not signify the absence of consciousness recovery. Indeed, patient records fluctuate over time and there is also a difference between the chronic and acute status of the brain injury for the presence or absence of MMN. In functional MRI, violation of local regularity activates the bilateral superior temporal gyri including the primary auditory cortex. In the Local-Global paradigm, we interpret MMN as the unconscious treatment of novelty.

2. P300: P3a and P3b In an odd-ball paradigm, we describe a difference in the latency phase between the rare stimulus and the frequent stimulus, which corresponds to a positive wave. This positive wave at the vertex appears around 300 ms after the stimulus [122, 48]. It reflects the activity of a cortico-thalamic network. The P300 has several subcomponents, P3a and P3b [119]. From 220 ms to 300 ms, a first subcomponent peaked at central sites: P3a (the earliest component) is found as soon as the stimulus is deviant regardless of the instruction or the expectation of the rare stimulus. It has been associated with alerting processes governing the direction of attentional move [22] or a preattentive and unconscious response [86]. From 300 ms to 380 ms, a second phase of P3 showed both a frontal and a parietal maximum, coined P3b. The amplitude depends on the importance in intensity of the deviating stimulus. P3b corresponds to the conscious detection of the deviant and therefore depends on the attention and the fact of being able to report it, it is also an index of working memory updating [41] is generally associated with conscious access [115]. P3b is therefore the result of conscious information processing. P300 has shown an importance in exploration in terms of information processing in patients with a disorder of consciousness. In several studies [14, 44, 43, 67, 118], P300 was mostly present in clinically conscious patients, as compared to MCS and to VS/UWS patients.

2.4 Functional imagery

Functional imaging in DOC patients is primarily a technical challenge, but also because this population is heterogeneous with various etiologies and brain lesions. Laureys has shown, using positron camera recordings (PET-CT) and then functional MRI (f-MRI), that there could still be islands of brain activa-

tion when we stimulate (auditory or visually) of patients in a vegetative state [73]. On the other hand, in such patients, who are awake but unconscious, there is no activation of the vast distributed brain network which accompanies consciousness. In Cambridge, Owen and his colleagues have developed a paradigm in which they ask patients to imagine several situations (“playing tennis”, “walking around at home”) while recording brain activation in f-MRI [98]. This test made it possible to reveal cognitive capacities more preserved in certain patients clinically considered in vegetative state, based on behavioral examination. More recently, it has been shown that f-MRI during a rest period, called resting state, also makes it possible to distinguish patients in a vegetative state and in a state of minimal consciousness [37]. This technique makes it possible to measure the functional connectivity of different regions by calculating correlations of the Blood-Oxygen-Level Dependent (BOLD) values over time series between these different regions. Two hypotheses have been raised to explain the origins of functional connectivity at rest: (1) it would reflect the direct current of the cognitive processes in progress and (2) it would reflect random fluctuations within networks constrained by the anatomical connectivity matrix. It has thus been shown that functional communication within the Default Mode Network, but also frontoparietal, salience, sensorimotor, auditory and visual networks was reduced in DOC patients compared to healthy subjects, but above all that this measure of connectivity made it possible to distinguish the vegetative state from the minimal state of consciousness, at the group level, but also at the individual level with an accuracy greater than 80% [37]. More recently, it has been demonstrated that during a resting sequence, the mapping of functional connectivity was dynamic and that this same dynamic provided information on the state of consciousness of primates under different anesthesia conditions [126]. Similar results to f-MRI were obtained with resting 18-FDG PET-CT metabolic imaging [120].

2.5 Tractography MRI

Tractography is a non-invasive MRI method for studying the structure of axons in white matter. Brain tissue is mainly formed of two tissues: gray matter and white matter. The gray matter is made up of the cell body of neurons. White matter contains axons that connect cortical regions to each other. This technique quantifies the diffusion of water molecules along the

axon. In fact, magnetic fields in MRI include a stochastic motion of water molecules of the brain, called Brownian motion. However, the movements of water molecules are still constrained by the structure of axons: water molecules tend to diffuse more along axons than in the plane transverse to the axon axis. In this way, diffusion MRI makes it possible to study the structure of white matter fibers from certain quantified diffusion parameters. We define, for example, the mean diffusivity (MD) and the fractional anisotropy (FA) (see figure 2.8).

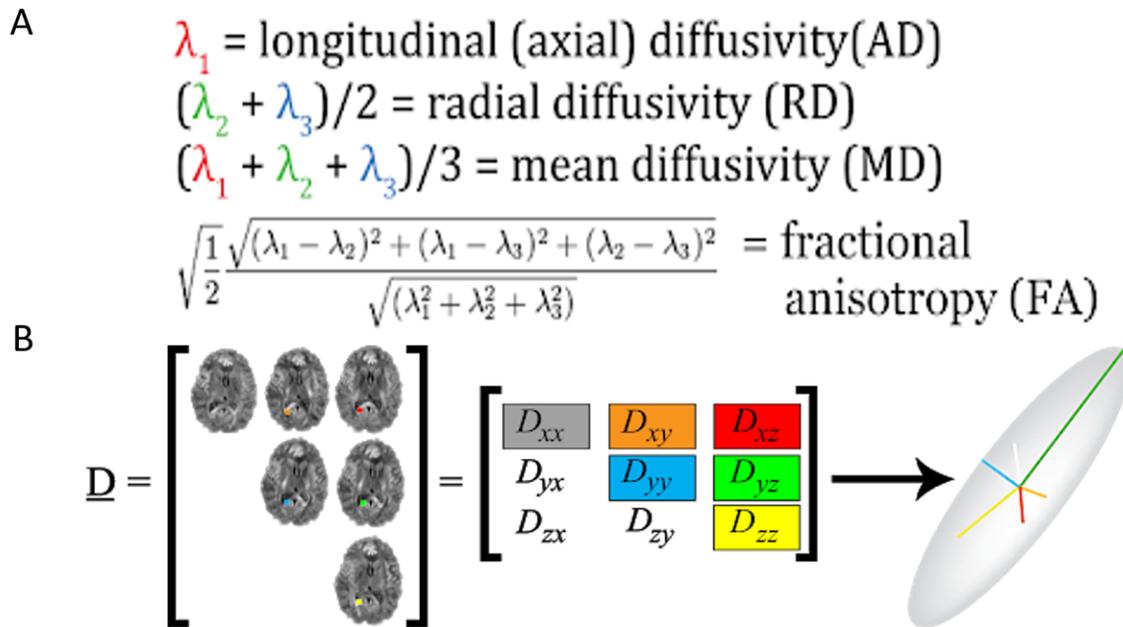


Figure 2.8: **Description of mean diffusivity and fractional anisotropy**

There are 6 number of ways that the molecule of water can take, in DTI (diffusion tensor imagery), there are 4 main measures: longitudinal axial diffusivity, radial diffusivity, mean diffusivity (MD) and fractional anisotropy (FA). 6 gradient directions, to calculate these different parameters, there are three main values (lambda 1, lambda 2 et lambda 3) corresponding at displacement/diffusion for each specific vector. MD is sensitive to cellularity oedema and necrosis, FA is sensitive to microstructural changes. From diffusion-imaging.com.

These diffusion parameters were studied by the Puybasset team in patients after cardiac arrest [127]. They showed that the FA of the patients with the best prognosis (Glasgow-Pittsburgh Cerebral Performance Categories = 1 or

2) had an FA mean overall white matter greater than 0.91. Studies are in progress to investigate diffusivity parameters and prognosis in patients with TBI, but studies [116, 91] have shown that FA is particularly reduced in the corpus callosum, cerebral peduncles, the posterior limb of the internal capsule, inferior longitudinal fasciculus and centrum semiovale. These lesions were more in favor of an unfavorable prognosis in these patients.

Perspective: article 2

As we have seen in this section, many techniques (behavioral examination, EEG, evoked potentials, MRI, DFG-PET) are available to diagnose the state of consciousness of DOC patients. We could see that the minimal contrast was often between VS patients and MCS patients. It turns out that if the will is to integrate all the techniques that are at our disposal today, new terminology should be found to better classify DOC patients. These diagnostic questions also underlie prognostic questions. Can these examinations predict the prognosis of these brain-injured patients? While it is undeniable that a better diagnosis of states of consciousness makes it possible to better predict the prognosis, it is important to make the link between the results of these different techniques and the prognosis of the patients.

In this perspective in 2009 a new cognitive test allowing the detection of both unconscious and conscious brain responses to violations of auditory regularities (the ‘Local-Global’ test) by measuring event-related potentials at bedside has been designed. Crucially, presence of a Global Effect appeared as a very specific signature of conscious processing of the auditory sequences. In the second part of this thesis, we prospectively explored the prognostic value of the Global Effect in a large cohort of DOC patients (N=429 patients).

Chapter 3

Brain body interaction

As we have seen, most studies interested in the characterization of states of consciousness have focused on the analysis of the brain signals using anatomical and functional neuroimaging methods (MRI and EEG). Our brain constantly monitors and regulates the activity of a large number of homeostatic processes (such as the activity of internal organs or proprioceptive information). Most of these body-brain interactions are processed by the autonomic nervous system and are traditionally considered unconscious. However, it is also possible that the interactions between brain activity and that of several organs that participate in interoception (eg cardiac, respiratory or metabolic activity) are informative to determine the state of consciousness of an individual.

In a recent review [6], Catherine Tallon Baudry's team leads us to reflect on a paradigm shift for neuroscience studies. Indeed, most studies in neuroscience focus on describing the interactions between the brain and the environment, but internal organs are also constantly providing information to the brain. The interaction between these internal organs and the brain could also participate in modulating complex cognitive functions.

3.1 Brain-heart interaction

Heart and heartbeat

The heart is a special organ because it includes a tissue that automatically generates electrical impulses responsible for the contraction of the heart muscle but also transmits these contractions to the whole heart. During a heart transplant, the heart muscle keeps its intrinsic cardiac activity even though the nerves are not reconnected in the transplant patient [65].

The sinus node is considered to be the pacemaker of the heart. It is from this node that the heart's electrical impulses (about 80-90 pulses per minute) originate. The electric current travels along the internodal conduction bundles providing conduction to the atrioventricular node. The atrioventricular node acts as a brake by slowing down the conduction speed, the electrical impulse is then transmitted to the trunk of the bundle of His and to the right and left branches of this bundle then to the fibers of the Purkinje tissue leading the excitation to the entire ventricle (see figure 3.1).

This automatic heartbeat has sympathetic and parasympathetic neurogenic modulation. The heart is innervated by two nerves that are extrinsic to the heart: the sympathetic and parasympathetic nerves (see figure 3.2). Parasympathetic innervation is distributed primarily to the sinus and atrioventricular node while sympathetic innervation is distributed throughout the heart. Parasympathetic stimulation via the vagus nerve decreases the rate of the sinus node and slows the transmission of cardiac impulses. In contrast, sympathetic stimulation increases the heart rate but also increases cardiac contractility.

In the resting metabolic state, there is a sympathetic and parasympathetic tone. Basically, it is the modulation of the basic tone that makes it possible to increase or decrease the activity of an organ. The autonomic nervous system is partly controlled by the brainstem. However, signals from the hypothalamus and the brain can modulate the centers of the autonomic nervous system. For example, stimulation of the hypothalamic areas may cause, depending on the location and intensity of the stimulation, an increase or decrease in heart rate and blood pressure [57]. These effects are largely transmitted by the cardiovascular control cells of the reticular regions of the bulb and protuberance. In another example, stimulation of the different nuclei of the amygdala can trigger behavioral stereotypes of rage, flight, fear, increasing heart rate [69].

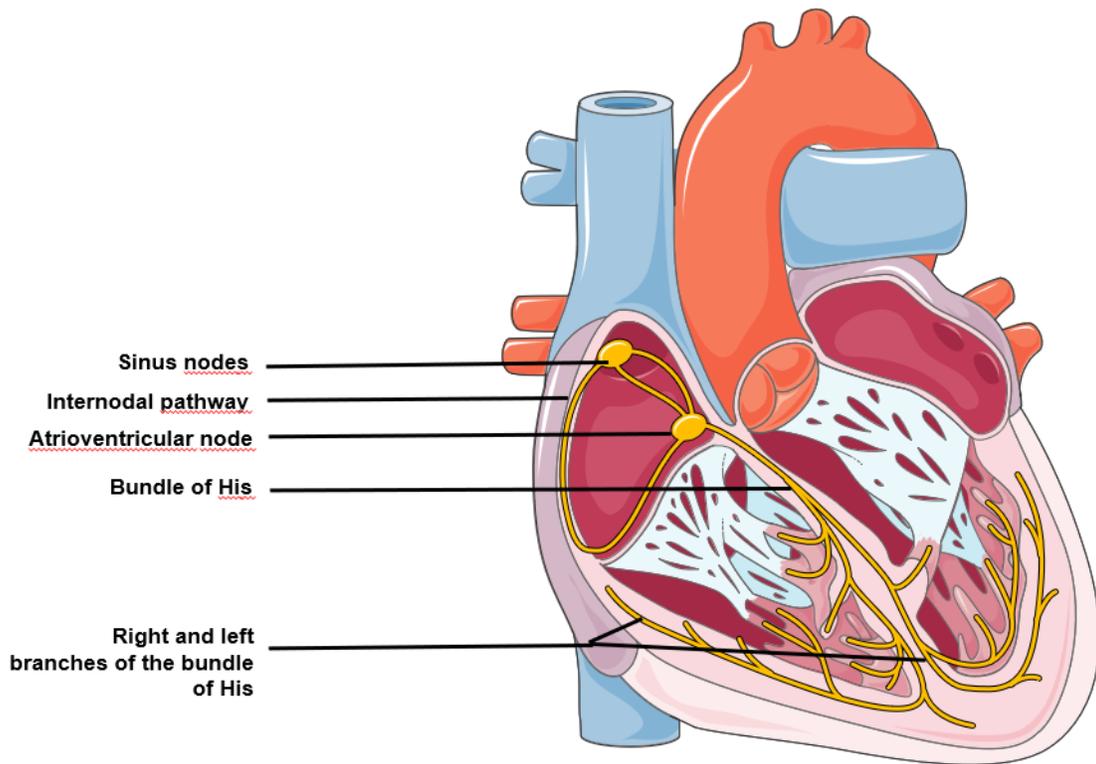


Figure 3.1: **electrical activity of the heart**

The electrical impulse begins at the sinus node. The sinus node is a region of the heart capable of self-activation (excitation and contraction, the rate of this self-activation is the highest - about 90 impulses per minute). It then spreads to the atrial internodal pathways and then to the atrioventricular node which is a brake, slowing down the conduction speed. The electrical impulse is then transmitted to the trunk of the bundle of His and to the right and left branches of the bundle of His.

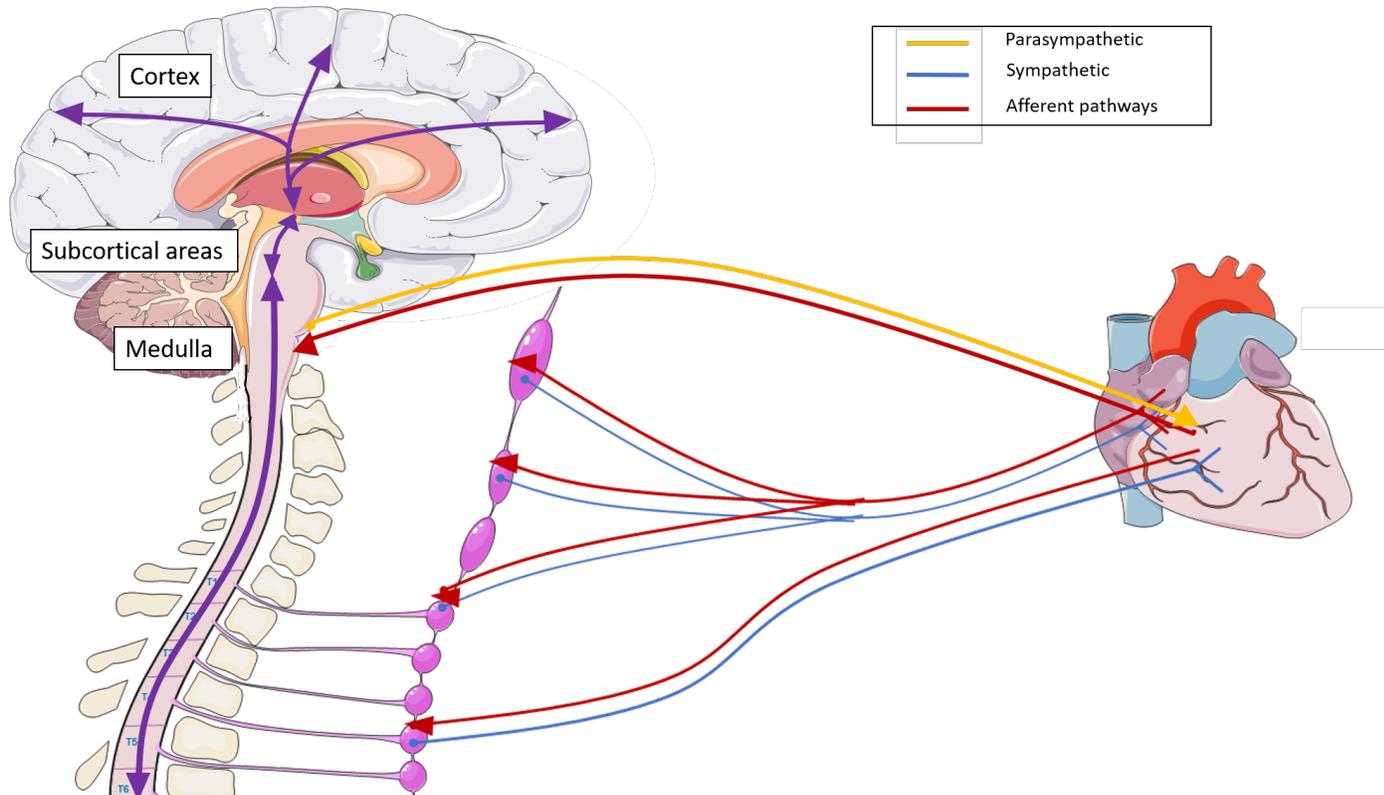


Figure 3.2: **Summary of afferent and efferent brain-heart communication pathways (inspired by heartmath institute and Guyton).**

The parasympathetic pathway (in yellow) innervates the heart via the vagus nerve. The sympathetic pathway (in blue) is based on a model with two neurons: a preganglionic neuron (whose cell body is located in the dorsal or lumbar spinal cord, not shown) which synapses on a postganglionic neuron (including the cell body is located in a paravertebral ganglion) innervating the heart. Efferent pathways (in red) carry information from the heart to the spinal cord. A complex bidirectional system between the spinal cord, the subcortical areas and the cortex exchanges information between heart and brain and between brain and heart.

The heart rate is obviously regulated by a much more complex system comprising the cardiovascular system as a whole, the humoral system, mechanical constraints by the heart-lung interaction. We have deliberately used a heart-nervous system model in this work .

Heart and Cognitive Function

Emotions Several hypotheses confront each other concerning heart and emotions. From antiquity, Aristotle believed that the heart was the seat of "sensations, passions and intelligence". The brain only served to cool the body. Hippocrates believed that it was in the brain that thoughts and emotions were born.

In 1884, William James became interested in this question by taking the example of our emotions in front of a bear: "In front of a bear, do we run away because we are afraid or are we afraid because we run away? For W.James, we feel fear precisely because we have this response of running away [62]. In fact, everyone who feels fear has experienced visceral reactions such as an accelerated heart rate, an increase in respiratory rate, sweaty hands... He notes that these sensations come first and that it is at the moment of awareness that the brain identifies it as fear and adapts a behavior to the situation. This conception is questioned by Walter Cannon who notes that all these visceral reactions are under the control of the autonomic nervous system via its sympathetic and parasympathetic branches. For him, emotions are created by the brain and visceral manifestations are consequences.

Stanley Schachter and Jerome Singer (1960) propose a new interpretation grid to the problems of emotions. According to them, cognition builds emotions. Indeed, it is the interpretation of the circumstances and the context, when one becomes aware of the visceral modifications, which would attribute the content of the emotion (joy, fear, love, anger...). In this way, researchers have described interception. Interception describes the related signaling, the processing at the level of the central nervous system and the neural and mental representations of internal body signals.

Based on recent studies, we can reconstruct the anatomical connectivity supporting emotion-related processes [103](see figure 3.3). The cortex and subcortex are part of vast systems of connection that link the body to the brain. Among the subcortical structures, the hypothalamus plays a central role. Hypothalamic nuclei such as the paraventricular nucleus innervate

all levels of preganglionic sympathetic exits [110]. Conversely, visceral information reaches many other structures, including the parabrachial nucleus (in the pons), the periaqueductal gray, the hypothalamus (paraventricular nucleus and lateral zone) and the amygdala (central nucleus) [94]. In the cortex, specific areas are known to affect vegetative responses: the medial orbitofrontal cortex, the cingulate gyrus and the insula [104]. In particular, the physiological condition of the whole body is transmitted to the posterior insular cortex, which can be considered an interceptive cortex, just as parts of the parietal cortex are the somatosensory cortex, for example [32].

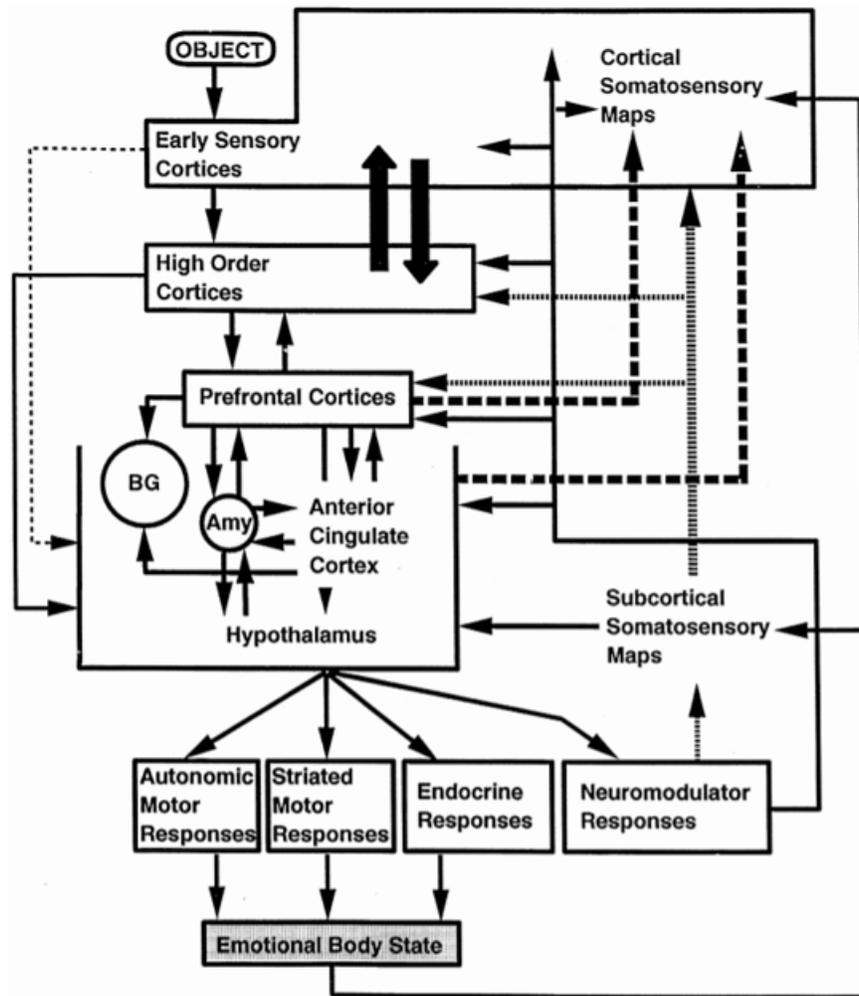


Figure 3.3: **Link between the different brain structures and body responses related to emotion.**

The limbic system is central in the creation of emotions but many other brain structures have an important role such as prefrontal cortices, somatosensory cortices, monoamine nuclei in the brain stem, periaqueductal gray and other nuclei in the brain stem and spinal cord involved in both afferent and efferent signaling relative to viscera. From Damasio [33]

Heart and Consciousness Beyond the link between heart and emotions, there is evidence for a link between heart and consciousness/attention. For example, engaging in a complex cognitive task causes a bradycardia called "attention bradycardia" [70]. More broadly, brain activity has a direct influence on the ongoing bodily states. A naive example is how our cardiac frequency can increase in moments of tension and how the feeling of our own heart beats maintain the stress level. There is a lot of evidence for a link between the body and the brain and more particularly between what is called the autonomous system and the brain . The autonomous system is a largely unconscious control system that regulates the primitive functions of the body such as heart rate, digestion, respiratory rate or pupillary responses. The link between this autonomous system and cognitive processes is not trivial, and the heart is the most studied organ in this field so far. The most common way to study the link between heart and brain is the heart-evoked potential. This technique is based on the analysis of the cortical response in EEG time-locked to the R-peak of the ECG. It represents the specific mechanism of afferent input from the heart to the brain. Recent studies in interoception in healthy subjects demonstrate that brain modulation of peripheral body functions can be affected by concomitant cognitive processes [49].

More specifically in the field of consciousness research, authors showed that the amplitude of brain response locked to heartbeats before subliminal stimulus onset predicted the conscious perception of a stimulus, postulating that heart-brain interactions participate in the consciousness of a stimulus [100] with an important role of the prefrontal cortex. In patients with disorder of consciousness, in the complex oddball paradigm allowing to determine a specific signature of conscious access to the violation of auditory regularities in EEG, the interval between the deviant sound and the next heartbeat was shorter in minimally conscious group than vegetative state group [105]. This work showed a link between residual cognitive processing and the modulation of autonomic somatic markers.

Regarding self-consciousness, Catherine Tallon Baudry's group studied the extent to which the self is engaged in an experience of spontaneous but interrupted thoughts by asking the subject if he thought that he was an actor in the thought that was going on (e.g., it's sunny or, I have to go shopping, or I'm hungry...). The researchers studied how the brain responds to the heartbeat if the subject said that self-engagement was high or not. Brain activity is recorded in MEG and they found a difference in heartbeat response in two regions in posterior cingulate cortex and in the ventromedial prefrontal cor-

tex with greater responses when engagement was high [8]. This experience showed again a link between heartbeat and consciousness. However, in most of these studies, HEP is constrained by a task. The issue of the liability of the responses evoked by a naturalistic audio visual stimulus has come up. Humans synchronize their brain rhythms [18] in many situations like human verbal communication or music listening [102, 77]. These synchronizations could be in relation to their sustained conscious engagement to given stimuli in the external world. In this perspective, Uri Hasson has developed a method named InterSubject Correlation (ISC) based on a comparison between neural response timeseries (MRI, EEG...) across different subjects during presentation of ecological stimuli [56, 55, 15, 85]. The most simple example is the study of engagement level during a popular movie viewing. When a subject watched freely a movie in the MRI, the ISC across multiple region of the brain was more elevated for a thriller movie than a segment of reality [56]. The ISC can also identify the degree of engagement and predict the audiency success [39]. Likewise, when watching a film, the ISC of two patients with impaired consciousness was calculated relative to healthy subjects [88]. It allowed to show that despite vegetative state behavior (eyes open, no contact, no response to orders), one of the patients had brain synchronization with the control group. This synchronization was not only in the auditory and visual cortices but also in the associative cortices, suggesting that the patient had a higher state of consciousness than his behavioral state prejudged. In the same way, the ISC decreased when the attention is modulated by a task perturbing the attention to a video [28].

Perspective: article 3

We would like to explore if physiological signals from the body can be used to extract evidence of conscious processing by studying the intersubject synchronization of cardiac signals with different emotional valences. We want to show firstly that the cardiac signal synchronizes with an auditory history and secondly that the ECG synchronization varies with attention and that this synchronization is not explained by the respiratory signal. Finally, we would like to show that patients with consciousness disorders do not synchronize the ECG with a healthy subject population during an ecological stimulus.

Part II

**Content-State Dimensions
characterize different
types of neural correlates
of consciousness**

Content-State Dimensions characterize different types of neural correlates of consciousness.

Authors:

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NOC = neuroscience of consciousness

Abstract

The identification of the neural correlates of consciousness (NCCs) is an important part of the scientific study of consciousness as they can constitute support to the different theories. NCCs can be defined to reflect either the brain activity associated with specific conscious content or the brain activity associated with different states of consciousness independently of content, two aspects that are traditionally studied separately. In this paper, we introduce a framework to characterize NCCs according to their behavior in both the 'state' and 'content' dimensions. We propose a two-dimensional space defined by the NCCs' capacity to distinguish the state-of-consciousness (conscious states versus non-conscious states, X-axis) and the content (accessed versus non accessed perceptual representations, Y-axis). According to the sign of the X and Y axis, the two-dimensional space can be characterized by four quadrants reflecting NCCs that are either correlated or anti-correlated in terms of state and content.

We present two implementations of the proposed framework with three types of EEG NCC-markers: markers of connectivity, markers of complexity, and spectral summaries. In both examples, the NCC-state is represented by the level of consciousness in patients with disorders of consciousness. The NCC-content is represented by the conscious content in healthy subjects in two perceptive tasks: 1) auditory local-global paradigm and 2) visual awareness paradigm. In both examples, we observe that the proposed NCCs are present in the four quadrants separating clusters of NCCs with correlated (i.e. theta power) and anti-correlated (i.e. complexity and connectivity measures) behavior leading to a different

interpretation of each NCCs cluster. As such, the proposed framework can constitute an important tool to better interpret the true neuronal mechanisms behind the neuronal correlates of consciousness.

Introduction

Giving a definition of consciousness with a coherent theoretical framework seems to be a colossal task. In this way, Identifying the neural substrates of consciousness (NCC) has become crucial to allow progress in the science of consciousness. Following the Koch & Crick seminal definition, neural correlates of consciousness are the minimal neural processes that must occur in the brain for a particular conscious experience to occur (Crick & Koch, 1990). However, this definition leaves the possibility of two types of NCCs, NCCs of conscious contents and NCCs of conscious states.

Traditionally, research on consciousness has been developed in these two pillars. On the one hand researchers primarily focus on the neuronal processes behind conscious access to specific content (e.g. seen versus non-seen stimuli). On the other hand, a large set of studies focus on global states of consciousness (Bayne et al., 2016; Boly et al., 2013; Owen & Coleman, 2008; Sanders et al., 2012). This research has been rather developed by physicians with questions of diagnosis and prognosis often sanctioned by ethical and end-of-life questions.

Neural correlates of conscious content (NCC-C) are usually the neural processes that occur in a specific experience. NCC-C are normally studied by comparing conditions where specific conscious content (perception of sound or image ...) is present or absent in the same state of consciousness. The difference between the neural activities averaged by trials of a perception compared to the absence of perception (for example, "seen" vs "unseen") is generally considered to be a neural correlate of visual consciousness. We use several paradigms such as paradigms of perceptual suppression, masking... (Dehaene & Changeux, 2011; Kim & Blake, 2005) Various methods such as EEG / MEG or fMRI allow us to study the neural correlates of these conscious perceptual experiences (Koch et al., 2016a; Tsuchiya et al., 2015) .From these studies, the NCC-Cs which differentiate the "seen" from the "not seen" range from the temporal zones of perceptual treatment to zones of superior and subcortical

association (Boly et al., 2017). Electrophysiological studies on monkeys and humans have revealed several signatures of auditory awareness: P3b and oscillations in α / β (9-30 Hz) and γ (> 40 Hz) bands between the visual cortex and the frontoparietal cortex (Dehaene & Changeux, 2011). Another example of the paradigms used to contrast conscious contents is the local-global paradigm (Bekinschtein et al., 2009). This auditory paradigm is designed to EEG potentials that are directly linked to conscious processing of hierarchical regularities. A key scientific debate concerns here the specific isolation of genuine NCC-Cs versus either post-perceptual (or 'downstream' NCC (Aru et al., 2012; C. Sergent & Naccache, 2012)) or pre-perceptual (or 'upstream' NCCs). Recent empirical developments of this question stimulated the design of 'no report' paradigms (Pitts et al., 2018; Tsuchiya et al., 2015). A important recent result obtained by Sergent and colleagues (Claire Sergent et al., 2021) demonstrated that NCC-C free of report is a brain-scale neural event engaging both parietal and prefrontal cortices, - as predicted by GNWT(Dehaene & Changeux, 2011) , by Higher-Order Theory(Brown et al., 2019; LeDoux & Brown, 2017) and by fronto-parietal model (Giacino et al., 2014; Laureys & Schiff, 2012)of conscious access -, but that it differed from the proposed P3b ERP component by the absence of SMA and premotor cortices that seem to be recruited only when an explicit subjective report or meta-report has to be made (Naccache, 2018b)

Neuronal Correlates of Conscious State (NCC-S) are used to differentiate states of consciousness. States of consciousness include conditions as diverse as sleep, partial complex seizures, general anesthesia or patients in a vegetative state or in a minimal consciousness state (Laureys et al., 2004). It is considered a basic condition for the emergence of consciousness, which would be an appropriate level to "ensure adequate cortical excitability" (Koch et al., 2016b). Consciousness disorders in patients with brain injury are a good model of different states of consciousness. The current taxonomy to describe these patients is based on the neurological evaluations (CRS-R, Coma Recovery Scale-Revised (Kalmar & Giacino, 2005)). This evaluation classifies these patients on a different clinical

conditions: the vegetative state patient (VS), characterised by a behavioral examination of eyes open without contact (Jennett & Plum, 1972), the minimally conscious patient (MCS), with visual pursuit or response to simple commands (Giacino et al., 2002), and the exit-MCS (EMCS) patient, which is able to maintain a communication code. These three clinical categories can be considered 'ordered' in gradient reflecting the richness of conscious experience (Bayne et al., 2016). These theoretical and behavioral findings are also verified - and in many cases enriched (Naccache, 2018a) - by NCC-S. For example, different electrophysiological markers derived from EEG recording in resting state (Sitt et al., 2014) are able to discriminate VS patients from MCS patients. In the same way, fMRI during a resting state period (Demertzi et al., 2014, 2015; Di Perri et al., 2016), PET with metabolic markers (Stender et al., 2014) or the calculation of an index reflecting the EEG reaction after stimulation by TMS are capable of discriminating against VS patients, patients MCS (Casarotto et al., 2016). This contrast is interesting because it makes it possible to study the vegetative state as a state of wakefulness without consciousness and the minimally conscious state as a state with minimal behaviors taking into account the environment or self-awareness.

All the presented results demonstrate a rich literature studying particular brain activity features as putative state NCC or content NCC. However, not much is known when it comes to comparing those given features in both NCC dimensions simultaneously, do the different NCC reflect identical neuronal processes relevant in each dimension?

In this work we propose a simple framework (a 2d space) that can be useful to contrast brain activity features in both NCC dimensions at the same time, and to characterize different types of NCC according to the location in the proposed 2d space. Finally, we provide two experimental examples using the proposed 2D characterization of NCC.

Proposition

Description of the 2D-representation: state versus content

We have shown the difficulty of studying the state and content of consciousness under the same spectrum. In order to be able to study the 2 concepts at the same time, we propose a two-dimensional space (see figure 1) representing the performance of the different NCCs to discriminate conscious states (X-axis) and conscious content (Y-axis). X-axis is the axis of state of consciousness. We represented the NCC marker performance corresponding to the area under the receiver operating characteristic curve (AUC) contrasting 2 different states of consciousness. The AUC represents the level of chance of the proposed NCC-S to discriminate 2 conditions, it is a value between 0 and 1 (0 means test incorrectly classifies all subjects, 1 correctly classifies all subjects, 0.5 is considered chance level). The origin of the axis begins at 0.5 because $AUC=0.5$ corresponds to the level of chance. In the examples in this article, we use the contrast between VS patients and MCS patients because they seem to be part of the same gradient: the vegetative state as a state of wakefulness without consciousness and the minimally conscious state as a state with minimal behaviors taking into account the environment or self-awareness.

Y-axis is the axis of conscious content. Conscious content is represented by the same markers used in the x-axis but in this case contrasting a perceptual task between a conscious condition and an unconscious condition. We also use the AUC of each marker to differentiate between conscious and unconscious conditions. In this article, we used two examples of perceptual tasks: 1) local-global paradigm in the auditive task using a complex oddball paradigm and 2) visual awareness paradigm using a visual backward masking paradigm (see methods).

The two proposed axes divide the plane into four quadrants. The location of each marker in a given quadrant determines how this marker behaves in terms of state and content (Figure 1). Top right ($AUC-X > 0.5$ and $AUC-Y > 0.5$) and bottom left ($AUC-X < 0.5$ and $AUC-Y < 0.5$) quadrants correspond to markers that behave in unity in the state and content dimensions (increase in conscious state and conscious content or decrease in both dimensions). In contrast, top left ($AUC-X < 0.5$ and $AUC-Y > 0.5$) and bottom right ($AUC-X > 0.5$ and $AUC-Y < 0.5$) quadrants correspond to markers that have opposite behaviors in both dimensions (increase in conscious state and decrease conscious content, or vice-versa). In addition, two bands around the X and Y axis correspond to markers that are only valid for state (X) or content (Y).

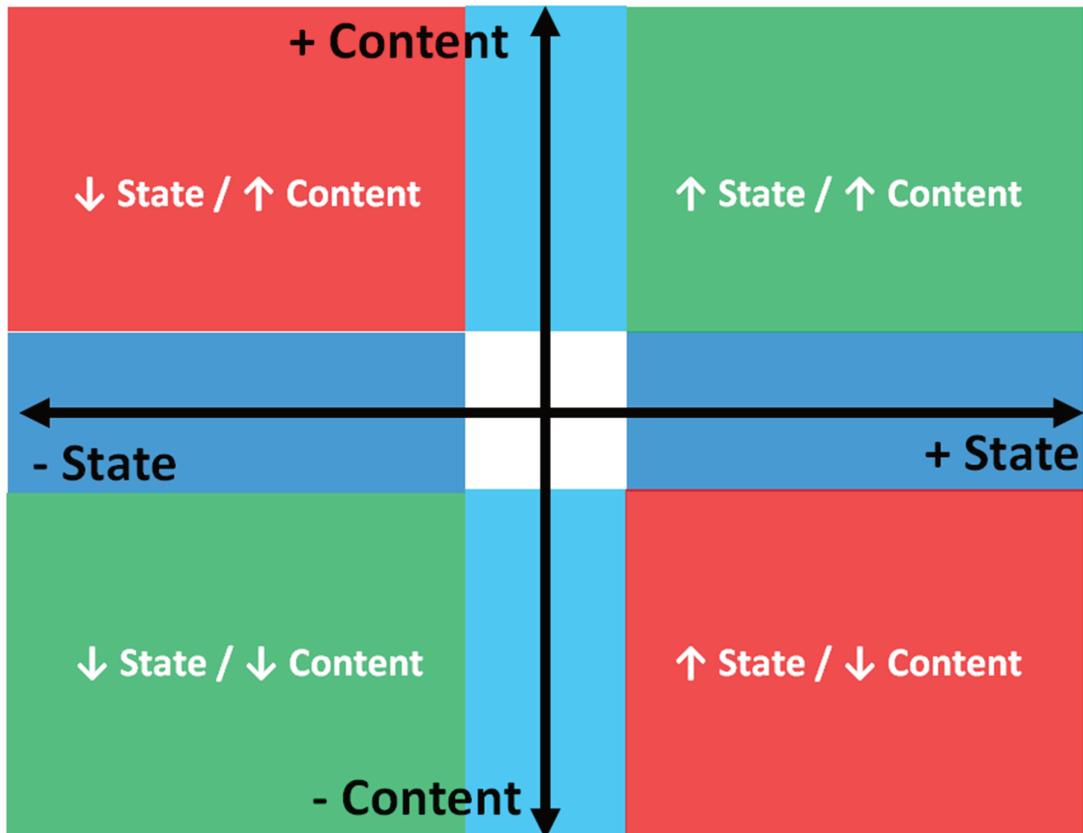


Figure 1: A 2D representation of state of consciousness and conscious content

NCC markers space can be divided into four quadrants and four bands of interest. The two green quadrants correspond to the quadrants in which the content markers decrease when the level of consciousness decreases and vice versa. The remaining two red quadrants are less intuitive and correspond to an increase of content markers when the level of consciousness decreases (or vice-versa). The blue bands are the pure NCC-state (dark blue) and the NCC content (light blue).

Example 1: local-global paradigm

We recorded high-density ERPs during the active 'local-global' task (see methods) in 388 patients (Behavioral exam according to CRS-R: 191 MCS and 197 VS) addressed to our team at the Pitié-Salpêtrière University Hospital in Paris for a diagnostic and prognostic evaluation of consciousness. The EEG of 36 healthy subjects is recorded with the same paradigm.

The local-global paradigm (see methods) seems particularly relevant because it is an oddball auditory paradigm that has two hierarchical levels of regularities: a "Local" regularity that triggers early responses that are preserved in conscious and unconscious states, and "Global" regularity which triggers late evoked responses that are only present in awake, conscious, and attentive subjects (Bekinschtein et al., 2009; J. R. King et al., 2013; Strauss et al., 2015; Wacongne et al., 2011). The neural responses to the violation of each of these regularities can be quantified from two complementary contrasts, the local contrast (Local deviant trials versus local standard trials) and the global contrast (Global deviant trials versus global standard trials). In addition this paradigm allows to compute different putative markers from segments of "pseudo resting-state" to contrast their power to index the different states of consciousness (Sitt et al., 2014).

Three types of marker are computed: 1) Markers of connectivity: wSMI in the theta band, 2) Markers of complexity: Kolmogorov-Chaitin complexity, spectral entropy and permutation entropy, 3) Markers of frequency power: alpha power, beta power, delta power, gamma power, theta power.

In this example we represent these different EEG markers in the proposed 2D plane in order to differentiate their behavior according to the state of consciousness or the conscious content (see figure 2). In the X-axis we use the patients data and we order the markers according to the AUC on the VS versus MCS contrast. For the Y-axis we used healthy participants data and we sorted the markers according to the AUC on the GD versus GS or the LD versus LS contrasts.

We report significant AUC for the content or the state if the AUC value is significantly different from 0.5 with a sign-test (distribution of marker values through the subjects is different from 0.5). At first glance we can observe the markers arranged in the most intuitive quadrants. Only $|\theta|$ is on the top-right quadrant (reflecting increasing values for both content - deviant trials versus standard trials - and for state - minimally conscious versus vegetative states -). Surprisingly, most of the markers ($|\alpha|$, $|\beta|$, KS, wSMI, PE) are located in the lower right quadrant, meaning that these markers increase with the state of consciousness but decrease with conscious content. Conversely, $|\delta|$ is on the upper left quadrant, indicating increasing values for conscious content but decreasing for the state of consciousness. Finally, other markers like $|\beta|$, $|\gamma|$, or KS were only significant for conscious content, these markers are the pure NCC-markers of content.

A sharp difference can be observed when Local or Global contrasts are used for the content dimension (Panels A and B in Figure 2), all of the proposed NCCs seem to better discriminate the Global contrast in comparison to the Local contrast. This different behavior can be better observed in Figure 3. All but one of the NCCs show a better discriminative performance for the Global effect in contrast to the Local effect.

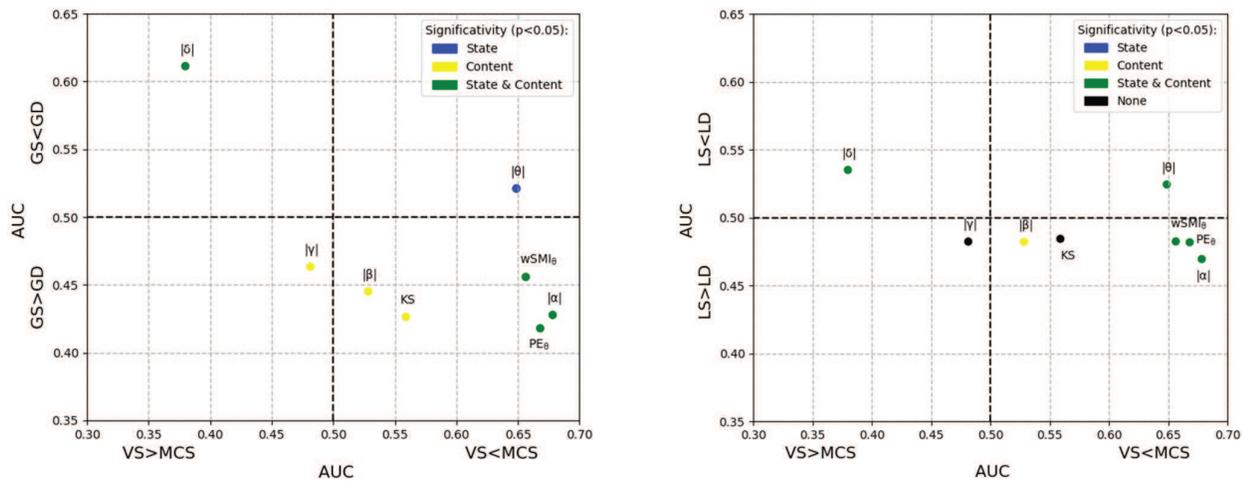


Figure 2: Example #1, Behavior of EEG markers in the state and content dimension for the local-global dataset.

Each point represents in the x-axis the ability of the marker to discriminate between VS and MCS patients. In the y-axis, we represent the ability of the marker to discriminate:

A/ the global deviant and the global standard trials in the local-global paradigm

B/ the local deviant and the local standard trials in the local-global paradigm.

Note that the zero of the y-axis is centered at 0.5. An AUC of 0.5 corresponds to a discrimination at the same level of chance.

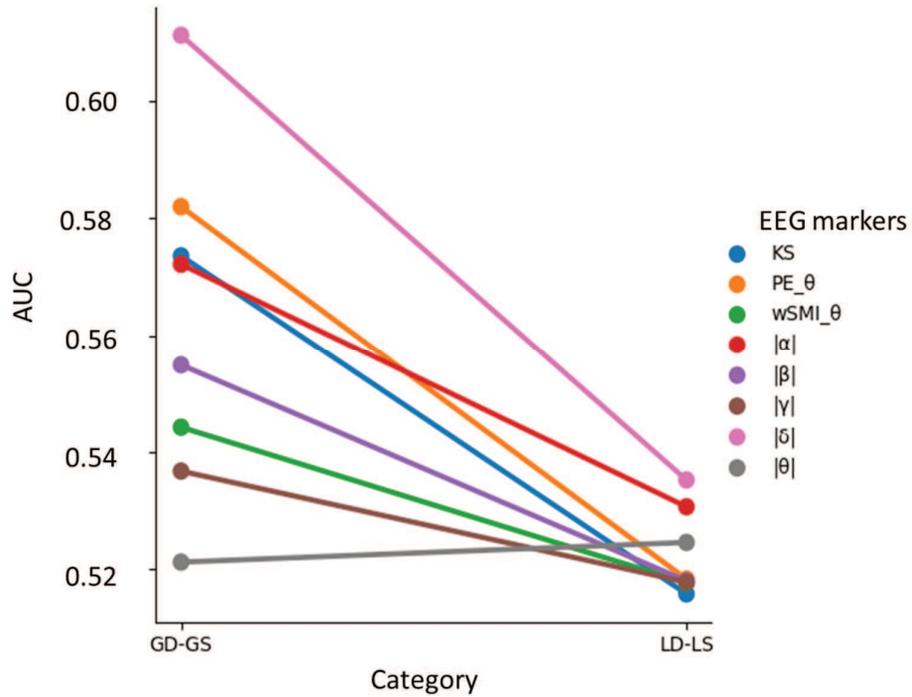


Figure 3: The proposed EEG markers show a better discriminative performance for the Global effect in contrast to the Local effect.

The power of EEG markers to discriminate GD to GS is higher than the power of EEG markers to discriminate LD to LS. The detection of the global deviant is a marker of conscious content whereas the local deviant is an automatic and unconscious response to novelty.

Example 2: Visual awareness paradigm

In this case we used 35 high density EEG recordings in healthy subjects during a visual, backward masking, awareness paradigm (Del Cul et al., 2007) in healthy participants. This experiment consists in reducing or suppressing a visual perception by presenting one visual stimulus (named mask) immediately after another visual stimulus (called target). This manipulation causes a failure of first stimulus perception. In this example, the values for each marker on the Y-axis are determined by the AUC when contrasting seen versus non-seen trials (Figure 4).

For the X-axis, we used the same subject and the same data ("pseudo-resting state") than in example 1. The originality of this example is to show that this graphical representation can be used with several types of contrast. In this example, we use a visual masking paradigm, a perceptual task and a visual modality.

Similar to the results obtained in experiment 1 most of the markers are on the lower right quadrant ($|\alpha|, |\beta|$, KS, wSMI, PE) but contrary to the first experiment, in this quadrant, only $|\beta|$ is a significant content marker, which means that its value increases with the state of consciousness but decreases with the content of consciousness.

Interestingly, the only significant markers for content are $|\beta|$, $|\gamma|$, $|\delta|$, $|\theta|$ with $|\beta|$ and $|\gamma|$ as a pure content marker and with $|\delta|$ and $|\theta|$ as state and content markers.

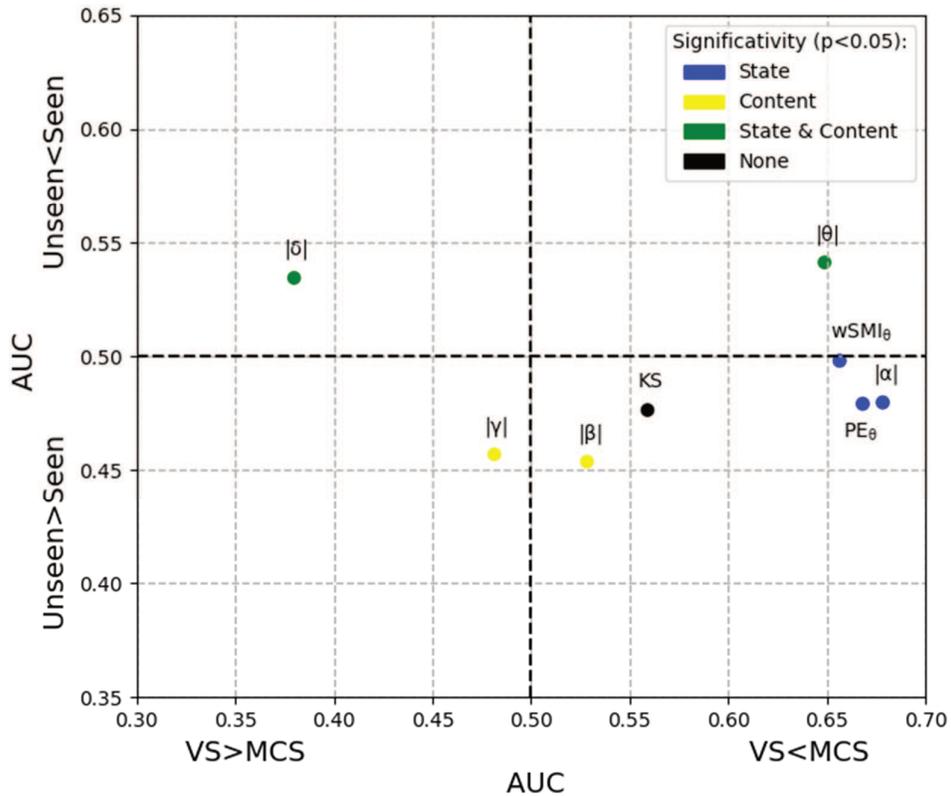


Figure 4: Example #2, Behavior of EEG markers in the state and content dimension for the Visual awareness dataset.

Each point represents in the X-axis the ability of the marker to discriminate between VS and MCS patients. In the Y-axis, we represent the ability of the marker to discriminate the target seen and unseen according to a visual awareness paradigm.

Discussion

We show through 2 examples that it is possible to project and represent the NCC-C and NCC-S dimensions of any proposed NCC marker in a simple 2D space. This simple analytical method proved robust and clear to discriminating these two complementary dimensions of consciousness in a set of two very different experiments.

Several studies have attempted to study content and state separately. A rather theoretical version proposes a 3d axis with x-axis corresponding to conscious content, the y-axis to the state of consciousness, and the z-axis to the subjective level of consciousness (Bachmann, 2012). The subjective level of consciousness corresponds in the paper to the phenomenal part of consciousness. But the difficulty is to find a technique to be able to quantify this concept. Bayne proposes a multidimensional graph like a radar chart with different axes (Bayne et al., 2016): content-related (e.g., content gating and content range) and functional dimensions (e.g., relating to attentional control, memory consolidation, verbal report, reasoning, action selection, etc.). The problem with this representation is that it is not a standardized method and the real quantification of each axis is not always possible. In a very interesting way, Sergent had created a paradigm allowing to explore 8 axes with the same paradigm but the construction of such a paradigm is complex (Claire Sergent et al., 2017).

For Chalmers, studying content and conscious state at the same time is difficult in experimental conditions (Chalmers, 1997). Indeed, one always studies variable content in a given state of consciousness. The idea of contrasting conscious state and content in a different way could be a first answer to this problem. Thus, the challenge in this 2D representation of NCC is to find a minimal relevant contrast. In these 2 examples, we contrast on the one hand the conscious state and on the other hand the conscious content but independently. Thus, the state was studied by contrasting VS patients and MCS patients classified in the clinic. This

seemed interesting to us in the sense that the MCS state was considered as an altered state of consciousness and the VS state as a state of wakefulness without consciousness.

A new perspective would be to study other contrasts in the graph we propose. we could have chosen higher level states of consciousness MCS + vs MCS- but also choose contrasts in other circumstances: sleep, anaesthesia in healthy patients....

The conscious content was studied in 2 modalities: auditory and visual. The contrast of the conscious content is also major between the different sensory modalities, but also the type of experience (masking, threshold vision, detection of novelty...), the challenge is to find a sufficiently salient contrast between the conscious and unconscious condition.

Example 1 (auditory modality) with the local-global paradigm seems particularly interesting to us because it allows for a double analysis. Firstly, it allows us to study the early, automatic response to novelty. This response does not require conscious awareness, although with healthy subjects, volunteers are often able to report novelty. In a second step, it allows us to study the late and conscious response. The first analysis of this experience is therefore a kind of control. In this example, we confirm in the LD/LS modality that the EEG markers are less able to discriminate the 2 conditions (LD or LS) compared to the GD/GS modality.

Example 2 informs us about the possibility of using this graphic representation with other content modalities such as the visual modality.

The proposals made are only examples and the discussion on each marker are hypotheses. We interpret states of consciousness as the baseline of brain activity. We expected more markers to be located in the most intuitive quadrants of the graphical representation (see figure 1), i.e. markers that increase with the state of consciousness and that also increase with the conscious content. The fact that the theta and alpha powers are higher in MCS patients than in VS patients is a fairly classic result. Nevertheless, the study of spectral markers (delta, theta, alpha, beta, gamma) in the post-perceptual state could inform us about the structure and connectivity of neural networks allowing the emergence of such intrinsic rhythms (top

down or bottom up). For example, gamma power increases with conscious content, which makes sense given the involvement of rapid gamma oscillations in auditory and visual awareness processes (Pitts et al., 2014; Tallon-Baudry, 2009). Less intuitive, alpha power seems to decrease in the post perceptual domain. This could be a reflection, as shown in a bistable perception study, that diminishing alpha power promotes a short perceptual stability to switch to the perception of the next stimulus (Piantoni et al., 2017).

The same is true for markers of complexity and functional connectivity that decrease in post perceptual with conscious content. This could be explained by a "gating" mechanism, where the conscious perceptual input would close the "doors" of connectivity, explaining the decrease of these markers in post-perceptual time. The underlying idea is that when one is in a conscious state, brain activity switches to the default processes in post perceptual time when one is engaged in a task. The reduction in complexity with conscious content is also compatible with the proposal of higher stability of neuronal activity during conscious access (Schurger et al., 2015).

We can therefore think that there is a temporal constraint on the functional cognitive architecture theorized under the name of cognitive cycle (Madl et al., 2011). Thus, according to its authors, awareness would consist of cascading cycles of recurrent cerebral events. Each cognitive cycle would then detect the current situation and interpret it according to a certain context. According to Franklin (*The Role of Consciousness in Memory — Brains, Minds & Media*, n.d.), "conscious events occur as a sequence of discrete, coherent episodes separated by quite short periods of no conscious content" similar to the frames of a movie, these frames of consciousness would be discrete but the conscious experience would seem continuous.

Conclusion

We show that it is possible to represent in a 2-dimensional graph content and state of consciousness in different perceptual modalities with many different contrasts. The stakes of this representation are both theoretical and experimental because it forces us to disentangle content and state of consciousness by studying multiple contrasts but also introduces the notion of "gating" mechanism where some markers (notably connectivity) decrease in the post-perceptual state.

The proposed framework can constitute an important tool to better interpret the true neuronal mechanisms behind the neuronal correlates of consciousness.

Methods

Population

- **Patients**

We included between 2008 and 2019, 443 patients in neuro intensive care at Pitié Salpêtrière for an expertise of their consciousness. During this evaluation, we performed several exams (clinical assessment, IRM, EEG, ERP, TEP) to determine more accurately the state of consciousness. The Ethical Committee of the Pitie-Salpetriere approved this research under the French label of 'routine care research'.

- **Healthy subjects**

Experiments were approved by the Ethical Committee of the Pitie Salpetriere Hospital, NeuroDoc protocol. 36 subjects for the local-global paradigm and 35 subjects for the visual awareness paradigm are recorded.

Paradigms

Experiment 1: Local-global paradigm

The local-global paradigm, developed by Bekinstein and al. 2009, is already reported (Bekinschtein et al., 2009)

Evoked potential response is recorded in response to auditory stimulation, using local global paradigm, in patients and healthy subjects. This paradigm is based on an oddball paradigm based on the repetition of 2 sequences of tones: XXXXX or XXXXY. In a low-level (local regularity), XXXXX is the local standard and XXXXY is the local deviant. The contrast between these two sequences reveal the occurrence of the Mismatch Negativity (MMN) . This response is in a short range and is also reproduced during the loss of consciousness associated with sleep, general anesthesia or vegetative state. In a high level (global regularities), the repetition of the XXXXY or XXXXX is the standard condition and establishes the rule. The violation of

this regularity by the other sequence: XXXXX or XXXXY respectively, is represented by the P3b waveform and requires conscious awareness and working memory. Local and global regularities are manipulated orthogonally 2*2: 1) First type of blocks: local standard-global standard (XXXXX) and local deviant-global deviant (XXXXY). 2) Second type of blocks: local deviant-global standard (XXXXY) and local standard-global deviant (XXXXX).

Experiment 2: Visual awareness paradigm

Near-threshold visual awareness was assessed using a visual backward masking paradigm modified from Del Cul et al. (Del Cul et al., 2007). In this paradigm, a para-foveal numerical target ('2', '3', '7' or '8', height = 1.7 cm, width = 1.1 cm) was presented for 16 ms either to the right or to the left of a central fixation point (8° visual angle) on a 60 Hz frame-rate screen. The numerical target was followed after a variable Stimulus Onset Asynchrony (SOA, to 16 ms at 83 ms) by a visual mask, consisting of letters surrounding the target, presented for 250 ms. 800 ms after target presentation, participants were asked to perform a subjective task of visibility rating of the target through a binary 'seen' / 'not seen' answer. Answers were collected via key press with a pseudo-randomization of response hand order and switch of response hand in the middle of the task. The entire task consisted in the presentation of 400 trials (64 trials per SOA and 80 catch trials in which only a mask was presented, without target).

EEG processing data

Experiment 1: Local-global paradigm

ERPs were recorded at 250 Hz with a 256-electrode geodesic sensor net (EGI®, Oregon, USA) referenced to the vertex. Trials were band-pass filtered (0.5-45 Hz) then segmented in epochs ranging from -200 ms to +1344 ms from first sound onset. Electrodes with voltages exceeding 100µV in more than more 50% of the epochs were removed. Moreover, voltage variance was computed across all correct electrodes. Electrodes with a voltage variance Z-score higher than 4 were removed. This process was repeated four times. Bad electrodes

were interpolated using a spline method 23. Epochs were labeled as bad and discarded when voltage exceeded $100\mu\text{V}$ in more than 10% of electrodes. Moreover, voltage variance was computed across all correct epochs, and epochs with a Z-score larger than 4 were removed. This process was also repeated four times. Remaining stimulus-locked epochs were averaged and digitally transformed to an average reference. An 200 ms baseline correction (before fifth sound onset) was applied. Pre-processing was implemented using the MNE-Python environment. Subtracting the ERP from single trials may also improve stationarity (Ding et al., 2000) , assuming that the ERP is present on each trial (Wang et al., 2008).

Experiment 2: Visual awareness paradigm

High-density scalp EEG were acquired using 256 electrodes Hydrocel Geodesic Sensor Net on a Net300 Amplifier (Electrical Geodesic, Eugene, Oregon, USA) with a sample frequency of 250 Hz during the behavioral task. Impedances were set to below 75 k Ω prior to the start of each recording. EEG were preprocessed using a fully automatic procedure (same preprocessing as for the local-global paradigm). The only change is that the epochs are segmented between -300 ms to 800 ms according to the onset of the target.

Mask subtraction

In order to get rid of the confound of evoked responses to the mask, we proceeded to a mask subtraction procedure as in the Del Cul et al. study (Del Cul et al., 2007). We first realigned all epochs to the mask onset and computed the evoked response to the mask from the catch trials. We then subtracted this evoked response from all other trials. Finally we realigned epochs on the target to obtain epochs stripped from the mask response (this procedure resulted in shortening the epochs which as a results went from -232 ms to 732 ms after target onset).

Two NCC dimensions according to local-global paradigm and Visual awareness paradigm

A set of previously proposed putative NCC (Engemann et al., 2018; Sitt et al., 2014) were computed in state of consciousness contrasts (NCC-S) and conscious content contrast (NCC-C). Importantly the algorithms and parameters used to compute the proposed markers were identical in both cases.

For the NCC-S, analyses were performed on the local-global EEG recording in the group of patients. Analyses were carried out from -100 ms before the onset of the first sound to the onset of the fifth sound (+600ms). All trials are selected independently of standard or deviant status.

In this range, three types of marker are computed: 1) Markers of connectivity: wSMI in the theta band, 2) Markers of complexity: Kolmogorov-Chaitin complexity, spectral entropy and permutation entropy, 3) Markers of frequency power: alpha power, beta power, delta power, gamma power, theta power.

The result is expressed with AUC corresponding to the estimation of the classifier's ability to discriminate between MCS and VS patients.

For the NCC-C, the local global EEG recording was used in healthy subjects from +600ms (onset of the fifth sound) and +1300ms. The EEG was also recorded during the visual awareness paradigm in the healthy subject, the window of interest is between the presentation of the numerical target (0ms) and +700ms. The same markers used as NCC-S were calculated but contrasting between deviant/ standard trials or seen/unseen trials. The result is expressed with AUC corresponding to the estimation of the classifier's ability to discriminate GD and GS trials, LD and LS trials, or seen/unseen trials.

Statistics:

AUC

The AUC is calculated from the receiver operating characteristic (ROC) curve. The ROC curve is a graph representing the performance of a classification model for all classification thresholds. It is plotted from the rate of true positives versus the rate of false positives. It is then possible to calculate the area under this curve, or AUC, using a sorting algorithm. The AUC provides an aggregate measure of performance for all possible classification thresholds. The AUC can be interpreted as a measure of the probability that the EEG marker used will correctly classify trials or conditions (here, VS/MCS patients, GD/GS or LD/LS or seen/unseen trials). A AUC value close to 1 shows that the marker is higher in the A condition than in the B condition, close to 0.5 the classifier is at random, a AUC value close to 0 shows that the marker is higher in the B condition than the A condition.

We report significant AUC for the content or the state if the AUC value is significantly different from 0.5 with a sign-test. The sign test returns $M = (N(+) - N(-))/2$ where $N(+)$ is the number of values above 0.5, $N(-)$ is the number of values below 0.5. P-value is calculated using the binomial distribution.

Computation of markers

Normalized power spectral analysis

Spectral analysis is a well-established method for the analysis of EEG signals. We estimated power in five frequency bands (delta to gamma: Delta (δ : 1-4 Hz), Theta (θ : 4-8 Hz), Alpha (α : 8-13 Hz), Beta (β : 13-30 Hz) and Gamma (γ : 30-45 Hz)). Mathematically, the power spectral density is estimated by the Welch method (Welch, 1967). The power in a given band is calculated as the integral of the spectral power density then it is linearized using a logarithmic scale. The normalized power is calculated by dividing the power in each band by the total energy in the trial. It is expressed in dB and therefore represents a percentage of power.

Markers of complexity

Permutation entropy (PE) was developed by Bandt & Pompe (Bandt & Pompe, 2002). The basic principle of this method is the transformation of the time signal into a sequence of symbols before estimating entropy. The complete description is given in Sitt, Brain, 2014(Sitt et al., 2014) The transformation is made by considering consecutive sub-vectors of the signal of size n , $n=3$ here, and a parameter defining a broad frequency-specific. After the symbolic transform, the probability of each symbol is estimated, and PE is computed by applying Shannon's entropy formula to the probability distribution of the symbols.

Complexity of Kolmogorov Chaitin (KS) is represented by the size of the smallest computer program that can be made to define this signal. The lower limit is therefore estimated by applying lossless compression, that is to say a compression which restores after decompression a series of bits strictly identical to the original. The degree of compression is then compared to the basic signal. We use here an open source compressor: gzip. It uses a compression algorithm, a method called Deflate including the LZ77 algorithm and Huffman coding.

The first is based on dictionary compression by transforming the sequence into 32 symbols, then we replace the recurring sequences by the position and the length of the occurrences in a sliding window. The second is based on the construction of a tree where we assign to each redundant sequence, a weight. Thus, after having calculated the number of occurrences of a sequence, the more redundant the sequence the more a small number of bits is allocated to code it. Compression by gzip is therefore based on signal redundancy. We then compare the size of the compression compared to the initial file. The more compressed the file, the less information it contains.

Markers of connectivity

The weighted symbolic mutual information (wSMI) can be used to evaluate long-distance connectivity, details of the calculation are developed in King(J.-R. King et al., 2013). The wSMI is a measure based on the prediction of the theory of the global workspace and of experiments concerning the conscious perception of subliminal stimuli. Indeed, several studies(Dehaene

et al., 2003) have (Dehaene et al., 2003)own a late use of the fronto parietal network and above all an increase in the sharing of information between brain areas. The EEG signal is transformed into a sequence of 6 symbolic figures then the permutation entropy (PE) is calculated: We then take each pair of electrodes and observe the conjunction of symbolic elements. Mutual information measures the quantity of information distributed on average by a realization of X over the probabilities of realization of Y. The SMI is weighted to ignore conjunctions of identical or opposite symbols that may come from a common source of artifacts. The connectivity measurement is obtained by taking the median value of all pairs of electrodes.

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Part III

**Auditory event-related
'Global effect' predicts
recovery of overt
consciousness**

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Auditory Event-Related “Global Effect” Predicts Recovery of Overt Consciousness

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Objective: To explore whether the presence of an event-related potential (ERP) “global effect” (GE+)—that corresponds to a correlate of conscious processing in the local–global auditory task—predicts behaviorally overt consciousness recovery in a large cohort of patients suffering from disorders of consciousness (DOC).

Methods: We conducted a prospective study on all DOC patients evaluated during the 2009–2018 period. Behavioral examination included Coma Recovery Scale-Revised (CRS-R) scores and bedside high-density EEG recordings. Consciousness recovery was evaluated at 6 months by a structured phone interview. The predictive value of a GE+ was calculated both on survivors and on all patients.

Results: A total of 236 patients with a documented outcome and technically valid EEG recordings could be included. Among them, 66 patients had a GE+ status (28%). Presence of GE+ predicted behaviorally overt consciousness recovery in survivors with high specificity (Sp = 84%) and high positive predictive value (PPV = 80%) but with low sensitivity (Se = 35%) and low negative predictive value (NPV = 42%). Positive likelihood ratio (LR+) of GE+ was superior to LR+ of initial clinical status and of ERP effect indexing unconscious auditory processing [local effect (LE)].

Interpretation: Our results demonstrate that the presence of a bedside ERP GE+ is highly predictive of behaviorally overt consciousness recovery in DOC patients, regardless of the delay, of behavioral status, and of the etiology of brain dysfunction. However, the absence of this effect is not a reliable predictor of negative outcome. This study provides Class III evidence that the presence of an ERP “global effect” predicts consciousness recovery in DOC patients.

Keywords: disorder of consciousness (DOC), prognosis, EEG–electroencephalogram, critical care, evoked potential

INTRODUCTION

The ability to predict consciousness recovery in patients suffering from disorders of consciousness constitutes a major clinical and neuroscientific challenge. A precise behavioral diagnosis of the type of disorder of consciousness (DOC) constitutes a first specific predictor of consciousness recovery, in addition to etiology and age. Indeed, recent studies converged on demonstrating that an early distinction between a minimally conscious state (MCS) and a vegetative state (VS, also coined unresponsive wakefulness syndrome or UWS) predicts consciousness recovery (1–4). However, this distinction requires a genuine behavioral expertise, as evidenced both by a rate of ~40% of initial diagnostic errors before expert behavioral evaluation (5) and by frequent errors in the use of the revised version of the Coma Recovery Scale (CRS-R), which is the gold standard tool to assess consciousness in DOC patients (6). Moreover, recordings of brain activity with PET-glucose imaging, functional MRI (fMRI), or EEG during cognitively passive or active conditions invariably revealed that around 15% of DOC patients diagnosed by CRS-R experts as being in a non-conscious VS/UWS show neural evidence in favor of an MCS or of a fully conscious state (7–16). All these limitations call for the use of additional diagnostic specific markers derived from brain activity that may also be useful to predict consciousness recovery.

In this context, we aimed at exploring the prognosis value of such a brain activity diagnostic marker that we previously conceived as a specific signature of conscious access to the violation of auditory regularities: the event-related EEG global effect (GE) (17). More precisely, we designed an auditory paradigm to probe cerebral responses to violations of temporal regularities that are either local in time (intra-trial) or global across several seconds and several trials. Local regularity violations (local effect or LE) led to an early response in the auditory cortex, independent of attention or the presence of a concurrent visual task, whereas global violations led to a late and spatially distributed response. Interestingly, GE was found significant in each of the healthy controls who attended to the series and sounds and counted occurrences of global violations. However, in the absence of instructions, this effect was present exclusively in those subjects who could report the existence of violations of global regularities. We could detect the GE in individual subjects using fMRI and both scalp and intracerebral event-related potentials (ERPs) (18), and more recently with pupillometry (19). Applied to DOC patients, our initial logic was to infer that the presence of such a signature of conscious access to a specific perceptual attribute (violations of global regularities) would, by definition, require the patient to be in a conscious state. In other terms, by probing conscious access to violations of the global regularity, we would indirectly probe conscious states

Abbreviations: CRS-R, Coma Recovery Scale-Revised; DOC, disorder of consciousness; EEG, electroencephalography; ERP, event-related potential; GNW, global neuronal workspace; GE+/-, presence/absence of global effect; LE+/-, presence/absence of local effect; LR+, positive likelihood ratio; LR-, negative likelihood ratio; MCS, minimally conscious state; NPV, negative predictive value; PPV, positive predictive value; Sp, specificity; Se, sensibility; VS/UWS, vegetative state/unresponsive wakefulness syndrome.

that are prerequisite to enable conscious access. In a set of six studies (11, 12, 17, 20–22), we confirmed that GE was mostly present in clinically conscious patients, as compared to MCS and to VS/UWS patients.

Encouraged by this cumulative set of results, we hypothesized that GE could be a specific tool to probe conscious patients among non-communicating patients who do not show univocal behavioral overt evidence of consciousness. More precisely, we aimed at testing if GE could be in advance, relative to behavior, to detect consciousness in these patients. We were encouraged in this hypothesis by a previous report in which the only two, out of 20, behaviorally VS/UWS patients with a GE improved to MCS, respectively, 3 and 4 days after ERP recording (20), strongly suggesting that they were actually conscious when tested.

In this study, we confirmed our hypothesis on a large cohort of patients with a documented outcome.

METHODS

Population

Patients hospitalized in the neuro intensive care unit of the Pitié-Salpêtrière Hospital for a multimodal assessment of consciousness during the 2008–2019 period were included in the present study. During their stay, several evaluations and exams were performed including neurological clinical assessment and CRS-R scoring, structural brain MRI, high-density EEG, ERP with the “local–global” auditory task. This “routine care research” study was approved by the CPP IDF1 ethics committee.

Standard Protocol Approvals, Registrations, and Patient Consents

This research was approved by the local ethics committee Comité de Protection des Personnes Ile de France 1 (Paris, France) under the code “Recherche en soins courants” (NEURODOC protocol, n° 2013-A01385-40). Patient’s family gave their informed consent for the participation of their relative, and all investigations conformed to the Declaration of Helsinki and the French regulations.

Coma Recovery Scale-Revised Scoring and Outcome Evaluation

The state of consciousness was determined by neurologists or intensivists who are trained users of the French version of CRS-R (LN, FF, BR, BH, PP). We used the CRS-R score measured immediately before “local–global” task ERP recording. The primary outcome of this study was patient conscious status at 6 months and was collected through a structured phone interview with patient’s relatives (**Supplementary Table 1**). This structured interview was inspired by the CRS-R items and aimed at distinguishing conscious individuals on the one hand (i.e., univocal functional communication) from VS/UWS and MCS individuals on the other hand. Subsequent analyses were conducted separately on the whole population of patients (including deaths) and on survivors only.

Local–Global Event-Related Potential Paradigm

The local–global paradigm derives from the classic auditory oddball, and it has been reported in several articles since its original publication in 2009 (17). This paradigm crosses two types of auditory regularities and enables to test neural responses to their respective violations. Each trial contains five sounds. While the first four are always identical, the fifth can be identical or different (local regularity). These trials are included in blocks structured by an inter-trial regularity (global regularity): in half of the blocks, the global regularity fits with the local regularity (more frequent trials have five identical sounds), whereas in the other half of blocks, global and local regularities are in opposition (more frequent trials have a distinct fifth sound). Habituation trials were not used to compute local effect (LE) and GE analyses. By comparing neural responses to local deviant vs. local standard trials, one can compute the LE, while the global deviant vs. global standard comparison defined the GE. See **Supplementary Methods** for more details.

EEG Preprocessing

ERPs were recorded at 250 Hz with a 256-electrode geodesic sensor net (EGI[®], Oregon, USA) referenced to the vertex. Trials were band-pass filtered (0.5–45 Hz), then segmented in epochs ranging from –200 ms to +1,344 ms from first sound onset. Electrodes with voltages exceeding 100 μ V in more than 50% of the epochs were removed. Moreover, voltage variance was computed across all correct electrodes. Electrodes with a voltage variance Z-score higher than 4 were removed. This process was repeated four times. Bad electrodes were interpolated using a spline method (23). Epochs were labeled as bad and discarded when voltage exceeded 100 μ V in more than 10% of electrodes. Moreover, voltage variance was computed across all correct epochs, and epochs with a Z-score larger than 4 were removed. This process was also repeated four times. Remaining stimulus-locked epochs were averaged and digitally transformed to an average reference. An 800s baseline correction (before fifth sound onset) was applied. EEG recordings had to satisfy the following two criteria to be further analyzed: they should include a minimum of 75% valid channels and 30% of valid epochs. Preprocessing was implemented using MNE-Python environment.

Event-Related Potential Analyses and Statistics

For individual subject statistics, unpaired Welch's tests were performed for each time sample. An effect was considered significant if it satisfied the following triple-threshold criterion that we previously used and validated (17): $p < 0.05$ on a minimum of five consecutive samples (20 ms) and on a minimum of 10 contiguous electrodes during the expected time window of the corresponding ERP effect. For the LE, an ERP was expected from 100 ms after first sound onset to the end of epoch for the LE, whereas the time window ranged from 200 ms to end of epoch for the GE. This 200-ms criterion was determined on the basis of previous results and on the following considerations: (i)

while early and late mismatch negativity (MMN) components occur within a 100-m–200-ms temporal window (24), the onset of GE typically occurs around 250 ms at the group-level statistics with a slope beginning a few tens of milliseconds earlier [see, for instance, Bekinschtein et al. (17) and Faugeras et al. (21)]; (ii) at the single-subject statistics, significant GE can occur around 200 ms [see, for instance, **Figure 4** in Faugeras et al. (21)]; (iii) note also that the local–global task design was conceived to cancel LE components when computing GE by balancing local standard and local deviant trials across global standard and global deviant trials (17). We therefore adopted the 200 ms criterion for GE onset.

Moreover, p -value of any cluster of interest satisfying this triple-threshold criterion also had to be smaller, or identical but longer in time, than any other cluster occurring before the relevant time window. This algorithmic procedure was implemented and batched in Python language. So, we did not impose any constraint of topography or polarity of ERP effects for both LE and GE aspects.

Statistics

The statistical analysis was performed with R software for the frequentist tests and with JASP 0.10.2.0 software for Bayesian tests.

More specifically, we used frequentist approach to compute sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), and positive (LR+) and negative (LR-) likelihood ratio. We also calculated Bayes factor (BF) of the corresponding contingency tables (25) using the JASP software (26) in order to test the following hypothesis: GE+ group > GE-group. We report the BFs using the Raftery terminology (27).

Data Availability

Data are available upon reasonable request but cannot be made open due to ethics protocol requirement and the sensitive nature of patient's data.

RESULTS

During the 2009–2018 period, we recorded high-density ERPs during the active “local–global” task in 429 non-communicating patients addressed to our team at the Pitié-Salpêtrière University Hospital in Paris for a diagnostic and prognostic evaluation of consciousness.

Some patients were recorded several times (for a total of 601 recordings performed on 429 distinct patients, see flowchart in **Figure 1**). Only 403 recordings (67%) satisfied data quality criterion defined in previous studies (see Methods). These 403 valid recordings corresponded to 309 different patients. We used the following two criteria to select only one of these multiple recordings: (i) in order to maximize the number of recordings showing a GE (GE+), if a GE was significant on one or several recordings, we kept the first recording showing a GE; and (ii) when no GE was significant on any of the recordings (GE-), we kept the first recording. Behavioral labeling of these patients was based on the best CRS-R scores (from a number of individual scorings ranging from 2 to 5) and revealed that

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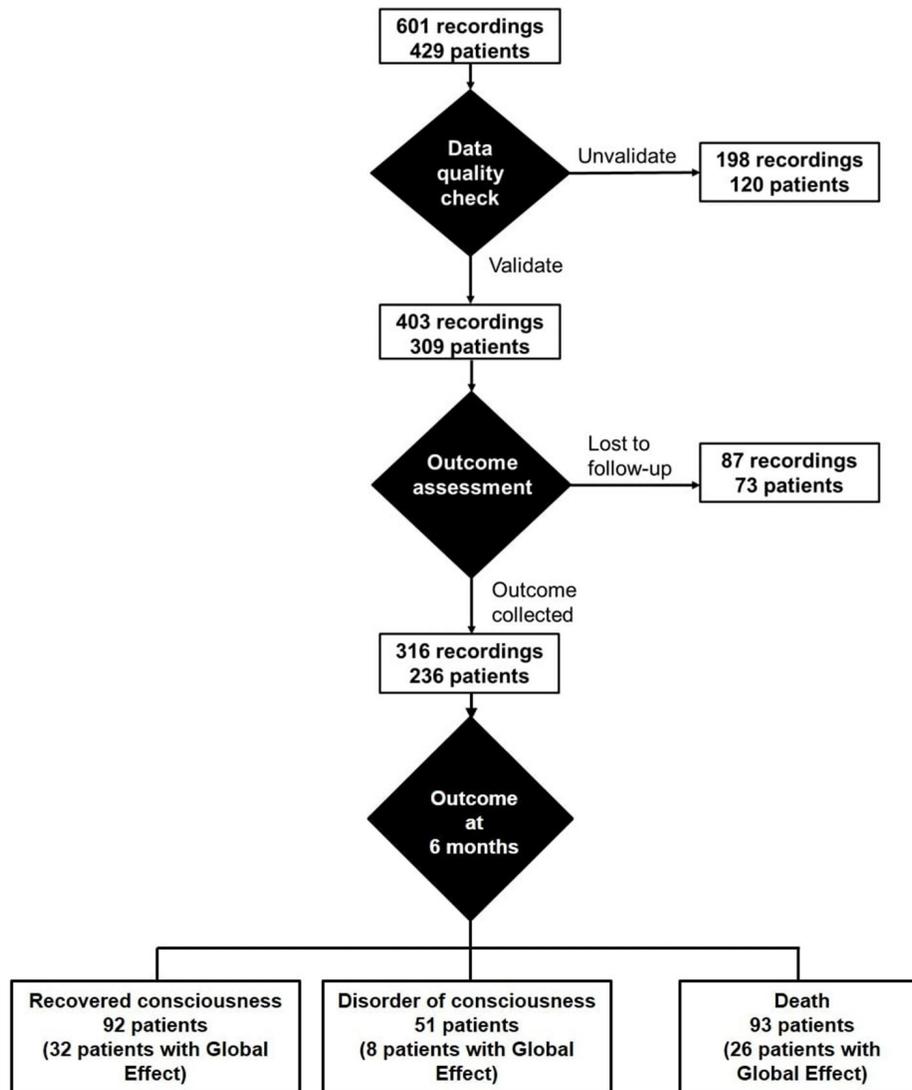


FIGURE 1 | Flowchart.

while most of them were either in MCS ($N = 141$) or in VS/UWS ($N = 138$), some of them were in a conscious exit-MCS (EMCS) state ($N = 30$). We kept all these patients in the main analyses of our results (see below for further analyses) because each of them was referred to us by their clinicians who could not determine their state of consciousness. Among these 309 recordings from distinct patients, 80 were GE+ (25.8%). Both the “patients-based” ($N = 309$) and the “recordings-based” ($N = 403$) analyses revealed the same pattern of results. For the sake of concision, we report in the main text the patients-based analyses (see **Supplementary Tables 2, 3** for the detailed results of “recordings-based” results).

Description of Patients

This 309-patient cohort was mainly composed of men (66.3% men; 47.6% younger than 45 years old; **Supplementary Table 6**). The most common etiology

was anoxia (32.7%), then traumatic brain injury (TBI) (22.7%). The other main etiologies included stroke or hematoma as well as encephalitis or toxic encephalopathy (see **Supplementary Table 6** for details). We regrouped all of these patients under the label “Other.” The delay between the brain lesion and the evaluation was <3 months for 219 patients (70.9%).

GE+ was more frequent in EMCS ($15/29 = 51.7\%$) than in MCS ($33/142 = 23.2\%$) and in VS/UWS ($32/138 = 23.2\%$) patients (Fisher exact test, $p = 0.007$). No difference of GE+ proportion was found between MCS and VS patients [Fisher exact test, $p = 1$; $BF_{+0} = 0.16$] and between MCS+ with MCS- patients (27.8 vs. 18.6%, respectively; Fisher exact test, $p = 0.23$; $BF_{+0} = 1.07$). Note the absence of effect of etiology on GE+ proportion both on the whole cohort ($N = 309$; Fisher exact test, $p = 0.13$) and on the subgroup of patients with a documented outcome ($N = 236$; $p = 0.25$).

TABLE 1 | Description of patients with a documented outcome in terms of etiology, delay between brain injury and evaluation, and GE status.

	≤3 months	>3 months
Anoxia	N = 67	N = 17
	GE+: 15 [5 (E)MCS; 10 VS]	GE+: 3 [2 (E)MCS; 1 VS]
	GE-: 52 [21 (E)MCS; 31 VS]	GE-: 14 [4 (E)MCS; 10 VS]
TBI	N = 30	N = 19
	GE+: 12 [10 (E)MCS; 2 VS]	GE+: 4 [3 (E)MCS; 1 VS]
	GE-: 18 [11 (E)MCS; 7 VS]	GE-: 15 [10 (E)MCS; 5 VS]
Other	N = 73	N = 30
	GE+: 21 [14 (E)MCS; 7 VS]	GE+: 11 [9 (E)MCS; 2 VS]
	GE-: 52 [31 (E)MCS; 21 VS]	GE-: 19 [14 (E)MCS; 5 VS]

(E)MCS, minimally conscious state or exit-MCS; GE, global effect; VS, vegetative state/unresponsive wakefulness syndrome.

Outcome and Consciousness Recovery

Among these 309 patients, we could document the outcome at 6 months in 236 patients (76%) including 92 (39%) who recovered consciousness, 51 (22%) who did not, and 93 (39%) who died. Among the missing data ($N = 73$), the initial conscious status was VS/UWS for 36 patients, MCS for 29 patients (MCS- = 16; MCS+ = 13), and EMCS for eight patients. The proportion of VS (UWS)/MCS/EMCS patients did not differ between the group of missing data and the group with a documented outcome (Fisher exact test, $p = 0.9$, $BF_{+0} = 0.53$).

We first replicated the relevance of following three classical predictors of outcome on survivors: etiology (Fisher exact test, $p = 0.003$, $BF_{10} = 18.9$), clinical state that corresponds to clinical diagnosis (Fisher exact test, $p < 10^{-5}$, $BF_{+0} = 9.7 * 10^6$), and delay since injury (Fisher exact test, $p < 10^{-5}$, $BF = 2.7 * 10^3$) [see Posner et al. (28) for a recent exhaustive review].

We then moved to the GE [see Figure 2 for global-field power (GFP) plots of each GE and LE subgroup]. The population of patients with a documented outcome included 66 GE+ patients and 170 GE- patients (Table 1, Supplementary Table 4, Figure 3). The proportion of GE+/GE- patients did not differ between the group of patients with a documented outcome and the group with an unknown outcome (Fisher exact test, $p = 0.16$; $BF_{+0} = 0.37$).

Predictive Power of Global Effect on Consciousness Recovery in Survivors

We first focused on survivors in order to minimize both the bias of a putative self-fulfilling prophecy that would link GE profile with withdrawing of life-sustaining therapies (WLST) decisions (e.g., more WLST for GE- patients) and to discard the impact of WLST in potentially conscious but extremely impaired patients.

As we hypothesized, GE status predicted consciousness recovery in survivors (Tables 2, Supplementary Table 6): the initial presence of a significant GE+ predicted consciousness recovery at 6 months (Fisher exact test, $p = 0.02$) with a high Sp (84%; see Table 2 for 95% CI) and PPV (80%). As previously reported, Se (35%) and NPV (42%) were low. This led to an informative LR+ of 2.22 and a poorly informative LR- of 0.77. Note that the more likelihood ratios depart from 1, the more

a test is informative. More specifically, in the present study, an LR+ value superior to 1 informs about the likelihood of consciousness recovery when GE is present, and an LR- value close to 0 informs about the likelihood of no consciousness recovery when GE is absent. A Bayesian analysis ($BF_{+0} = 8.85$) confirmed the value of GE+ in favor of positive outcome prediction of GE+. Interestingly, 3/8 survivor patients with a GE who did not recover consciousness had a refractory epilepsy with worsening of their neurological status after the initial evaluation, suggesting a deterioration of their cognitive and conscious status after the GE recording. Of special interest, all GE+ MCS+ patients who survived recovered univocal behavioral evidence of consciousness (Figure 4).

Given the large proportion of GE+ patients in the EMCS group, which corresponds to conscious patients, our results suggested that the presence of a GE could rather confirm the presence of conscious processing in the absence of obvious overt behavioral evidence of consciousness, rather than predicting its later recovery. Indeed, among the 40 GE+ survivor patients with a documented outcome, 14 were initially in an EMCS (35%), whereas 11 were in an MCS+ (27.5%), seven in an MCS- (17.5%), and eight in a VS/UWS (20%). We therefore replicated our main analysis after removing the patients who were in an EMCS during EEG recording. Clearly, GE+ status did not predict recovery of consciousness (Fisher exact test, $p = 0.26$).

Note that the same main analysis (including EMCS patients) performed on the whole population of patients, including dead patients, still showed a similar pattern of results (Supplementary Table 5), but with a less significant effect [$p = 0.07$ and $BF_{+0} = 1.9$ (anecdotal evidence); Se = 35%; Sp = 76%; PPV = 48%; NVP = 65%; LR+ = 1.47; LR- = 0.85].

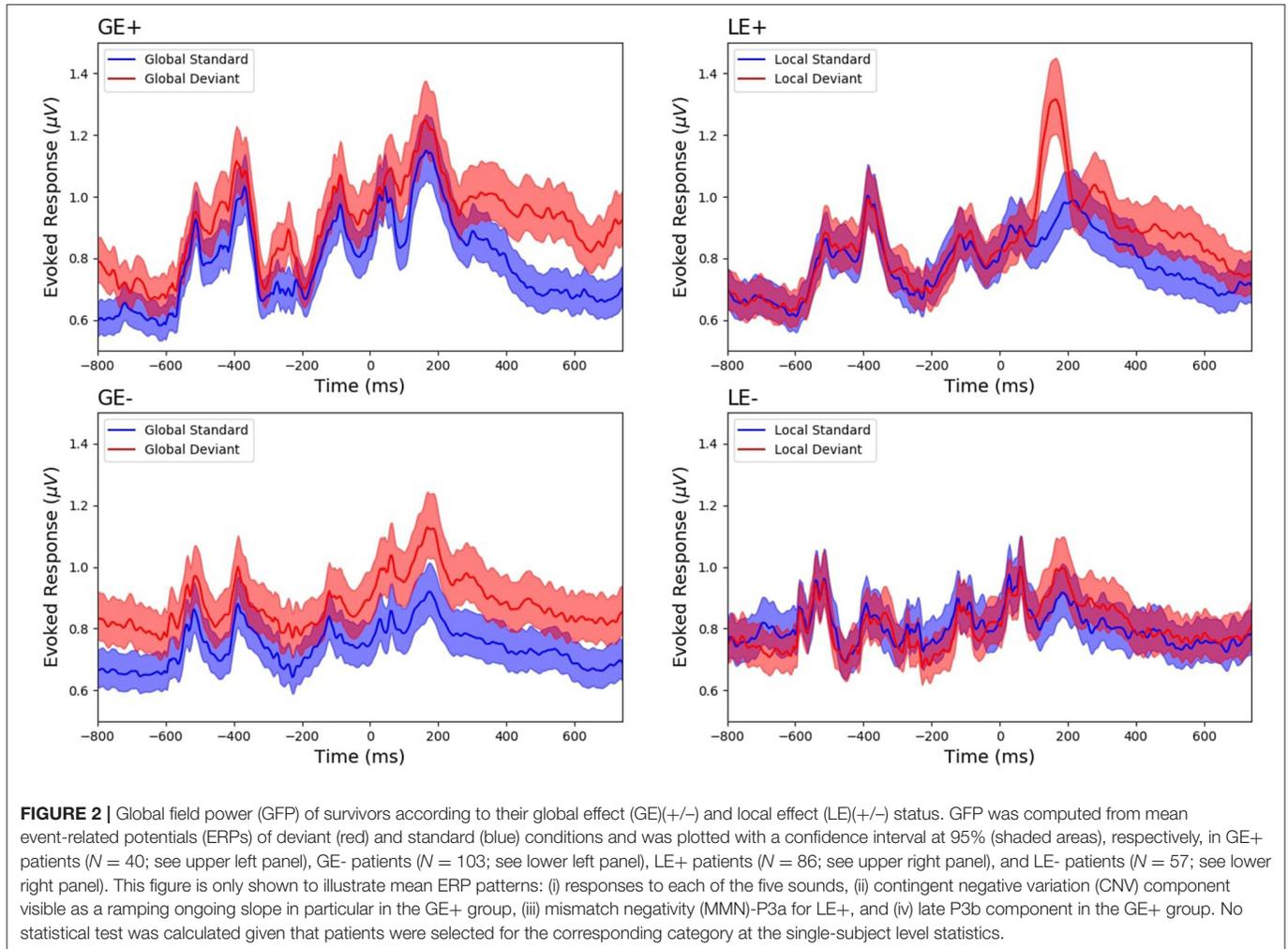
Analyzing the Impact of Deaths

In order to test the potential impact of a self-fulfilling prophecy on survival (i.e., more WSLT for GE- than for GE+ patients), we checked that the proportion of deaths did not differ between GE+ and GE- patients [26/66 (39.4%) vs. 67/170 (39.4%); $p = 1$].

Given that we interpret the presence of a GE as a signature of conscious access, we predicted that GE+ patients were in a behaviorally overt or covert conscious state during the initial EEG recording. Therefore, we explored the cause of death in the GE+ population ($N = 26$; 36.1%): could it be related to secondary degradation that occurred after our evaluation or to other factors independent from the cognitive/consciousness status. Eighteen patients died from WLST including at least five patients who degraded neurologically after initial evaluation and before WLST decision and one patient with severe brainstem lesions with a very poor predicted motor outcome. One patient died in a context of organ donation after cardiac death (Maastricht III). We ignore the cause of death for the eight remaining patients.

Predictive Power of Initial Clinical Status and Local Effect on Consciousness Recovery

We then computed the outcome prediction value of the initial clinical state and replicated the findings of previous studies



(1, 4). When excluding the deaths, initial CRS-R scoring category (VS/UWS vs. MCS or EMCS) indeed predicted consciousness recovery ($p < 10^{-8}$; $BF_{+0} = 5.6 \times 10^{14}$), but with a different pattern of prediction than GE (Table 2, Figure 3): indeed, while sensitivity (89%), NPV (74%), and LR- (0.19) clearly outperformed the GE (35%, 42%, and 0.77, respectively), the PPV was comparable (79 vs. 80%), and the GE was superior to the CRS-R behavioral scoring in terms of specificity (84 vs. 57%) and LR+ (2.22 vs. 2.07).

Note that similar results were found when keeping the patients who died ($p < 10^{-15}$; $BF_{+0} = 1.11 \times 10^7$; Se = 89%; Sp = 64%; NPV = 90%; PPV = 61%; LR+ = 2.47; LR- = 0.17).

Finally, the ERP LE that indexes non-conscious cortical processing of novelty also predicted consciousness recovery at 6 months in survivors ($p = 0.007$; $BF_{+0} = 16.0$), with the following pattern: Se (68%), Sp (55%), PPV (73%), NPV (49%), LR+ (1.52), and LR- (0.57). The same analysis while including dead patients replicated this outcome prediction performance ($p = 0.003$; $BF_{+0} = 14.6$). The same analysis performed after exclusion of EMCS patients showed a trend of an effect ($p = 0.06$).

Interestingly, while the Sp, PPV, and LR+ showed higher numerical values in GE than those in LE, Se, NPV, and LR- were higher in LE than those in GE. This pattern may suggest that while the presence of GE would be predictive of a positive outcome, the absence of LE would be predictive of a bad outcome (LR+ = 2.22 vs. 1.52; LR- = 0.77 vs. 0.57).

DISCUSSION

The main result of our study reveals the presence of an ERP GE as a specific predictor of behavioral recovery of consciousness. In our study, all EMCS or MCS+ patients with a significant GE recovered a univocal overt behavioral evidence of consciousness. This finding has both clinical and theoretical implications.

Given the large set of evidence showing that GE+ requires conscious processing of the series of sounds and given that the largest category of GE+ patients in the present study corresponded to initially conscious EMCS patients, one may consider the GE as a diagnostic tool to probe consciousness, rather than as a prognosis tool of its later recovery. Indeed,

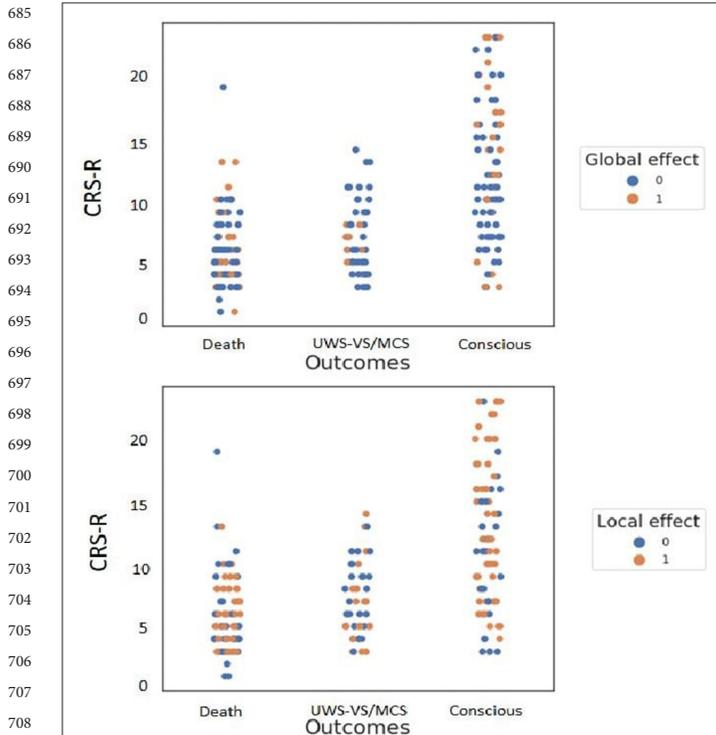


FIGURE 3 | Repartition of patients' outcomes according to their initial clinical state and to global effect (GE) (upper figure) and to local effect (LE) (lower figure) presence. GE was a specific predictor of consciousness recovery in survivors. Note the few GE+ patients with a bad outcome (8/51 = 16%; see upper middle orange dots) contrasting with a higher proportion of LE+ patients with a bad outcome (23/51 = 45%; see lower middle orange dots). Inversely, LE was a sensitive predictor of consciousness recovery. The proportion of LE+ patients who recovered consciousness was larger than the proportion of GE+ with a good outcome (63/92 = 68 vs. 32/92 = 35%; see rightmost upper and lower orange dots).

after excluding EMCS patients from the analysis, we could not observe any reliable prognosis value of GE on consciousness recovery in clinically VS/UWS or MCS patients. However, two factors have to be taken into account. First and as noted above, all these patients were addressed to our structure because clinical neurological examination could not determine if they were conscious or not. This was also the case for the EMCS patients: while we could categorize them as conscious after careful and repeated behavioral evaluations using the CRS-R methodology (EMCS category), patients' caregivers including MDs, nurses, and nurse assistant colleagues, as well as patients' relatives could not categorize these patients as being conscious. In contrast, outcome evaluation through our structured phone interview did not require such a subtle expertise, and patients considered as conscious showed univocal and obvious behavioral evidence of consciousness. Therefore, the behavioral status of the GE+ EMCS patients did improve since ERP recording. In other terms, GE+ did not only diagnose consciousness in a specific way, but it also predicted a behavioral improvement of consciousness. Note also that the non-significant trend of an effect in the expected direction after removing initially EMCS patients probably reflects

a lack of power. Indeed, simulating a three times larger effect was sufficient to reach significant values (Fisher exact test, $p = 0.03$). A key question, however, remains unsolved: was this behavioral improvement of consciousness associated with a parallel and equivalent cognitive improvement of consciousness, or was this behavioral improvement occurring under a constant level of preserved consciousness since ERP recording? Under the first hypothesis, one may consider that the presence of a GE reflects the preservation of a necessary but insufficient component of consciousness and therefore constitutes a predictor of behavioral and cognitive improvement. Note however that, obviously, the absence of GE cannot exclude the preservation of such a component. Under the second hypothesis, one would rather consider that the presence of a GE is a direct signature of conscious processing and therefore constitutes a strong diagnostic tool of consciousness and a prognosis tool restricted to behavioral evidence of consciousness. This discussion is clearly beyond the scope of the present report, but the strong relation we discovered between the presence of a GE and the ability to report subjectively global deviance advocates for this second hypothesis (19). Moreover, scalp topography of the ERP GE corresponds to a P3b component (17), and a current scientific debate questions the meaning of P3b: is it a direct neural signature of conscious access, or rather a post-perceptual correlate of cognitive events that are posterior in time to conscious access (29–38)? Interestingly, the single consensual point of this debate consists of considering that P3b presence does require conscious processing (even if it is not the neural signature of conscious access). Within the context, GE presence would rather be interpreted as an evidence for conscious processing of global deviance and, therefore, as an evidence of consciousness during ERP recording.

From a medical perspective, this new marker may improve predictions of cognitive and consciousness recovery in DOC patients. It is noteworthy that a full automatization of the “local–global” task is a realistic objective: delivery of instructions and of auditory stimuli during EEG recording while sending time stamps for each trial, as well as EEG preprocessing and ERP statistics can be fully automatized, including data quality evaluation steps (22). Therefore, while expert behavioral evaluation, which also conveys a strong predictive information of consciousness recovery, is currently limited by a human factor (up to ~40% of behavioral errors, see above), the use of the “local–global” task could be of very valuable help in the absence of human expertise of behavioral examination of DOC patients. Moreover, even after expert and repeated evaluation, we could identify a proportion of ~15% of clinically VS/UWS patients with evidence for conscious processing of the stimuli as indexed by the presence of a GE. This proportion is very close to the ones reported with other functional brain imaging tools and confirms the existence of dissociations between overt behavior and covert cognition and consciousness, even in non-trivial situations such as in the locked-in syndrome (39, 40). The cognitive–motor dissociations (CMDs), as coined by Schiff (13), further confirm the necessity to use such tools in routine when evaluating the current clinical state of patients and when trying to predict their outcome. For instance, we recently reported the presence of a GE in a clinically VS/UWS young patient after severe fat embolism

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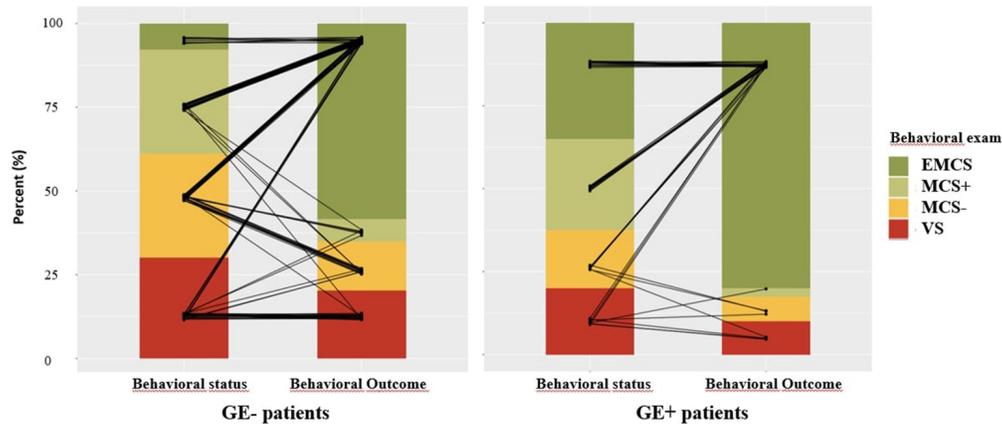


FIGURE 4 | Outcome of global effect (GE)+ and GE- surviving patients. Outcome of GE- patients (left panel) represents each patient by a black segment connected to the patient's initial behavioral status [vegetative state/unresponsive wakefulness syndrome (VS/UWS), minimally conscious state (MCS)-, MCS+, exit-MCS (EMCS)] and to the patient's behavioral outcome (same categories) at 6 months. Outcome of GE+ patients is represented using a similar method in the right panel. Note in particular that all MCS+/GE+ surviving patients recovered overt behavioral evidence of consciousness.

syndrome who then recovered full consciousness and a cognitive and motor autonomy <2 months later (41). Note however that this promising approach also presents limitations. First, 33% of recordings were discarded for data quality issues, mostly related to motor artifacts precluding further analysis of EEG activity. This figure almost replicates our previous report on the diagnosis utility of the “local-global” task (21) in which 35% of recordings had to be discarded. Second, if the GE outperforms clinical evaluation in terms of positive likelihood ratio, it clearly has a poor sensitivity and misses many cases of positive outcome. This limitation probably originates from the rationale of our approach: not only an individual has to be conscious to show a GE, but he has to perceive auditory stimuli to attend to them, to understand the structure of trials, to keep this information is working memory, and to identify global deviant trials. Understanding task verbal instruction can also be compromised in aphasic patients and may decrease the chances to observe a GE, as shown in our previous comparisons between active explicit and passive attentive versions of the task (17, 19). This multiplication of associated probabilities of each of these conditions may explain the high specificity and poor sensitivity of this marker. Rather than probing directly conscious state, we infer such a state by probing conscious access to a specific attribute of the stimuli (violation of the global rule). This set of necessary conditions may explain why the GE does not discriminate well between clinically MCS and VS/UWS patients, and why only roughly half of conscious patients present such an effect.

While GE proved to be a poorly sensitive (Se = 38%) but very specific (Sp = 84%) marker of overt consciousness recovery, LE also showed a complementary and interesting pattern of predictive power (Se = 68%; Sp = 55%). Previous studies established that the two major components of LE [MMN and P3a ERP components (17)] can be observed both in conscious individuals for unconsciously perceived stimuli and in unconscious individuals [e.g., comatose state (42–44), deep

TABLE 2 | Performance of GE, LE, and clinical status on consciousness recovery in survivors only.

	GE	LE	Clinical status
Se	0.35 [0.25, 0.45]	0.68 [0.58, 0.78]	0.89 [0.81, 0.95]
Sp	0.84 [0.71, 0.93]	0.55 [0.40, 0.69]	0.57 [0.42, 0.71]
PPV	0.80 [0.64, 0.91]	0.73 [0.63, 0.82]	0.79 [0.70, 0.86]
NPV	0.42 [0.32, 0.52]	0.49 [0.36, 0.63]	0.74 [0.58, 0.87]
LR+	2.22 [1.11, 4.44]	1.52 [1.09, 2.12]	2.07 [1.50, 2.85]
LR-	0.77 [0.64, 0.94]	0.57 [0.39, 0.85]	0.19 [0.10–0.36]
BF	8.85	15.97	1.12 × 10 ⁷

Numbers indicated in brackets correspond to the 95% confidence interval (CI). BF, Bayes factor; GE, global effect; LE, local effect; LR-, negative likelihood ratio; LR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value; Se, sensitivity; Sp, specificity.

anesthesia (45), sleep (46), and in VS/UWS (17, 20, 21)]. So, the predictive value of consciousness recovery of LE in DOC patients is most probably explained by its value as a marker of residual function preservation of a local cortical network (i.e., auditory cortex and MMN). In other words, the presence of significant LE allows to infer the existence of cortically mediated processes (47). LE presence would therefore play as a necessary but insufficient condition to conscious state, as predicted by several theoretical models such as the global neuronal workspace theory (GNWT) (48).

Our findings also speak to biological theories of consciousness. We previously showed that the presence of a GE corresponds to a late (>250 ms after the delivery of the fifth sound) and sustained brain-scale pattern of activity that includes both auditory areas and a distributed frontoparietal network. We interpret this signature of conscious access as the broadcasting of a complex and differentiated representation (49) in a global

neuronal workspace (GNW) (48). Here, by revealing that this signature predicts overt recovery of consciousness, our results consolidate the plausibility of such a GNWT.

Finally, most GE+ results were found in conscious EMCS patients. Indeed, MCS and VS/UWS patients showed the same proportion of GE+ recordings, as previously reported on a smaller population of patients (21). These two findings support the recent reinterpretation of MCS category (47) as a cortically mediated state (CMS) that informs us with certitude about the behaviorally overt residual integrity of some cortical networks, but that does not speak univocally about an elusive conscious state. In sharp difference with VS/UWS whose behavioral items do not recruit cortical networks (e.g., auditory startle is a brainstem-mediated behavior), each of the MCS items of the CRS-R solicits a specialized cortical network (e.g., visual pursuit requires an occipital-parieto-FEF cortical network) and therefore reveals its functional integrity. As a consequence, and given that multiple examples of cortical unconscious processing has been shown in conscious and in unconscious individuals, the links prevailing between MCS and consciousness is probably less strong than the MCS acronym states and suggests. Indeed, while cortical processing is a necessary condition for consciousness (*all conscious individuals have cortical processing*), this generic condition is not sufficient (*many unconscious individuals still have some forms of cortical processing*). In other terms, if MCS rather indexes a CMS, it is indeed expected to be associated with an overall better prognosis of consciousness recovery, but not as strongly and clearly as suggested by its name. This is precisely why additional prognosis markers, such as the GE, may be of prime interest.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

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ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CPP IDF1 Ethical committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

PP, BR, JS, and LN contributed to the study concept and design. PP, BH, MV, FF, and BR contributed to the data collection. PP, BR, JS, and LN contributed to the analysis and interpretation of data. PP and LN contributed to the drafting of the manuscript, statistical analysis, had full access to all the data in the study, took responsibility for the integrity of the data, and the accuracy of the data analysis. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Part IV

Conscious processing of
narrative stimuli
synchronizes heart rate
between individuals

Conscious processing of narrative stimuli synchronizes heart rate between individuals

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Abstract

Heart rate has natural fluctuations that are typically ascribed to autonomic function. Recent evidence suggests that conscious processing can affect the timing of the heartbeat. We hypothesized that heart rate is modulated by conscious processing and therefore dependent on attentional focus. To test this, we leverage the observation that neural processes can be synchronized between subjects by presenting an identical narrative stimulus. As predicted, we find significant inter-subject correlation of the heartbeat (ISC-HR) when subjects are presented with an auditory or audiovisual narrative. Consistent with the conscious processing hypothesis, we find that ISC-HR is reduced when subjects are distracted from the narrative, and that higher heart rate synchronization predicts better recall of the narrative. Finally, patients with disorders of consciousness who are listening to a story have lower ISC-HR, as compared to healthy individuals, and that individual ISC-HR might predict a patients' prognosis. We conclude that heart rate fluctuations are partially driven by conscious processing, depend on attentional state, and may represent a simple metric to assess conscious state in unresponsive patients.

Introduction

In healthy individuals, heart rate fluctuates with breathing and changes in parasympathetic and sympathetic tone¹⁻³. Physical activity naturally increases heart rate, but also just thinking about physical activity may increase heart rate⁴. Similarly, mental exercises such as meditation can reduce heart rate⁵. The effect of cognition on heart rate is perhaps even more direct than these traditional accounts^{6,7}. We also know that suspense and surprise can transiently increase heart rate⁸. Most likely these immediate effects of the mind on the heart subserved the purpose of preparing the body for imminent action⁹. Despite this evidence, the role of (un)conscious perception¹⁰ on heart rate is less clear. It is well established that the brain can unconsciously detect novelty in the stimulus, as demonstrated with event-related potential studies (e.g. MMN¹¹⁻¹³, and N400^{14,15}). Recent evidence shows that the timing of an individual heartbeat may be affected by the perception of an unexpected sound, but only when consciously perceived¹⁶. We hypothesize that conscious processing of perceptual information will affect heart rate. Therefore, we predict that fluctuations in heart rate will depend on top-down attention to the stimulus and predict memory performance, a known factor¹⁷ and a correlate of conscious perception.¹⁸

To test these predictions, we will leverage the observation that natural narrative stimuli guide cognitive processes resulting in reliable neural responses. This was first observed by measuring hemodynamic brain activity during movies: when humans watch the same movie, they have similar fluctuations in brain blood oxygenation¹⁹. Specifically, the temporal fluctuations of the signal measured with functional magnetic resonance (fMRI) are correlated between subjects. Significant inter-subject correlation of brain activity has now been observed with other neuroimaging modalities, including EEG, MEG and fNIRS¹⁰⁻¹³. Thus, neurophysiological fluctuations appear to synchronize on a wide range of time scales, from milliseconds to several minutes. This phenomenon is also not constrained to movies but has been observed for speech, music, or during driving²⁰⁻²². There are even significant correlations in the spatial patterns of fMRI activity between speakers and listeners²³ or the time-courses of EEG signals of two individuals engaged in a conversation²⁴. This similarity of neural activity in

response to narrative stimuli suggests that these stimuli elicit similar perceptual and cognitive processes in different subjects.

Consistent with this, inter-subject correlation crucially depends on the cognitive state of the participant. Subjects that are not attentive or do not follow the narrative show significantly reduced inter-subject correlation, both in EEG and fMRI²⁵⁻²⁷. A drop in inter-subject correlation is also observed in patients with disorders of consciousness relative to healthy controls²⁸⁻³⁰. Indeed, a cohesive narrative is crucially important to elicit synchronized brain activity in fMRI, in particular at long time scales.³¹ It comes as no surprise then that inter-subject correlation has been found to be predictive of a variety of behavioral outcomes, such as audience retention, memory of content, efficacy of advertising, efficacy of communication and political speeches, and more^{23,32-36}.

There are many studies reporting a correlation of physiological signals across subjects.³⁷ Generally this has been linked to physical or social interaction,³⁸⁻⁴⁰ or at the very least a co-presence at the same place and time.⁴¹ However, consistent with our hypothesis, the simultaneous experience is not crucial for synchronization. A few recent studies report a correlation of heart rate fluctuations across subjects watching the same movie at different times, and ascribe this to shared emotions elicited by the film.^{42,43}

Our conscious processing hypothesis predicts that this synchronization phenomenon will occur not just for the film, but more generally for narrative stimuli, that inter-subject correlation of heart rate will be modulated by attention, that it will correlate with cognitive performance, and more dramatically, that it will be reduced in patients with disorders of consciousness. We confirm these predictions in a series of four experiments and conclude that heart rate synchronization has the potential to become a marker of cognitive state in a clinical setting.

Results

In all four experiments we presented narrative stimuli to each subject while recording their electrocardiogram (EKG, Figure 1A), in experiments 3 and 4 we also recorded respiratory activity. Recordings were aligned in time between subjects and instantaneous HR was estimated as the inverse of the RR intervals (Figure 1B). Mean and standard deviation of these instantaneous measures provide HR and HR variability (HRV) for each subject. The instantaneous HR signals are upsampled to a common sampling rate and correlated between all pairs of subjects (Figure 1C). Inter-subject correlation of HR (ISC-HR) is then defined for each subject as the average Pearson's correlation with all other subjects (Figure 1D).

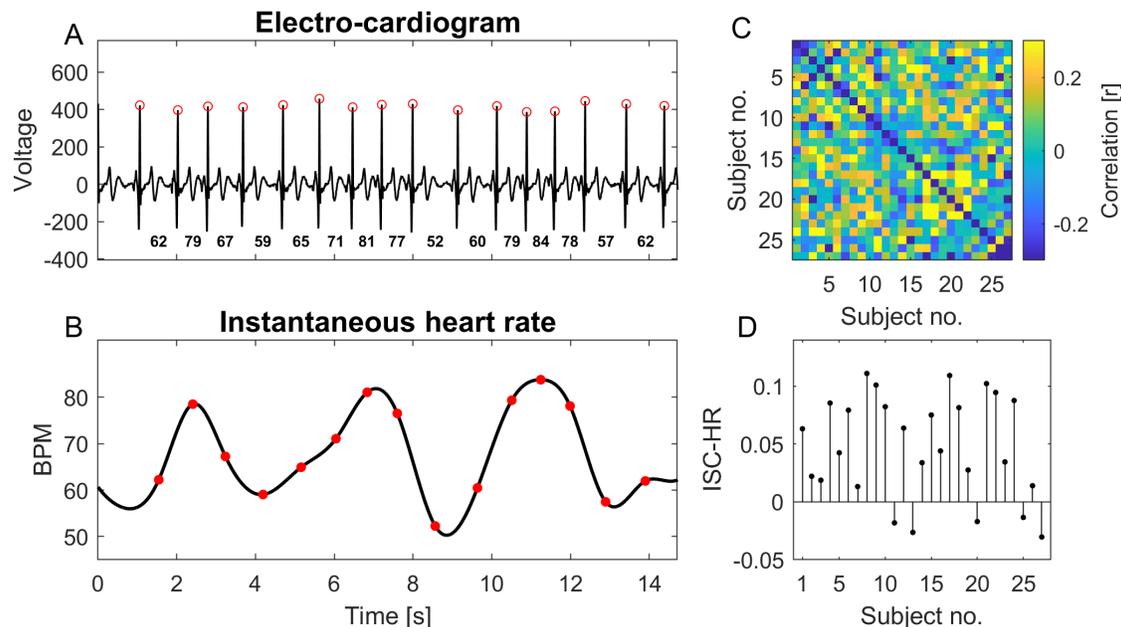


Figure 1: Inter subject correlation of heart rate (ISC-HR), A: Electro-cardiogram with peak of the R-wave detected (red o). **B:** The inverse of the interval between two R-waves defines the instantaneous heart rate (red o). This is interpolated (black) to convert heart rate into a signal with a uniform sampling rate across subjects. **C:** Pearson's correlation coefficient of this instantaneous heart rate between pairs of subjects. **D:** Inter-subject correlation of heart rate (ISC-HR) is computed for each individual as the mean across a row of this correlation matrix. Example in this figure is taken from history segment #1, dataset #1.

Auditory narratives synchronize listeners' heart rate fluctuations

The objective of the first experiment was to determine whether a common auditory narrative elicits similar heart rate fluctuations in healthy volunteers (Experiment 1). Subjects were presented with one-minute segments of an audiobook of Jules Verne's "20,000 leagues under the sea". First we tested whether there was significant inter-subject correlation of the instantaneous HR. To this end we compared the ISC-HR values to values computed on signals randomly shifted in time within-subjects (see methods). When this analysis is performed on individual one-minute segments, only a few subjects show significant non-zero ISC-HR (Fig. 2A, black dots, FDR at 0.05). When averaging ISC-HR values over the 16 minutes, 17 of the 27 subjects show statistically significant HR correlation (Fig. 2B; FDR at 0.05). No significant negative correlations were found. As an additional control, we randomly shuffle the one-minute story segments between subjects breaking the narrative synchrony across subjects. As expected, we observed a significant drop in ISC values between the original and permuted conditions (Fig. 2C, paired t-test (26) = 9.20, $p = 2.10 \cdot 10^{-9}$). In total, we conclude that the narrative stimulus induces similar HR fluctuations across subjects. ISC-HR therefore captures how strongly the stimulus drives the fluctuations of HR in each subject.

Results on average HR and HRV and their potential relation to ISC-HR are generally unremarkable for these data and are discussed in the Supplement (Fig. S1).

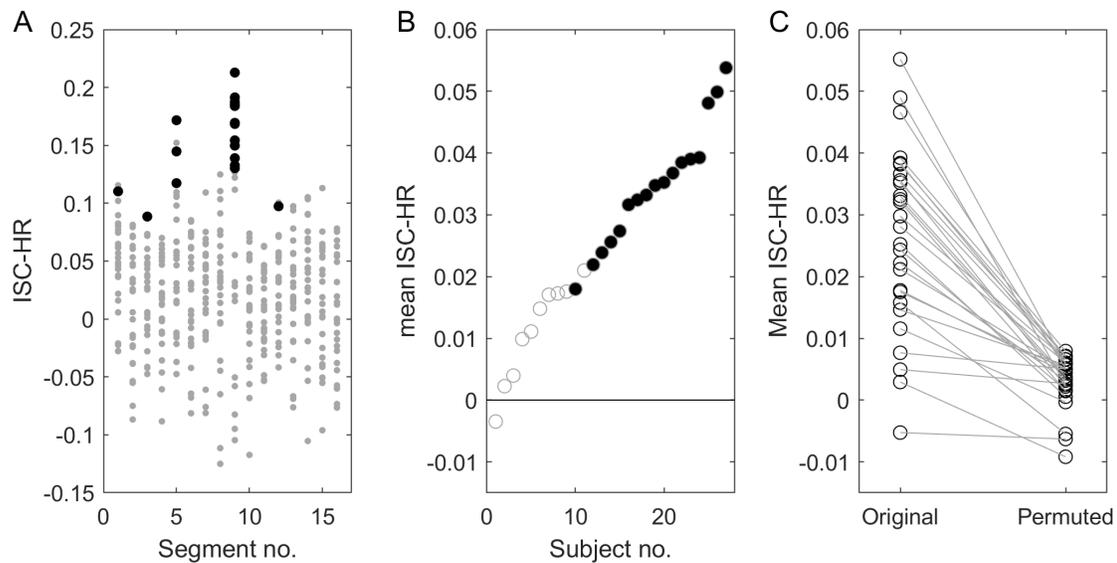


Figure 2: ISC-HR resolved in time and by subject. In Experiment 1, subjects listened to segments of audio narratives of 60 seconds each (N=16). **A:** ISC-HR is computed for each subject (N=27) and each segment. **B:** For each of the 27 subjects ISC is averaged over the 16 segments. Subjects are ordered by their ISC values. Black points (panel A and B) indicate statistically significant ISC values. Gray points are not statistically significant. Statistical significance is determined using circular shuffle statistics (10,000 shuffles and corrected for multiple comparisons with FDR of 0.01). Specifically, the heart rate signal of each subject is randomly shifted in time. **C:** As additional control here ISC is compared to the ISC obtained when story segments are swapped across subjects at random.

Attention modulates synchronization of HR fluctuations during audiovisual narratives

We demonstrated above that an auditory narrative can synchronize HR fluctuations across subjects. In the second experiment we aim to determine if this synchronization is modulated by attention to the stimulus (Experiment 2). Here we used short and engaging instructional videos of 3-5 minute duration, similar to our previous work²⁶. Each subject viewed 5 videos in sequence normally. Then they view the same videos a second time, but now with the instruction to count backward silently in their mind in step 7 starting from a random number. This secondary task aims to distract subjects from viewing the video^{25,26}.

We find that ISC-HR drops in the distracted condition relative to the normal attentive state (Fig. 3A). A repeated-measures ANOVA shows a strong effect of attention ($F(1,238)=73.45$, $p=1.32e-15$) and an effect of the video ($F(4,238)=14.59$, $p=1.14e-10$) as well as a subject effect ($F(26,238)=2.86$, $p=1.34e-05$). The effect of attention is significant for each story individually (follow up pairwise t-test, all $p<0.05$) and when averaging over all 5 videos with a total duration of 22:33 minutes we see a numerical drop in ISC-HR with distraction in all but one of the 27 subjects (Fig. 3B).

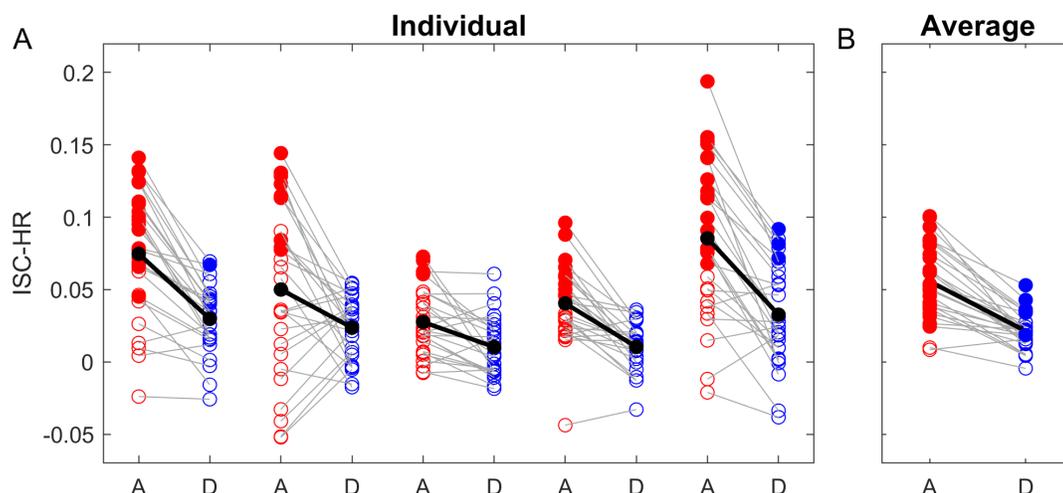


Figure 3: Intersubject correlation (ISC) of the instantaneous heart rate is modulated by attention.

In Experiment 2, 27 subjects watched 5 educational videos of 3-5 minute duration each. Here ISC is measured against the attentive condition, i.e. both attentive and distracted subjects are correlated against the HR collected during the attentive condition. Filled points indicate individually statistically significant ISC-HR (FDR < 0.01). **A:** Subjects watched the same videos twice, either in an attentive (A, red) or distracted (D, blue) condition. ISC was systematically higher in the attentive condition for the five videos. Gray lines indicate individual subjects and the black lines the group average. **B:** Same results when average across the five videos.

Attention modulates HRV, but this is not the driving factor in modulation of ISC

For this Experiment 2, in addition to ISC we also analyzed heart rate variability (HRV), defined here as the standard deviation of instantaneous HR (Fig. S2B). We see an increase in HRV when subjects are distracted. An ANOVA shows a fixed effect of attention ($F(1,211)=63.60$, $p=9.54e-14$), random effect of subject ($F(23,211)=29.56$, $p=1.57e-53$), but we see no significant video effect ($F(4,211)=0.77$, $p=5.44e-01$). Perhaps the increase in HRV in the distracted condition could explain the drop in ISC-HR. If this was the case, we would expect that HRV correlates negatively with ISC-HR as, by definition, the two are inversely related. However, the opposite seems to be the case: subjects with higher HRV have also higher ISC-HR (Fig. S2D). Therefore, it appears that the modulation of HRV and ISC-HR are independent phenomena. The effects on mean HR were generally unremarkable (Fig. S2A & S2C).

Synchronization of HR fluctuations is modulated in the time scale of 5-10 seconds

It is well established that during waking rest HR fluctuates at various timescales⁴⁴. This is reproduced in the present context of video presentation (of Experiment 2) by computing HRV after band-pass filtering the instantaneous HR in different frequency bands (Fig. 4A). To determine which time scale dominates ISC and its modulation with attention we computed ISC similarly resolved by frequency band (Fig. 4B). We find that ISC and its modulation with attention are dominant in the low-frequency range from 0.09 Hz to 0.15 Hz ($p < 0.00001$ as a single cluster). It is worth noting that ISC was not modulated by attention in the high-frequency peak (around 0.3Hz), which corresponds to the dominant frequency of breathing (Supplementary Fig. S5).

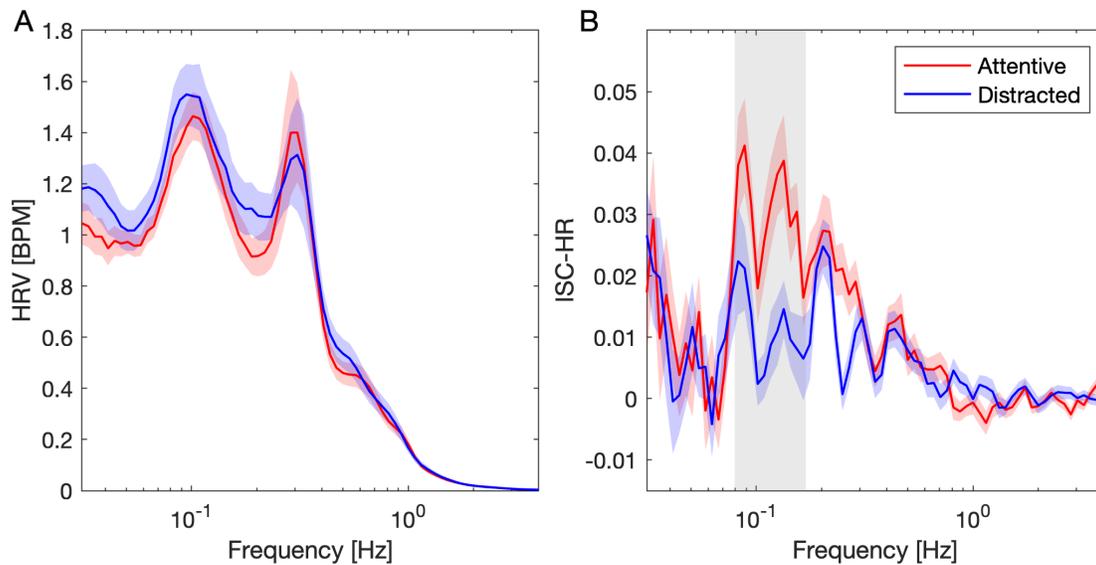


Figure 4. Spectrum of instantaneous HR and ISC-HR and its modulation with attention. For Experiment 2, instantaneous HR was band-pass filtered with center frequency on a logarithmic scale and a bandwidth of 0.2 of the center frequency. **A:** HRV is computed here as the root mean square of the band-passed instantaneous HR averaged over the 5 videos (~15 min total). The greyed area around the curves in both panels is the standard error. **B:** ISC-HR is computed as before, but now on the band-passed instantaneous HR and averaged over the 5 videos. In both panels significant differences between attending and distracted conditions are established in each band with a paired t-test over the 27 subjects (multiple comparison corrected with one-dimensional cluster statistics, $p < 0.05$). Colored-shaded areas indicate standard error of the mean.

Attention modulates synchronization of HR fluctuations during audio-only narratives, but does not synchronize breathing

Given the dependence of HR fluctuations on attention, we expected that HR would be predictive of cognitive processing of the narrative. In the next experiment (Experiment 3) we, therefore, recorded HR during the presentation of auditory narratives, and afterward asked adult subjects to recall factual information presented in the story, e.g. “What was the name of the two main characters?”. Subjects listened to four auditory narratives, in either an attentive or distracted condition. This time the narratives were children’s stories of 8-11 minute duration, and the secondary task consisted of counting target tones that were inserted in the audio asynchronously across subjects. To rule out order effects we now divided the participants in two groups. In group 1 (N=9) subjects listened to stories 1 and 2 in the attentive condition and stories 3 and 4 in the distracted condition. In group 2 (n=12) subject listened to the same stories with the attention condition reversed.

We find again that ISC-HR drops significantly when subjects are distracted (Fig. 5A, paired t-test $t(20)=8.2$, $p < 10^{-7}$). Similarly to experiment 2 with video, here 15 out of the 21 subjects show a statistically significant correlation of HR in the attentive condition and none in the distracted condition. As expected, subjects performed significantly better in recalling elements of the story in the attentive condition as compared to the distracted condition (Supplementary Fig. S3, Wilcoxon Signed-Rank Test, $z = 4.03$, $p = 5.7e-5$).

Our hypothesis postulates that ISC-HR is the result of similar conscious processing of the narrative stimulus, thus, we predicted that subjects with higher ISC-HR will be better at remembering elements of the stories. Indeed, we find that ISC correlates with memory recall performance across conditions (Fig 5B, $r(40)=0.767$, $p=3.1e-9$, Spearman's correlation is used here due to the bounded nature of the percent measure). More importantly, even within the normally attentive condition with a normal fluctuation of HR we find that ISC-HR is predictive of memory performance ($r(19)=0.57$, $p=7.3 e-3$). In the distracted conditions there was no correlation with memory performance ($r(19)=-0.1$, $p=0.67$, $BF_{01} = 4.88$) possibly because ISC-HR was not statistically significant for any of the subjects. Overall, we conclude that ISC-HR is indicative of conscious processing of the narrative.

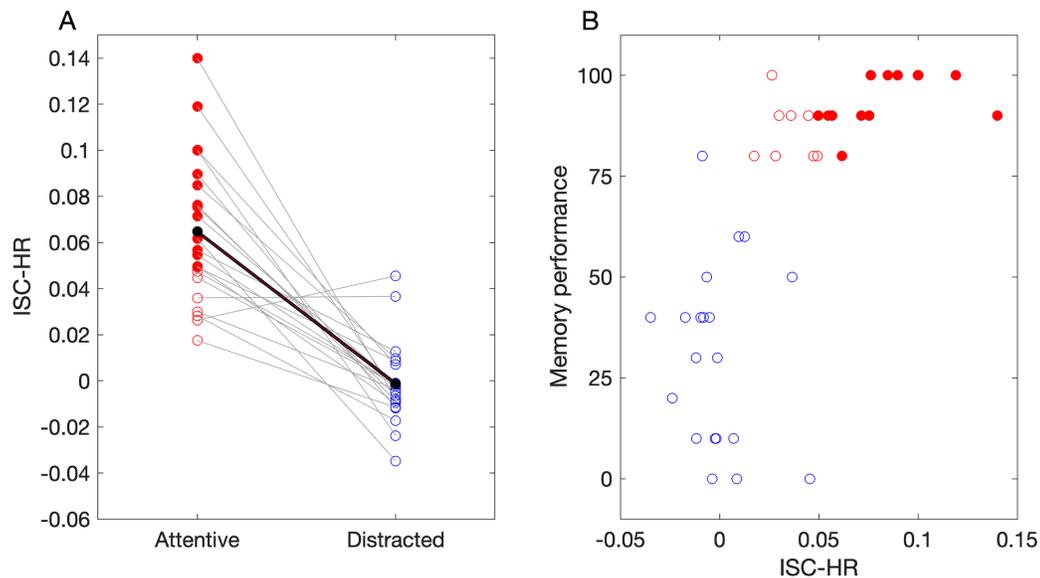


Figure 5: Intersubject correlation is higher when subjects were attentive to the auditory narrative and this correlation indexes the subjects' memory performance. In Experiment 3, Subjects listened to four recordings of children's stories 8-10 minutes in duration. Subjects were instructed to either attend to a story normally (attentive, red), or to count backward when they heard a target sound inserted in the audio (distracted, blue). Again, ISC is measured against the attentive condition, i.e. both attentive and distracted subjects are correlated against the HR collected during the attentive condition. Filled points indicate individually statistically significant ISC-HR ($FDR < 0.01$). **A:** ISC-HR for each subject ($N=21$) averaged over four stories. **B:** Memory performance measured as percent of correct answers to free recall questions about the content of the stories. Filled and empty circles indicate significant and non-significant ISC-HR respectively ($p < 0.05$ shuffle statistics)

Intersubject correlation of heart rate is not driven by synchronous breathing

It is well established that HR fluctuations are driven in part by breathing.⁴⁵ This phenomenon is known as respiratory sinus arrhythmia and can affect a range of frequencies^{46,47}. It is possible that the attentional modulation in this frequency band is caused by synchronization of breathing between subjects. We, therefore, collected in Experiments 3 respiratory movement concurrently with the EKG and measured inter-subject correlation of breathing. First, we tested if the power spectrum of the raw respiratory signal changes with attention and found small increases in power at "high" frequencies (above 0.3Hz, Supplementary Fig. S5). Second, we

validated the relationship between respiratory and cardiac activity by computing the correlation between respiratory signal and instantaneous HR. In the attentive condition twelve (out of 21) subjects showed a significant cardio-respiratory coupling, and in the distracted condition it was fifteen (out of 21) (Supplementary Fig. S6A). In addition, we found a non-significant reduction in breathing-HR correlation in the distracted condition versus the attentive (Fig S6A, $t(20)=2.0$, $p=0.18$ (FDR corrected), $BF_{10} = 1.2$, $BF_{01} = 0.83$). Third, we tested for significant ISC in the raw breathing signal and various of its features, specifically, the instantaneous respiratory frequency and amplitude computed separately for inspiration and expiration (using the breathmetrics toolbox⁴⁸). We did not find a significant ISC of the raw breathing signal in any of the subjects, nor was there any effect of attention when comparing across all subjects (Fig. S6B, paired t-test, $t(20)=-0.8$, $p=0.75$ (FDR corrected), $BF_{01} = 3.21$). Similarly, none of the respiration features showed significant ISC, nor a drop in ISC for the distracted conditions (Supplementary Fig S6C-F). In other words, the auditory narratives did not reliably entrain the subjects breathing nor was this modulated by attention. On the flipside, while Bayes factor analysis provides some evidence for a lack of synchronized breathing, the evidence is only moderate (in all instances $1 < BF < 4$ in favor of this Null hypothesis, Supplementary Fig S6).

Finally, to determine if delayed influences of respiration could explain the results obtained from HR, for each subject and condition we subtracted from the HR signals any instantaneous or time delayed linear correlation of the respiratory signal and recomputed the ISC-HR. We obtained similar modulation of ISC with attention (Supplementary Fig S7, t-test: $t(20) = 5.57$, $p = 1.9e-05$, $BF = 1251.3$).

In conclusion, while we do not have strong evidence against a synchronization of breathing, these results do suggest that the effect of cognition on synchronizing HR cannot be explained in this study by the synchronization of breathing.

Synchronization of heart rate fluctuations is disrupted in patients with disorder of consciousness

Given the dependence on attention and conscious processing of these synchronized HR fluctuations, we predicted that patients with disorders of consciousness (DOC) will have diminished HR synchronization when presented with an auditory narrative. We recorded EKG in 19 DOC patients, in addition to 24 healthy controls (Experiment 4). The patients were hospitalized to determine their state of consciousness and neurological prognosis. Patients were behaviorally assessed using the standard Coma Recovery Scale-revised⁴⁹. State of consciousness was determined using the currently accepted categorization⁵⁰, patients were classified either in (1) Coma, (2) Vegetative state/Unresponsive wakefulness syndrome (UWS), (3) Minimally conscious state minus (MCS-), (4) Minimally conscious state plus (MCS+), and exit Minimally conscious state (EMCS) (See Supplementary Table 3 a detailed description of the patients). Patients and healthy subjects listened through headphones to a children's story of 10-minute duration. Using the data from healthy subjects we first replicated the results of Experiment 3 showing that ISC computed for HR is systematically larger than the ISC of any of the respiratory features tested (Supplementary Fig. S8). We then computed ISC-HR by correlating HR with that of healthy controls. As expected ISC-HR values were lower in patients (Fig 6A, t-test: $t(41) = 3.14$, $p = 0.003$, $BF_{10} = 12.4$). Within patients no significant correlation was found between ISC-HR and state-of-consciousness (Fig. 6A, Spearman correlation, $R(17) = -0.28$, $p = 0.24$, $BF_{01} = 4.07$) nor between ISC-HR and the Coma Recovery

Scale-Revised (CRS-R⁴⁹; Fig 6B, Spearman correlation, $R(17) = -0.3$, $p = 0.22$, $BF_{01} = 3.36$). Reduced HRV is sometimes found in traumatic brain injury patients.⁵¹ We therefore analyzed HRV to verify that the drop in ISC-HR is not a noise-floor effect, i.e. if HRV drops in patients it may be difficult to measure inter-subject correlation above random fluctuations (Fig. S9B). Contrary to what was expected we found higher HRV in the DOC patients compared to healthy controls ($t(41) = 2.34$, $p = 0.02$, $BF_{10} = 2.53$), ruling out a noise-floor effect. We also found higher mean HR in DOC patients compared to healthy controls (Fig S9A; $t(41) = 4.7$, $p = 2.9e-05$, $BF = 639$). However, given the previous lack of correlation between ISC and mean HR we do not believe this contributed to the decrease of ISC-HR in patients.

When measured individually, only two of 19 patients showed statistically significant ISC-HR (FDR corrected $p < 0.05$, Fig. 6, purple filled circles). For these two patients' outcomes at the six-month follow-up were mixed; one patient fully regained consciousness whereas for the other, life-sustaining therapies were withdrawn before the follow-up assessment. Among the remaining 17 patients only one additional patient recovered consciousness, although in a completely aphasic condition. These results suggest that the patients' ISC-HR might carry prognostic information with a specific emphasis on conscious verbal processing. To test this hypothesis, we first correlated the patients' ISC-HR to the CRS-R improvement after six months of the initial assessment. We found a positive correlation between ISC-HR and CRS-R improvement, although not statistically significant (Fig 6C, Spearman correlation, $R(14) = 0.43$, $p = 0.097$, $BF_{10} = 0.58$, second assessment was available only for 16 patients). A limitation of behavioral assessment of patients is that it cannot detect covert awareness^{52,53}, a condition that can occur in up to 15% of the UWS patients⁵⁴. Therefore, we also correlated the patients' ISC-HR to an anatomical measure of brain integrity -- whole-brain white matter fractional anisotropy. This FA index has been linked to neurological recovery in DOC patients⁵⁵. We found a significant correlation between ISC-HR and FA Index (Fig. 6D, Spearman correlation, $R(9) = 0.73$, $p = 0.01$, $BF_{10} = 5.65$, FA Index was available only for 11 patients).

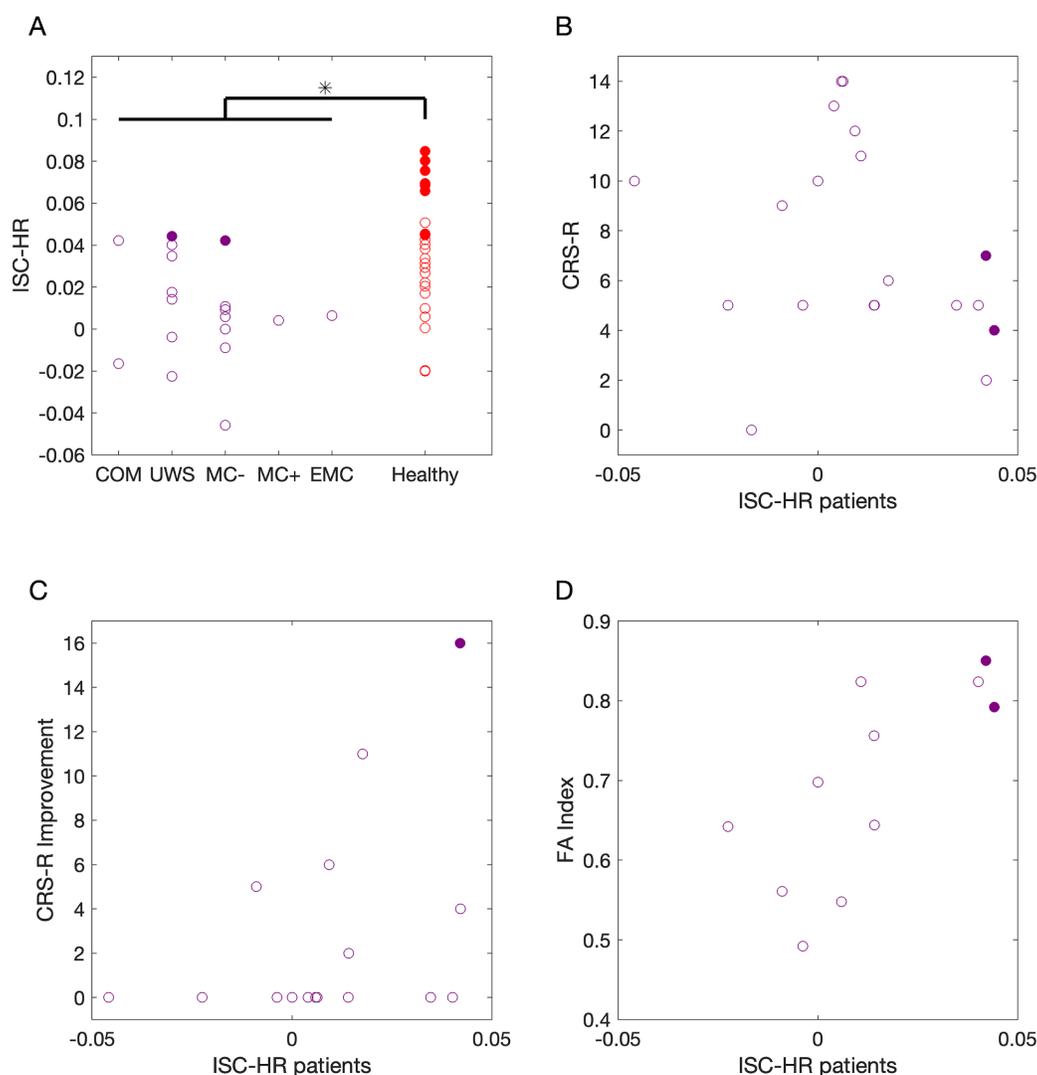


Figure 6: Audio narratives synchronize HR fluctuations in healthy controls but not in patients with disorder of consciousness. In Experiment 4, subjects listened to a children’s story (*La part des ancêtres* from Leonora Miano; 10 minutes). **A:** ISC-HR is measured by correlating instantaneous HR with that of healthy subjects. Filled cycles indicated statistically significant ISC. **B:** Comparison of the ISC-HR with Coma Recovery Scale-Revised in patients (N=19). **C:** Comparison of the ISC-HR with improvement of Coma Recovery Scale-Revised six months after the first assessment (N=17) **D:** Comparison of ISC-HR and whole-brain white matter fractional anisotropy in patients, were available (N=11).

Discussion

The hypothesis that motivated this set of experiments was that conscious processing of information modulates instantaneous heart rate. This fluctuating heart rate will synchronize across subjects when presented with narrative stimuli that are processed similarly. We tested the predictions resulting from this hypothesis in a series of four experiments. In the first experiment with healthy volunteers we confirmed that heart rate fluctuations correlate between

subjects for auditory narratives. In the second and third experiment we confirm that distracting the participants with a secondary task reduced this correlation, for video and audio narratives alike. Importantly, we confirm the prediction that synchronization of HR fluctuations is predictive of memory performance. We also determined that HR synchronization is likely not driven by synchronous breathing across subjects for the present audio narratives or educational videos. Finally, in the fourth experiment we presented an auditory narrative to patients with disorders of consciousness and found that their heart rate fluctuations do not correlate with that of healthy subjects. In total, we found that natural stimuli induce small but highly reliable correlations of HR, which are detectable in individual subjects and readily reproduced across four different experiments. We found a robust link between this HR synchronization and conscious processing of the audiovisual stimuli. To establish the causal direction of this link future work will require simultaneous neural recordings and prospective interventions.

There is an extensive literature demonstrating that physiological signals such as heart rate, respiration, and skin conductivity can synchronize between individuals.³⁷ This literature emphasizes physical interaction and social relationships as the factors driving this synchronization. Even in the context of music, theater, or film, the emphasis is on the concurrent and shared experience of an audience that synchronizes heart rate to one-another.^{38,39,56,57} Here we have emphasized instead that it is the stimulus that synchronizes HR, or more precisely, a similar processing of a common stimulus. There is no need for individuals to directly interact, be related to one another or perceive the stimulus together at the same time. Consistent with our hypothesis, previous reports already show that emotional movies can synchronize the HR of viewers, even when watching the movie individually.^{42,43} The present findings go beyond this previous literature in that this HR synchronization phenomenon is not specific to live experiences or emotional movies. Rather, it occurs with many narrative stimuli, as we demonstrated here with audio recordings of children's stories or animated educational videos.

There is also an extensive literature on the inter-subject correlation of brain signals evoked by dynamic natural stimuli, starting with experiments in fMRI while subjects watched movies.¹⁹ This work demonstrated that subjects process natural stimuli similarly, and that similarity of brain activity is predictive of memory performance.⁵⁸ Subsequent experiments replicated these findings with EEG.^{59,60} Additionally, ISC of EEG is reduced when subjects are distracted²⁵ and is reduced in patients with disorder of consciousness,⁶¹ similar to what we find here with the instantaneous heart rate. Given these parallels we expect that HR fluctuations will also synchronize across subjects listening to engaging music,²¹ and that HR synchronization will be a good indication of how engaging a narrative is.^{33,62,63}

We suggest that some previous work on physiological synchronization of autonomic signals can be reinterpreted in the context of the present conscious processing hypothesis. For example, the same performance is judged differently depending on the social relationship of performer and audience member, suggesting that it is a different way of processing information in the audience member.³⁸ In our view, it is the processing of the common stimulus, and not the co-presence in the same physical space that causes the synchronization of the heart rate fluctuations. We predict that many results obtained with live performances^{38,39,57} or in-person interactions²⁶ could be recovered with asynchronous playback of the same experience recorded with video. Evidently the experience may be less powerful than live in-person

experiences,⁴¹ but the modulating factors of relationships, emotions, or empathy may still prevail in this virtual context.

We postulate that factors intrinsic to the story, such as semantics and emotions, drive a synchronized heart rate. This may include semantics of single-word to syntactic and multi-sentence level of representation as well as prosody, valence of single words, and more complex semantically mediated emotions. Capturing semantics and emotions require attention to the stimulus and some level of language comprehension. In this view, it is the narrative content that drives attention, engagement, interest and emotions. It is possible, indeed likely that the variations in ISC are due to this differing narrative content. Indeed we find a strong difference in ISC between stimuli, even within the same type of animated educational videos. Dependence of ISC on the stimulus has been found in previous EEG studies^{33,36,64} and for heart rate in studies involving live performance for different pieces of classical music.⁵⁷ In contrast to EEG, we may expect that ISC-HR is less sensitive to low-level features of a stimulus. Neural evoked responses can be driven by low-level features such as luminance or sound fluctuations, which can elicit strong responses that would be trivially synchronized across subjects.^{19,65} To us it is less clear how such low-level stimulus fluctuations could drive HR fluctuations.

We have shown here that the effect on HR synchronization is dominant in the **low** frequency band around 0.1Hz, which falls in the frequency range of respiratory sinus arrhythmia.⁴⁵ However, we show here that breathing does not synchronize between subjects during passive listening or watching, nor was respiratory sinus arrhythmia dependent on attention. While there are a variety of studies demonstrating a synchronization of breathing, most are contingent on synchronization of movement (e.g. speaking, singing, dancing)⁶⁶⁻⁶⁸. Studies with individual playback of video or speech have shown only very limited synchronization effects^{69,70} and to our knowledge there is no study that demonstrates that this synchronization depends on attention, consistent with our present result. Furthermore, it is worth noting that ISC was modulated by attention in the low-frequency peak of HRV but not the high-frequency peak around 0.3Hz which is the predominant breathing frequency. This parallels the observation in sleep, whereby the LF but not the HF peak is attenuated during slow-wave sleep⁴⁴, a period of deep sleep characterized by sensory decoupling⁷¹ and a breakdown of cortical connectivity⁷². Given the link between respiratory sinus arrhythmia and parasympathetic cardiac control,⁷³ we therefore conclude that attention does not affect parasympathetic activity. One caveat to this conclusion is that respiration fluctuates on a slower time scale. It is possible that with longer recording or narrative stimuli different from those used in this study one may find a synchronization of breathing. Indeed, a framework of embodied cognition would predict a range of brain-body interactions to underlie consciousness and cognition.

To measure synchrony, we used here linear instantaneous correlation. Physiological synchrony is sometimes measured with more complex analysis methods in order to capture time-delayed or non-linear relationships^{38,74}. Such relationships may be expected in asymmetric scenarios such as an audience synchronizing with performers³⁸ or mother and child³⁷. However, in the present study we have a group of participants who experience the stimulus in an identical setting and we found reliable synchronization of HR without the need to employ more complex analysis methods. For respiration, it is possible that individual subjects may have systematically delayed or differing responses compared to others. While we accounted for delayed influence of respiration on HR, we avoided more complex analysis

of interaction between individual pairs of subjects, as the duration of the recordings may not support the increase in number of modeling parameters.

Finally, we made a proof-of-concept that the ISC-HR could be used as a simple marker for cognitive state in unresponsive patients. Note that this is in line with previous work on ISC of EEG²⁸, fMRI³⁰, and similar findings with galvanic skin response⁷⁵. While we were able to distinguish patients from healthy controls, we were not able to resolve conscious states among patients. When contrasted to other methods (e.g. using EEG⁷⁶, PET⁷⁷, or fMRI⁷⁸) this limitation - for the moment - curbs the potential use of this method to detect consciousness in patients. However, the results do suggest that the ISC-HR might carry information related to the patients' recovery. Further validation with a larger sample of patients is needed to assess the clinical impact of the proposed method and to determine the optimal combination with other paraclinical tests. One of the limitations of this method is that it requires that the patients be conscious, but also to be able to process language. This double requirement may explain the positive test in one patient who recovered with preserved language processing, and a negative test in a patient who recovered in an aphasic condition. In addition, we believe that the 10 minutes story we used may have been too short for a reliable measure of ISC-HR. In the present experiments we required at least 15 minutes of instantaneous heart rate to detect significant ISC, and a link to memory. We suggest that future studies should use one or several narratives totaling at least 30 minutes of concurrent heart rate recordings. In addition, our results also indicate that the actual content of the story, and how engaging it is for the subject, plays a role in the individual ISC. Given the limited cognitive status of the patients it is critical to maximize this factor. We also suggest that the narratives should be adapted for every single patient, for instance by changing the name of the leading character using the patients' own name. By doing so we will amplify the patients' attention while keeping the overall structure of the story comparable across subjects.

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Methods

Datasets

Experiment 1 : auditory narratives with healthy participants

Twenty-seven native English speakers and healthy participants (22 females, age range 18-26, median 21 years old) listened to a 16-minute extract of an audiobook read by a male British English voice (20,000 leagues under the sea. Author: Jules Verne. Read by: David Linski. Public Domain (P) 2017 Blackstone Audio, Inc.) while their EKG was recorded. The audiobook extract was taken from the first chapter and half of the second chapter. The text is relatively suspenseful as it describes reports of an unknown monster that destroys ships. We divided the story into essays of approximately 1 minute each so that participants could take breaks between segments if they wished.

The instructions given to the subject were 'to listen to the story and look at a fixation cross'. The stimuli were delivered by headphones - ER-1 Insert Earphones (Etymotic Research), using Psychopy v3.1.2. The EKG was recorded with two electrodes on the chest using SenseBox of ANT Neuro, sampled at 500Hz.

EKG data was cut into the 16 epochs of approximately 1-minute corresponding to each audio-segment.

This study was approved by the STEM ethics committee of the University of Birmingham, England.

Experiment 2: instructional videos with healthy participants

Thirty-one students watched 5 instructional videos while their EKG were recorded (19 females, age range 18-46, median 28 years old) in an attentive condition (A), where they were instructed to simply watch videos as they would regularly watch a video. Each educational video was 3-5 minutes long, chosen from popular YouTube channels covering biology, physics, and computer science. These are new recordings on videos we had tested previously.³⁶ After the students had watched all 5 videos, they were asked to answer 10-12 questions about factual information about material conveyed in each video. Lastly, students were instructed to watch the video again in a distracted condition (D). In this condition participants were asked to silently count in their mind backwards from a random prime number above 800 and below 1000, in steps of 7.

The experiment was carried out at the City College of New York in a sound-attenuated booth. Subject wore headphones and watched the videos on a 19" monitor. The EKG was recorded with a BioSemi Active Two system at a sampling frequency of 2048Hz. 2 EKG electrodes were placed below the left collar bone and one on the left lumbar region. For segmentation of the EKG signal onset and offset triggers were used, in addition a flash and beep sound was embedded right before and after each video which were recorded using a StimTracker (Cedrus) to ensure precise alignment across all subjects. Of the thirty-one participants 4 were removed from analysis due to bad signal quality resulting in usable data for N=27 participants. The experimental protocol was approved by the Institutional Review Boards of the City University of New York. Documented informed consent was obtained from all subjects for laboratory experiments.

Experiment 3: auditory narratives with healthy participants and respiration

The EKG of 25 french native healthy participants (15 females; age range 22-28, median age 25 years old) listened to four stories while their EKG and respiration was recorded using a Polygraph Input Box (PIB of EGI-Geodesic's physiological measurement system). This includes a chest belt to measure respiratory movement (Respiration Belt MR - Brain Products) and 2 EKG electrodes placed on the left subclavicular area and below the left axillary area. Of the twenty-five participants four were removed because of missing respiratory and/or cardiac data. The four audio stimuli come from <https://www.franceinter.fr/emissions/une-histoire-et-oli> : (1) Nadine et Robert les poissons rouges- Delphine de Vigan (8 min) (2) les villages du versant – Alice Zeniter (8 min) (3) Opaque et Opaline - Alex Vizorek (11 min) (4) le renard et le poulailler – Guillaume Meurice (10 min).

To test whether the ISC-HR is modulated by attention we divided the subjects into 2 groups: Group 1 (9 subjects) was recorded with stories (1) and (2) in a distracted condition, and (3) and (4) in an attentional condition. In group 2 (12 subjects) the stories were counterbalanced, stories (1) and (2) in the attentional condition, and (3) and (4) in the distracted condition. In the attentional condition (A), the subject's task was to pay attention to the story while disregarding tones (320/360/400/440/482 Hz, 400ms long) that were played in random intervals (between 800ms and 1100ms) in the background of the story. After each story the subjects received a control debriefing questionnaire including 5 questions testing the memory performance of the story content. In the distracted condition (D), the subject's task was to count backwards starting from 100 indexing the occurrence of 'counting' tones (same tones as in the attentional condition) in-between 2 'reset' tones (Audacity- the type of tones is a linear decay between 1300 and 400 Hz during 400ms). The reset tones were added uniformly and randomly every 14 seconds on average. After each 'reset' tone, subjects had to reset the counting back to 100. At the end of the block the subjects had to report the smallest number obtained between 2 'reset' tones. Subjects were instructed not to pay attention to the story and also receive the same debriefing questionnaire. The present research was promoted by the Inserm (CPP C13-41) and approved by the Comité de Protection des Personnes Ile-de-France 6. All subjects provided written informed consent.

Experiment 4: Auditory narratives with disorder of consciousness patients and healthy controls

Nineteen patients (8 females, age range 18 to 77, median age 50 years old) with disorders of consciousness (mostly resulting from brain lesions) and 24 healthy control subjects (14 females; age range 23-27, median 25 years old) listened to an auditory narrative (La part des ancêtres - Leonora Miano - 10 minutes, from: <https://www.franceinter.fr/emissions/une-histoire-et-oli>) through headphones while their EKG was recorded with a Polygraph Input Box (PIB of EGI-Geodesic's physiological measurement system). The only instruction given to all subjects (healthy controls and patients) was to listen to the story. These patients were hospitalized in neurointensive care at Pitié Salpêtrière (medical center with expertise in disorder of consciousness) to determine their state of consciousness, to adapt treatment, and to evaluate their neurological prognosis. During this evaluation, we performed several exams: clinical assessment, MRI, EEG, evoked response potential, and positron emission tomography. The state of consciousness is determined with some⁶¹ behavioral assessments,

using the Coma Recovery Scale-revised⁴³ - a score which allows differentiating between consciousness states: Coma (the patient does not open their eyes), Vegetative State (VS - Eye-opening, and alternance between wakefulness and sleep), Minimally Conscious State (MCS - the patient is able to follow their own face in the mirror or to follow a simple instruction) and Exit Minimally Conscious State (EMCS - patient can communicate with code). Among the 19 patients, we diagnosed 2 patients in coma, 8 VS patients, 8 MCS patients (7 MCS- and 1 MCS+) and 1 EMCS (see supplementary data for more details). The Ethical Committee of the Pitie-Salpetriere approved this research under the French label of 'routine care research'.

Computation of intersubject correlation of heart rate (ISC-HR)

Previous studies have relied on the quantification of synchrony of neuroimaging based time series (i.e. BOLD in fMRI³² or signals from EEG electrodes²⁶). We follow a similar logic for the electrocardiographic (EKG) signal. We focus on the modulation of heart rate, by doing so we can determine if subjects increase or decrease their heart rate simultaneously, independently of their absolute level of heart rate. Step 1: We measure the EKG signal and detrend it using a high-pass filter (0.5 Hz cutoff) and subsequently notch filtered at either 50Hz (Experiment 1, 3 and 4) or 60 Hz (Experiment 2). We compute the instantaneous HR by detecting RR intervals from the EKG (Figure 1A). Peaks of the R-wave were found using *findpeaks* (built-in matlab function). Step 2: The instantaneous HR signal is then interpolated to keep the same sampling frequency for all subjects (Figure 1B). Step 3: This interpolated instantaneous HR signal is used to compute an inter-subject correlation matrix by calculating the Pearson's correlation between each subjects' instantaneous HR signal (Figure 1C). Step 4: Finally, the intersubject subject correlation of heart rate (ISC-HR) for each subject is obtained by computing the mean of correlations of that given subject to the rest of the group (Figure 1D).

For Experiment 2 (Fig 3. and 4) in step 3 we computed the inter-subject correlation matrix between the instantaneous HR signals in the attentive and distracted conditions with the instantaneous HR in the attentive conditions rather than within condition. In Experiment 3 (Fig. 5) we again used the instantaneous HR signals obtained when the groups were attentively listening to the stories as reference when computing the inter-subject correlation matrix for step 3 (Fig. 6.). For Experiment 4 we used the healthy participants as reference in the computation of the inter-subject correlation matrix in step 3. All other steps were as explained above.

Statistical significance of ISC-HR

The instantaneous HR signals for a given epoch are first aligned across subjects. Then ISC-HR was calculated for all subjects in all epochs and the ISC across epochs. To test whether the ISC-HR value for each epoch was statistically significant (for Fig. 2A), circular shuffle statistic was used: Each subject's instantaneous HR is circularly shifted by a random amount within the 60 second segments and the ISC-HR is re-computed. This procedure is repeated 10.000 times and the ISC-HR of the epoch is compared to this distribution of ISC-HR values for the circular shifted instantaneous HR signals. The p-value is obtained by counting how many circular shifted ISC-HR values were below the actual ISC-HR value. For Fig. 2B we repeat the circular shift to compute ISC-HR values and then average across epochs; p-values are then computed on these averaged ISC-HR values. For Figure 2C, instead of circular shifts within 60 s story segments, we instead randomly swapped segments between participants.

Cluster statistics

One dimensional cluster statistics was computed by adapting the procedure described in ⁷⁹ as follows. First, for each subject, we subtracted the spectrum in the attentive condition versus the distracted condition. Second, for each frequency we computed a t-test comparing the contrast to zero. Third, we identified clusters of consecutive frequencies with p-values < 0.05 and stored the sum of t-values within the cluster. Fourth, we run 10000 permutations in which we randomly reversed the sign of the subjects attentive versus distracted contrast and repeated steps 2-3 while keeping the sum of t-values of the largest cluster. Finally, we compared the clusters' t-values obtained in step 3 with the distribution of permuted cluster t-values obtained in step 4. Clusters with larger than 95 % (corresponding to p-value<0.05) of the permuted distribution were considered significant after multiple comparison cluster correction.

Bayesian Factors

Bayes Factors are an established approach⁸⁰ to compare the likelihood of a Null hypothesis to the likelihood of an alternative hypothesis expressing a measurable effect size. In our case, we were not able to measure a significant effect of synchronized breathing, and the question becomes whether there is sufficient evidence for a lack of synchronization, i.e. is there sufficient evidence in favour of the Null hypothesis. A Bayes Factor (BF) is the likelihood ratio between the Null and alternative hypothesis. When a BF lies between 3 and 10 it is considered moderate evidence in favour of the Null hypothesis. A crucial assumption when computing a BF is the effect size of the alternative hypothesis. If no specific effect size can be assumed a-priori, it is common to assume a distribution over a range of effect sizes. Rouder et al. formalizes this approach for the t-test.⁸¹ The conventional Null hypothesis for the t-test states that there is no difference between mean values of two groups and that mean values are normally distributed. For the alternative hypothesis Rouder assumes the Jeffreys-Zellner-Siow prior, which states that the effect size follows a Cauchy distribution, where effect size is the difference of means over the standard deviation. A similar default prior can be used for ANOVA⁸² and regression problems⁸³. These default prior methods have the advantage that one can compute the BF directly from sample sizes and the t-statistics, F-statistics, or R-square, respectively. To compute a BF we use the matlab code of Bart Krekelberg, which implements these default priors (<https://github.com/klabhub/bayesFactor>).

Frequency analysis of heart rate fluctuations

To investigate which time scale the inter-subject correlation and HRV is modulated by attention we do a frequency analysis of the instantaneous HR signal (Figure 4). The instantaneous HR signal was band-pass filtered using a 5th order butterworth filters with logarithmic spaced center frequencies with a bandwidth of 0.2 of the center frequency. The ISC was computed in each frequency band referenced to the attentive group (Fig. 4A). The HRV was computed as the standard deviation of the instantaneous HR normalized with the average HR (Fig. 4B).

Computation of Fractional Anisotropy index (FA index)

Diffusion Tensor Images (DTI) were acquired on a 3T Siemens Skyra scanner (64 diffusion gradient directions, b value = 1000 s/mm², TR/TE = 3000/80 ms, voxel size = 2x2x2 mm³). DTI data were pre-processed using the FDT package from the Functional MRI of the Brain (FMRIB) software library (FSL) package 5.01⁸⁴. This consisted of: 1) correcting for motion and distortions caused by eddy currents; 2) brain segmentation using the brain extraction tool algorithm; 3) computing the fractional anisotropy (FA) maps using the diffusion-tensor model; 4) registration of the FA and MD maps on the FA template in the standard Montreal Neurological Institute (MNI) space using linear as well as nonlinear spatial transformations. FA values were averaged within a deep white-matter mask defined in the MNI space as the outline of the ICBM-DTI-81 white-matter labels atlas⁸⁵. For each subject, this FA value was normalised with the mean of FA values measured from 10 healthy volunteers acquired with the same imaging protocol, such that an average FA index of 1.0 can be considered normal.

Data availability

All healthy participants data and code to generate analysis and figures in this paper is accessible at <https://osf.io/mhvy7/>. In the case of patients, raw physiological data cannot be open due to consent limitations. In that case group data and code to generate the figures is available.

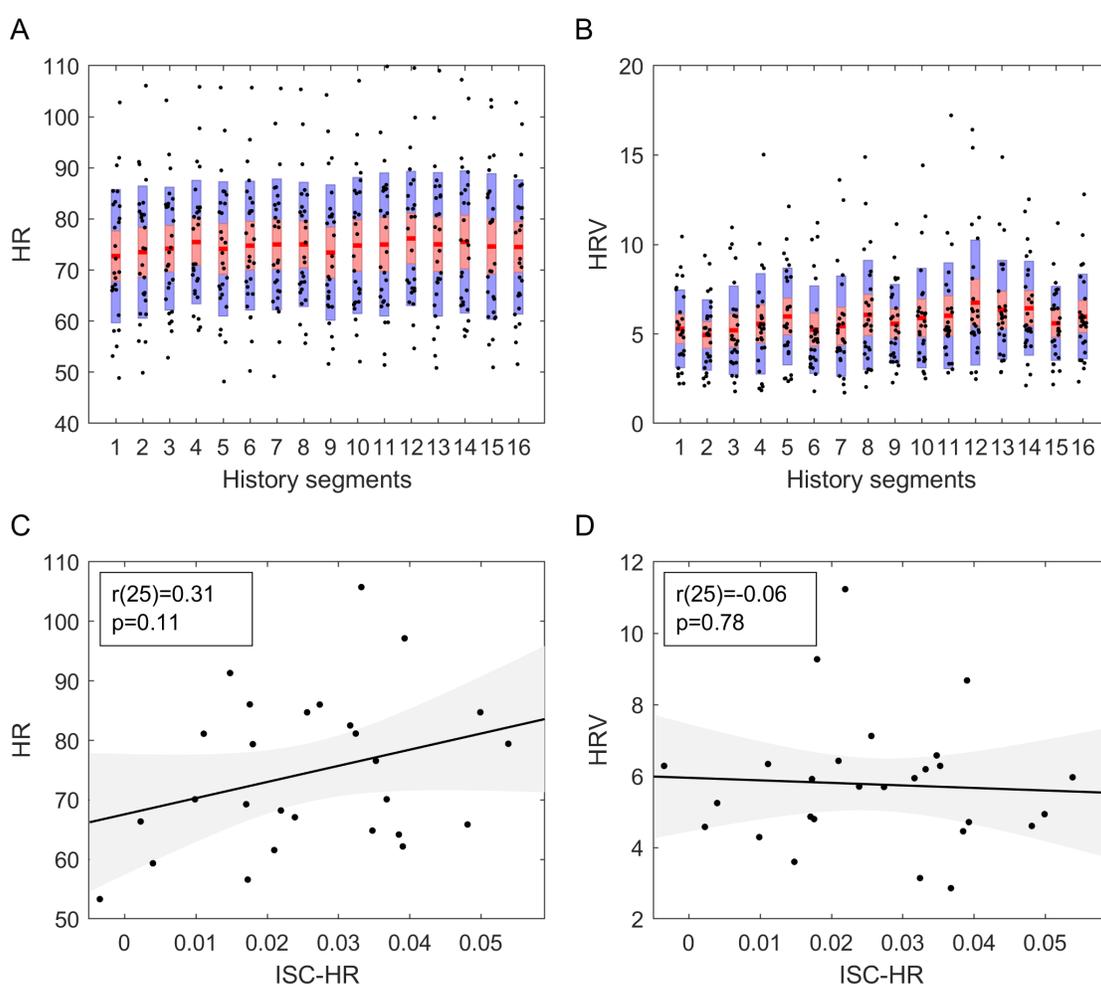
Acknowledgements

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Supplementary materials

Analysis of mean HR and HRV for experiment 1

For experiment 1 we also checked whether mean HR or HR variability (HRV) differed between story segments or between subjects (Fig. S1A and S1B). ANOVA with segment as fixed effect and subject as random effects shows that mean and standard deviation of HR differed between segments (HR: $F(15,390)=2.46$, $p=1.89e-03$, HRV: $F(15,390)=1.73$, $p=4.26e-02$), and between subjects (HR: $F(26,390)=316.92$, $p=2.93e-244$, HRV: $F(26,390)=13.52$, $p=4.92e-40$). We did not see a relationship between HR-ISC and mean HR (Fig. S1C, $r(25)=0.31$, $p=0.11$, $BF_{01} = 1.95$) or between HR-ISC and HRV (Fig. S1D, $r(25)=-0.06$, $p=0.78$, $BF_{01} = 6.47$).

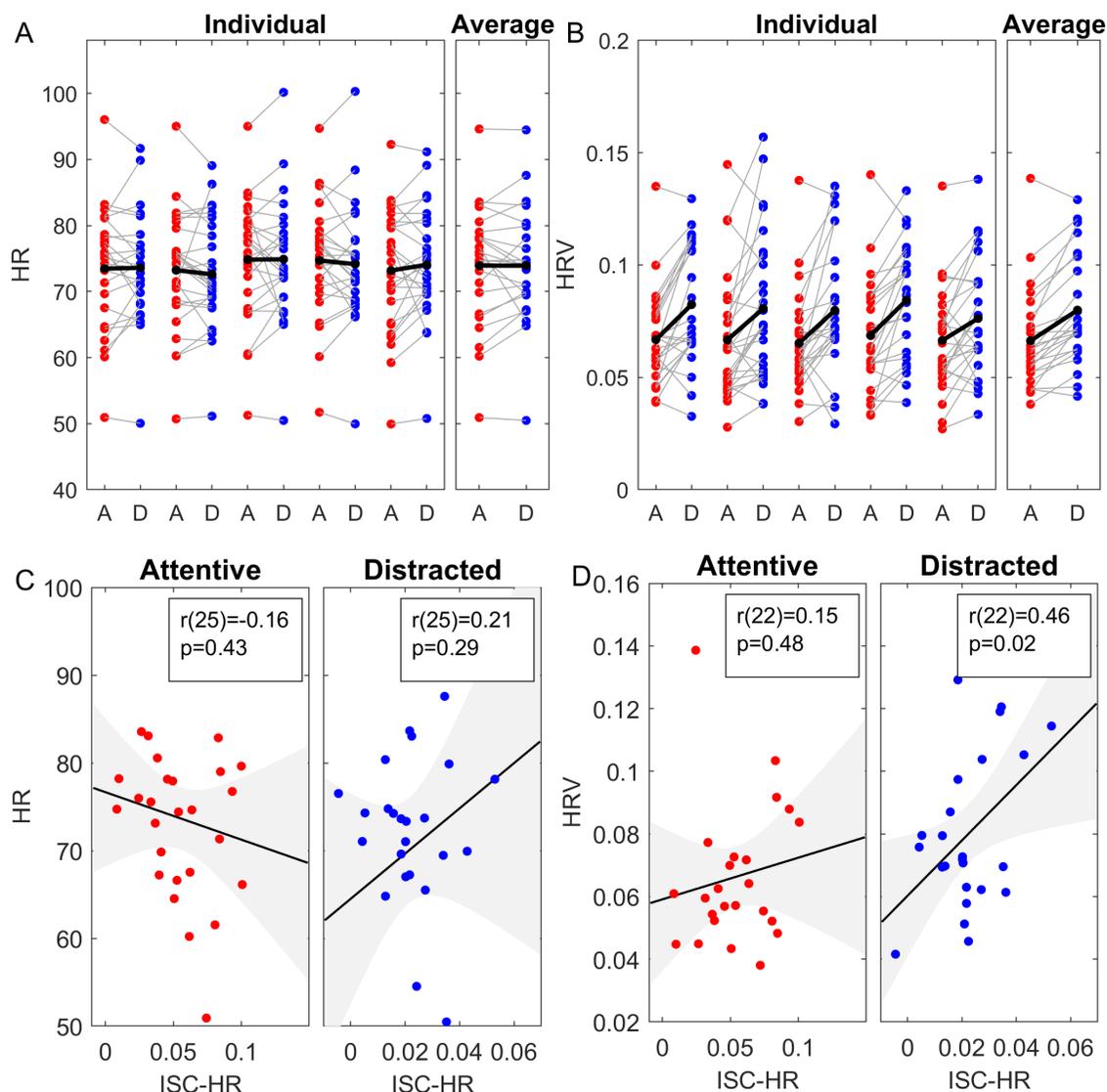


Supplementary Figure 1: **A:** The instantaneous heart rate shows modulation across segments (Anova $F(15,390) = 2.46$, $p=1.89e-03$), and differences across subjects (Anova $F(26,390)=316.92$, $p=2.93e-244$). **B:** Heart rate variability measured as the standard deviation across the instantaneous heart rate for each subject (Anova $F(26,390) = 13.52$, $p=4.92e-40$), and differences across segments (Anova $F(15,390)=1.73$, $p=4.26e-02$).

C: ISC-HR for each subject averaged across segments versus corresponding mean HR (each subject is a dot). We found no linear relationship between these two variables ($BF_{01} = 1.95$).
D: ISC-HR for each subject averaged across segments versus corresponding HR variability (each subject is a dot). We found no linear relationship between these two variables ($BF_{01} = 6.47$).

Analysis of mean HR and HRV for experiment 2

For experiment 2, in addition to the attentional effects reported in the main results section, we also checked whether mean HR or HR variability differed between each educational video and between subjects (Fig. S2A and S2B). ANOVA with video and conditions as fixed effect and subject as random effects shows that mean HR differed across videos (HR: $F(4,211)=3.04$, $p=1.82e-02$), but not standard deviation ($F(4,211)=0.75$, $p=5.58e-01$), and both differed significantly between subjects (HR: $F(23,211)=89.26$, $p=1.74e-95$, HRV: $F(23,211)=29.61$, $p=1.39e-53$). We did not see a relationship between ISC-HR and mean HR (Fig. S2C, Attentive: $r(25)=-0.16$, $p=0.43$, $BF_{01} = 4.92$, Distracted: $r(25)=0.21$, $p=0.29$, $BF_{01} = 3.83$) or between ISC-HR and HRV (Fig. S2D, Attentive: $r(22)=0.15$, $p=0.48$, $BF_{01} = 4.96$, Distracted: $r(22)=0.46$, $p=0.02$, $BF_{10} = 1.95$).

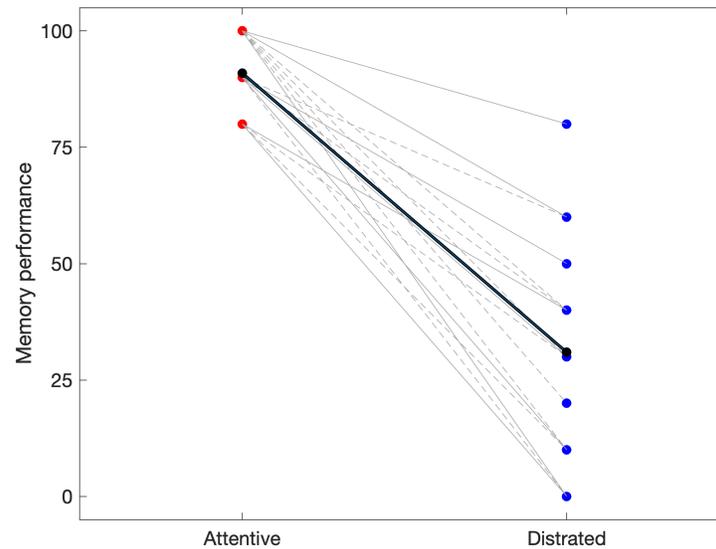


Supplementary figure 2: A: mean HR, **B:** HRV, **C:** correlation of ISC with HR. **D:** correlation of ISC with HRV

Behavioral results of experiment 3

For experiment 3, we checked the modulation of memory performance in the attentive and distracted condition like a proof that the task was correctly completed. After each story, subjects answered 5 short questions about the story content testing their memory performance (i.e name of protagonist?, place?...). Memory performance was significantly higher in the attentive condition than in the distracted condition (Figure S3, Wilcoxon signed-rank test: $z = 4.03$, $p = 5.7e-05$, $BF_{01} \sim 1e8$). In none of the conditions we found a difference between group 1 and 2 in terms of memory performance. In both groups the performance was always similar, in the attentive condition (Median group 1 = 90; Median group 2 = 90; Mann-Whitney U test, $U = 93$, $p = 0.67$, $BF_{01} = 2.3$), in the distracted condition (Median group 1 = 40; Median group 2 = 30; Mann-Whitney U test, $U = 106$, $p = 0.66$, $BF_{01} = 2.2$), or in the contrast between the

attentive and distracted conditions (Median group 1 = 40; Median group 2 = 65; Mann-Whitney U test, $U = 86.5$, $p = 0.39$, $BF_{01} = 2.04$)

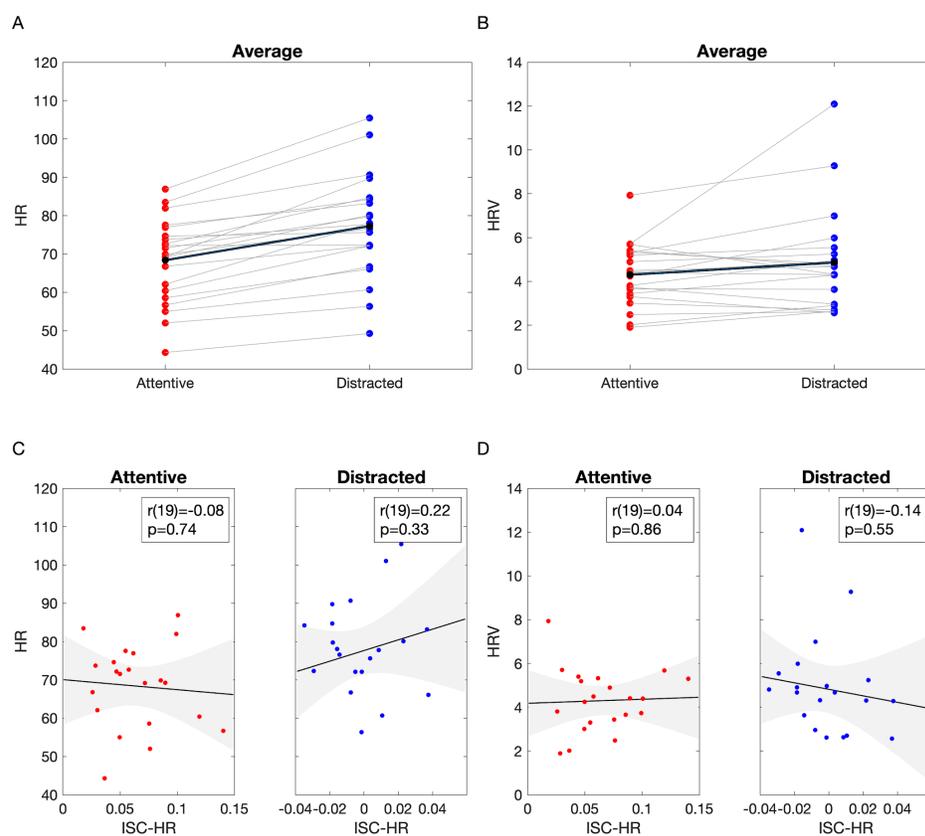


Supplementary figure 3: Behavioral responses attentive and distracted conditions (n=21). Solid lines correspond to subjects in group 1 and dashed lines to subjects in group 2. Each group listened to 2 two stories in the attentive condition and two in the distracted condition. Subjects answered 5 short questions about each story content. The memory performance (rate of good response) was systematically higher in the attentive condition compared to the distracted conditions. We observed no differences in memory performance between groups.

Analysis of mean HR and HRV for experiment 3

For experiment 3 we also checked whether mean HR or HR variability differed between each condition and between subjects. We found that the mean HR was significantly higher in the distracted condition compared to the attentive condition (Fig S4A, paired t-test, $t(20) = 7.32$, $p = 4.5e-7$, $BF_{10} = 37574$). We found no differences in HRV between the attentive and distracted conditions (Fig S4B, paired t-test, $t(20) = 1.64$, $p = 0.12$, $BF_{01} = 1.41$).

We also did not see a relationship between ISC-HR in and mean HR (Fig. S4C, Attentive: $r(19) = -0.08$, $p = 0.74$, $BF_{01} = 5.67$, Distracted: $r(19) = 0.22$, $p = 0.33$, $BF_{01} = 3.74$) or between ISC-HR and HRV (Fig. S4D, Attentive: $r(19) = 0.04$, $p = 0.86$, $BF_{01} = 5.9$, Distracted: $r(19) = -0.14$, $p = 0.55$, $BF_{01} = 5.01$).



Supplementary figure 4: **A:** mean HR, **B:** HRV, **C:** correlation of ISC with HR in the attentive condition (left), and distracted condition (right), **D:** correlation of ISC with HRV in the attentive condition (left), and distracted condition (right)

Respiration and HR and for experiment 3

Breathing is known to be a determinant of the heart rate. First, we tested whether attention affected the breathing signal itself. We computed the spectrum of the respiratory time-series in the attentive and distracted conditions (Fig. S5). We found two cluster corrected significant clusters, the first one from 0.34 Hz to 0.43 Hz ($p = 0.0489$) and from 0.63 Hz to 0.72 Hz ($p = 0.0428$).

Second, we extracted additional features: (1) cardio-respiratory coupling (Fig. S6A), (2) ISC computed from the raw respiratory signal (Fig S6B), (3) ISC computed from the instantaneous inspiratory frequency (Fig S6C), (4) ISC computed from the instantaneous expiratory frequency (Fig S6D), (5) ISC computed from the instantaneous inspiratory amplitude (Fig S6E), and (6) ISC computed from the instantaneous expiratory amplitude (Fig S6F). None of these respiratory features showed a significant ISC nor a modulation according to the attentional state (FDR corrected paired t-tests comparing the attentive and distracted conditions).

Statistical significance at the single-subject level of the computed features was determined by circular shuffling statistics.

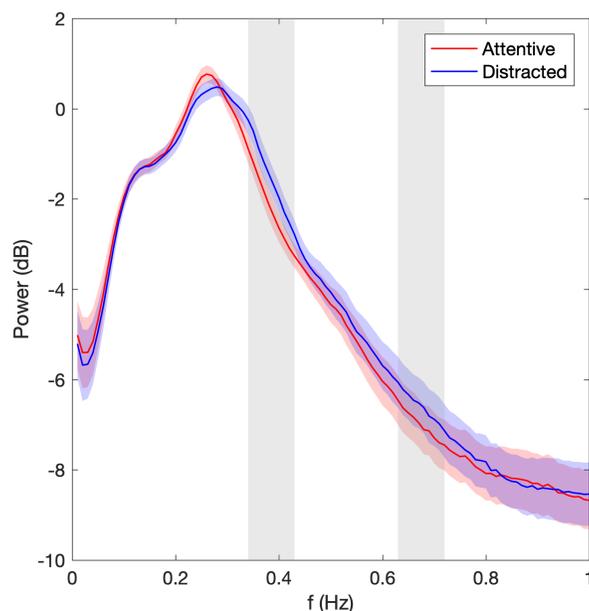
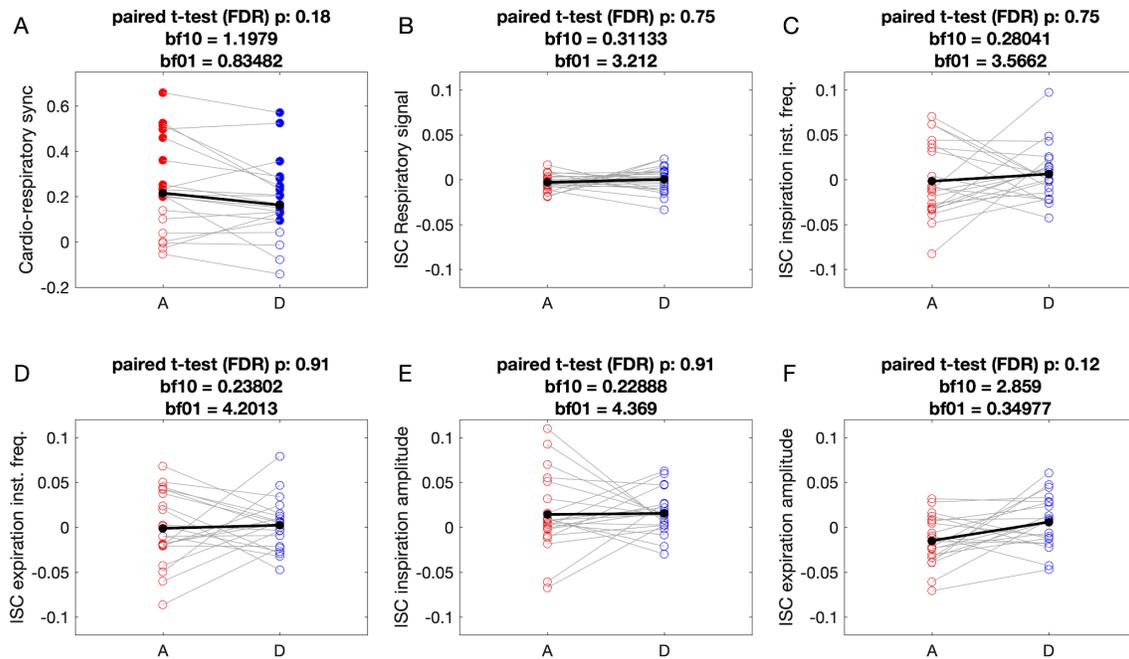


Figure S5: Power spectrum of breathing signal. multiple comparison corrected with one-dimensional cluster statistics, $p < 0.05$). Colored-shaded areas indicate standard error of the mean.

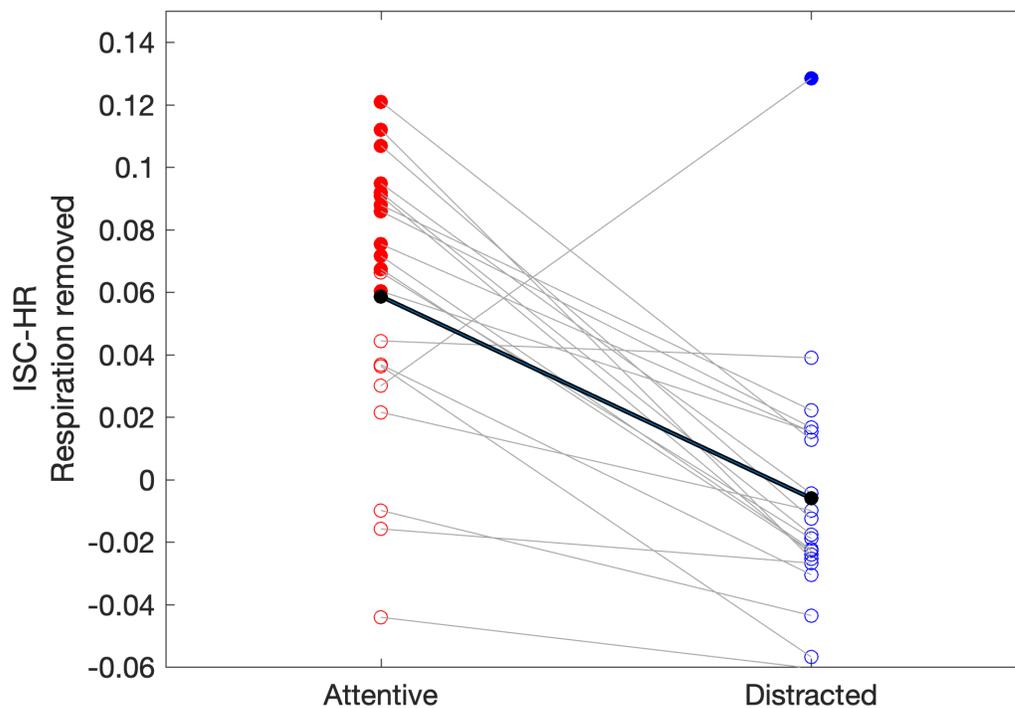


Supplementary figure 6: Attention modulation does not affect respiratory features synchronization.

(A) Cardio-respiratory synchronization was significant in 12/21 subjects in the attentive condition and 15/21 in the distracted condition. However, we found no modulation of this synchrony with the attentional condition. (B-F) No individual significant ISC and no modulation of ISC with attention was found for raw respiratory signal (B), inspiratory instantaneous frequency (C), expiratory instantaneous frequency (D), inspiration amplitude (E), and expiration amplitude (F). Filled and empty circles indicate subject-level significant and non-significant respectively (FDR $p < 0.01$ permutation statistics, circular shuffling statistics)

Removal of respiration from heart rate signal

To remove any instantaneous or delayed effect of respiration on HR we estimate a linear impulse response from respiration to HR signals and subtract the HR signal estimated from the respiration using this impulse response. The residual HR signal is guaranteed to be uncorrelated from respiration at any delay. The filter is estimated separately for each subject and attention condition using 20s of data and ISC is computed on the remaining data using the residual HR signal. The ISC results reported in the main paper (Fig. 5) are reproduced here for the residual HR signal (Supplementary Fig. 6). With the exception of one outlier subject in the distracted conditions, the modulation with attention is essentially unchanged (t-test: $t(20) = 5.57$, $p = 1.9e-05$, signrank: $p = 0.00048$, BF = 1251.3)



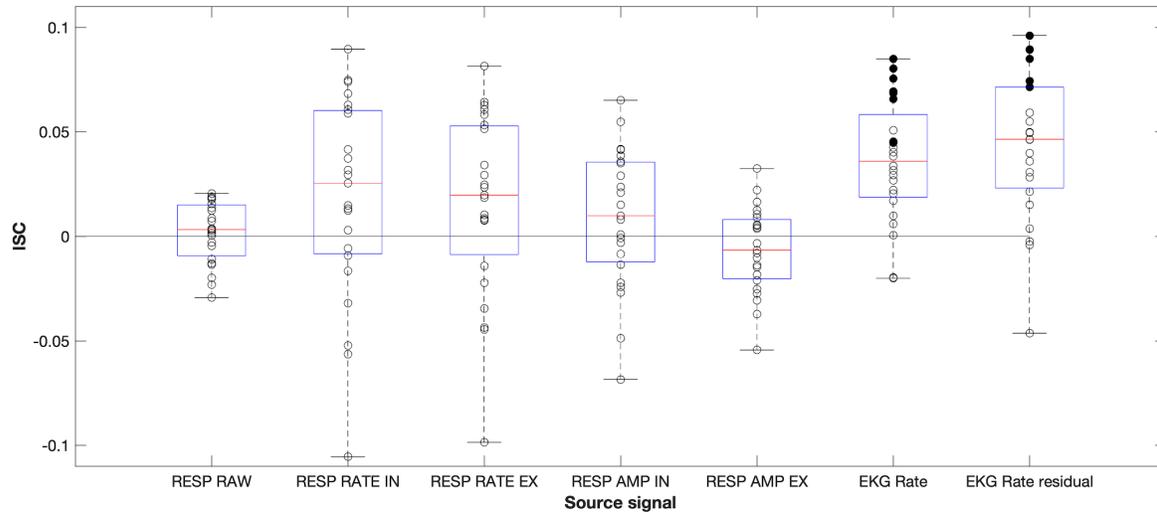
Supplementary Figure 7: Same as Fig. 5A but computed after removing the effect of respiration on HR allowing for potentially delayed correlation. Filled and empty circles indicate subject-level significant and non-significant respectively (FDR $p < 0.01$ permutation statistics, circular shuffling statistics)

Respiration and HR and for experiment 4

In experiment 4 we replicated the analysis comparing cardiac and respiratory features in healthy participants. We computed the ISC from the: raw respiration (RR), instantaneous inspiratory rate (IIR), instantaneous expiratory rate (IER), inspiratory amplitude (IA), expiratory amplitude (EA), instantaneous heart rate (IHR), (7) instantaneous heart rate after respiratory removal (IHR_r). While none of the respiratory ISCs show a significant difference to zero at the group level, both HR-ISC were different to zero (Table 1).

In addition, both IHR and IHR_r were systematically higher than the ISC computed from respiratory features (Table 2).

Finally, IHR_r was significantly higher than IHR (p -value (t-test, FDR) = 0.006, BF10 = 7.3)



Supplementary figure 8: EKG-ISC synchronization outperformed respiratory features synchronization. Filled and empty circles indicate subject-level significant and non-significant respectively (FDR $p < 0.01$ permutation statistics, circular shuffling statistics)

	ISC	T-stats	p-value	p-value (FDR)	BF10	BF01
Resp.	Raw Signal	$t(22) = 0.64$	0.53	0.53	0.26	3.86
	Inst. Insp. Rate	$t(22) = 1.80$	0.08	0.17	0.86	1.16
	Inst. Exp. Rate	$t(22) = 1.72$	0.10	0.17	0.77	1.30
	Insp. Amplitude	$t(22) = 1.27$	0.22	0.25	0.44	2.27
	Exp. Amplitude	$t(22) = -1.51$	0.14	0.20	0.58	1.71
Heart	Inst. HR	$t(23) = 6.06$	$3.52e-6$	$2.01e-5$	5636	$1.7e-4$
	Inst. HR (-resp)	$t(22) = 5.93$	$5.75e-6$	$2.01e-5$	3635	$2.7e-4$

Table 1. Experiment 4, respiratory and cardiac features stats at the group level compared to zero.

	Instant. HR					Instant. HR (-resp)				
	T-stats	p-value	p-val (FDR)	BF10	BF01	T-stats	p-value	p-val (FDR)	BF10	BF01
Raw Signal	$t(22) = 5.24$	$2.9e-5$	$7.3e-5$	823	0.001	$t(22) = 5.33$	$2.37e-5$	$5.93e-5$	1001	0.001
Inst. Insp. Rate	$t(22) = 2.20$	0.04	0.04	1.61	0.62	$t(22) = 2.83$	0.01	0.01	5.0	0.2
Inst. Exp. Rate	$t(22) = 2.81$	0.01	0.01	4.83	0.20	$t(22) = 3.5$	0.002	0.003	19	0.05
Insp. Amplitude	$t(22) = 2.78$	0.01	0.01	4.57	0.21	$t(22) = 3.20$	0.004	0.005	10.3	0.1
Exp. Amplitude	$t(22) = 5.35$	$2.27e-5$	$7.36e-5$	1044	0.001	$t(22) = 5.6$	$1.2e-5$	$5.9e-5$	1807	0.0005

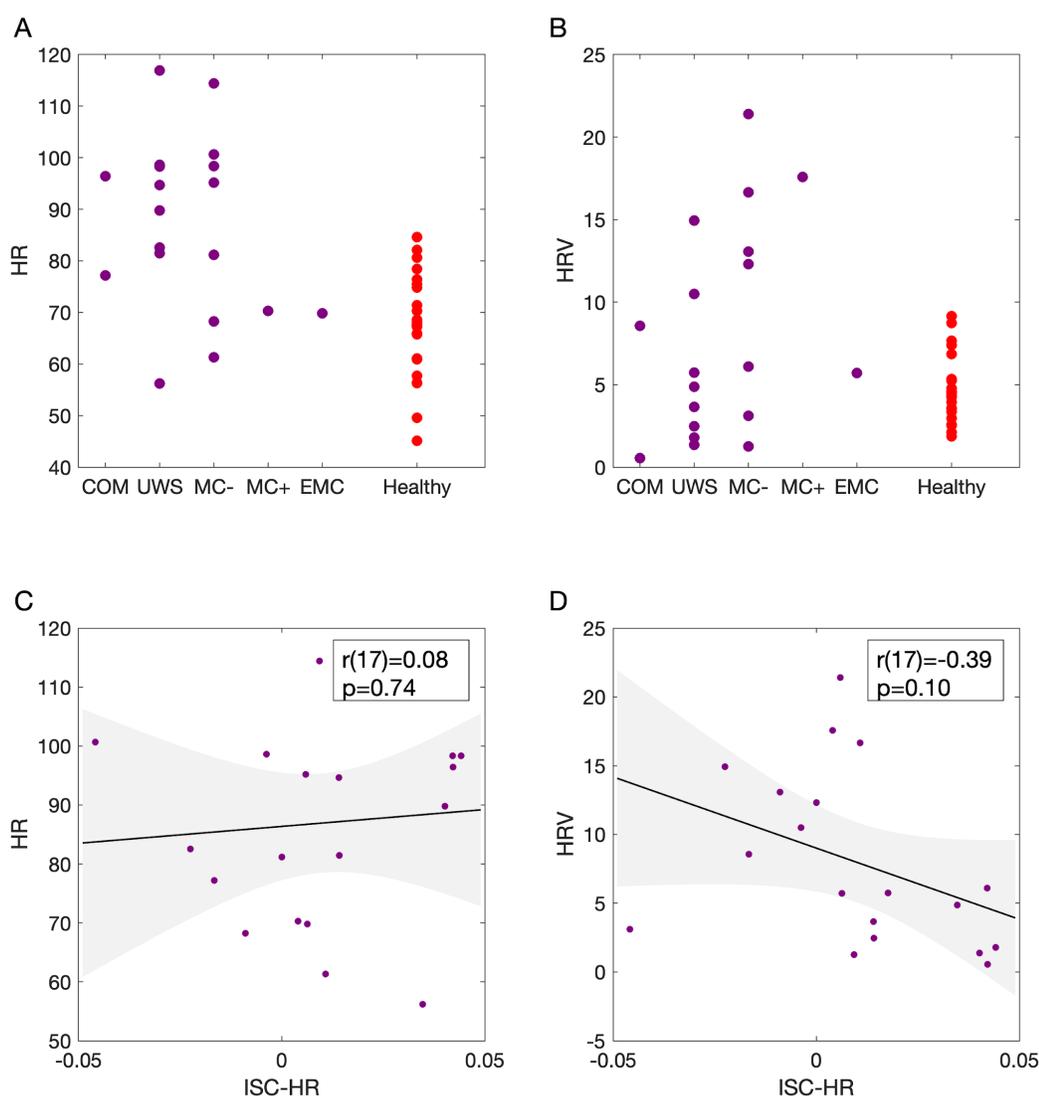
Table 2. Experiment 4, comparison between respiratory and cardiac features.

Analysis of mean HR and HRV for experiment 4

For experiment 4 we also checked whether mean HR or HR variability differed between the different states of consciousness (Fig. S9). The mean HR of DoC patients was significantly higher than healthy participants (Fig S9A, $t(41) = 4.7$, $p = 2.9e-05$, $BF10 = 12.4$). To test if HR

changed with the state-of-consciousness among the DoC patients we performed a Spearman correlation between state-of-consciousness (Coma = 1, VS = 2, MCS- = 2, MCS+ = 3, EMCS = 4) and HR and found no significant correlation ($R(17) = -0.18$, $p = 0.45$, $BF01 = 3.37$). Similar for the HR variability, HRV was significantly higher in DoC patients compared to healthy controls (Fig S6B, $t(41) = 2.34$, $p = 0.02$, $BF10 = 2.54$). We found no significant relationship between the patients' state-of-consciousness and HRV (Spearman correlation, $R(17) = 0.41$, $p = 0.08$, $BF01 = 2.11$).

We also controlled the relationships between HR and ISC, and HRV and ISC for patients. In none of the cases the relationship was significant (Fig. S9C, HR versus ISC, $r(17)=0.08$, $p=0.74$; $BF01 = 5.42$, Fig. S9D, $r(17)=-0.4$, $p=0.09$, $BF01 = 1.45$).



Supplementary figure 9: **A:** mean HR for DoC patients and healthy participants (Note that DoC patients are ordered in individual columns corresponding to their clinical state-of-consciousness (1=Coma, 2=VS/UWS, 3=MCS-, 4=MCS+, and 5=EMCS) **B:** HRV, idem to A **C:** correlation of ISC with HR for DoC patients. **D:** correlation of ISC with HRV for DoC patients.

Subject	Sex	Age (years)	Etiology	Delay (days)	State	CRS-R	FA	Outcome
1	M	71	Acute Polyradiculoneuritis	12	Coma	0	no exam	VS/Death*
2	F	77	Meningitis	86	Coma	2	no exam	VS
3	M	18	TBI+Anoxia	170	VS	5	0.756	VS
4	M	29	TBI+Anoxia	510	VS	5	artefacted	VS
5	M	29	Anoxia	556	VS	5	0.492	VS
6	M	55	TBI	27	VS	6	artefacted	MCS+
7	F	53	Anoxia	328	VS	5	0.824	VS
8	F	24	TBI	68	VS	5	0.644	MCS-
9	F	63	Anoxia	41	VS	5	0.642	VS
10	M	18	Anoxia	59	VS	4	0.792	VS/Death*
11	F	50	Anoxia	5852	MCS-	10	0.698	MCS-
12	M	26	Status Epilepticus	209	MCS-	9	0.561	MCS+
13	M	50	Anoxia	60	MCS-	7	0.85	EMCS
14	F	61	Status Epilepticus	90	MCS-	10	noDTI	MCS-
15	M	58	Anoxia	302	MCS-	14	0.548	MCS -
16	M	56	TBI	478	MCS-	11	0.824	MCS-*
17	F	36	Left hematoma	121	MCS-	12	noDTI	EMCS
18	F	49	TBI	980	MCS+	13	noDTI	MCS+
19	M	28	Status Epilepticus	313	EMCS	14	no exam	EMCS

Table 3 Description of patient cohort: summary table including patients with sex, age, etiology of brain lesion, delay between brain lesion and the evaluation, state of consciousness, CRS-R (Coma Recovery Scale-Revised), Fractional anisotropy (FA) from MRI and outcome. *Outcome collected before 6 months.

Part V

Discussion

3.2 Summary of the main results

We show in the first study that it is possible to study the conscious content and the state of consciousness independently using a 2-dimensional graphical representation. In the proposed examples, we study EEG markers but it is possible to reproduce the same graphs with the markers from other neuroimaging techniques (fMRI, MEG, ERP, PET). One of the major results of this study is that some markers decrease post-perceptually in the same time window as awareness.

In a second study, using the local global paradigm, we were to predict the outcome of patients with brain injury. we show that the global effect is able to predict the outcome of patients with brain injury. The local global paradigm is used here as a passive paradigm of conscious content because of the patients' inability to report whether they have been aware of the violations of auditory regularities. By only studying their brain responses with the EEG, we could predict with good specificity the return to consciousness. Obviously, this examination is less efficient than the clinical examination performed by trained personnel. However, it shows that some patients who do not exhibit conscious neurological behaviors, in fact have a more complex cerebral processing of their environment than their behavior would indicate. This study reinforces the idea that conscious content is a subjective first-person experience, and its clinical practice is limited to evaluating patients' motor responsiveness [71]. Furthermore, this study questions the decisions to be made in the ICU if the clinical examination and brain imagery have different conclusions: for example, a patient in a vegetative or a minimally conscious state on clinical examination but showing a global effect on EEG.

In a third study, we show through several experiments that cardiac activity is modulated by cognitive processing and by conscious or attentional content. The originality of this study is that it did not focus on the brain signal but on the body signals such as cardiac or respiratory activity. We were able to verify this model by applying it to patients with consciousness disorders and by showing that patients do not synchronize with healthy subjects. Furthermore, in healthy subjects, cardiac activity seemed to synchronize more than respiratory activity.

3.3 The importance of contrast for a more accurate study of conscious states and contents

In all these studies, we emphasize the importance of contrast in the study of consciousness disorders. Classically, contrast is based on VS versus MCS patients. It is determined by the CRS-R scale, which is based on the patient's spontaneous or stimulated behavior. Many neuroimaging studies [96, 74] show that this behavior does not always reflect the actual conscious processing of the information, as we saw in Study 2. Indeed, some VS or MCS patients had an global effect and were conscious at 6 months, suggesting that their conscious content (detection of the violation of a complex rule) was higher than what their evoked behavior at that moment. This has important clinical implications especially in end-of-life decisions. In study 3, the conscious processing was more complex compared to the local global paradigm because the content of the stimulation was a 10 min story. Comprehension of the story required many processes such as consciousness and attention but also working memory, semantic access to words, processing of the emotional content or empathy on which cardiac synchronization with healthy subjects could depend. The absence of cardiac synchronization with healthy subjects could be due to cerebral lesions exceeding the regions involved in perceptual access such as insular lesions [30], aphasia or lesions of the memory networks... This finding shows us that the importance of using stimuli at different complexity levels to probe a patient's conscious activity. It has been shown in healthy subjects that a stimulus with a strong emotional valence or very engaging (e.g. a movie or a political speech) provokes higher levels of synchronization between subjects [40, 112]. Thus, in the laboratory, we defend the idea that the distinction between VS and MCS may be historical but not well adapted to new neuroimaging data [96, 21, 83]. We prefer the distinction VS-MCS- vs MCS+ or VS-MCS- vs CMS [87]. Indeed, some behaviors are mediated by the cortex such as following an object with the eyes, and on the contrary, opening only the eyes which is a subcortical reflex activity. Nevertheless, only some complex behaviors require a cortical activity distributed within the whole brain such as responding to a simple command or having a functional use of an object. This distinction between reflex behaviors, cortex-mediated behaviors and distributed cortex-mediated behaviors, seems essential to us when

we talk about consciousness [87]. Thus, reflex and cortex-mediated behaviors would not be conscious whereas complex behaviors mediated by a distributed cortex would be conscious. In DOC patients, optimizing the contrast between patients and discussing the notion of VS and MCS seems therefore a major progress on the study of consciousness in these patients.

3.4 The study of content and state: a theoretical breakthrough

The study of content and conscious state independently but on the same graph is an original vision. Indeed, it allows us to conceive the signatures of consciousness in different spaces and to try to understand how each marker contributes to the conscious state or the conscious content. In Study 1, we were surprised that some markers are in the least intuitive quadrants of our graph, i.e these markers increased with the level of consciousness (VS<MCS) but decreased with the conscious content . It has already been shown in other studies that these markers were higher in MCS patients than in VS patients (contrasting state of consciousness). The novelty is that most of these markers decrease with the content of consciousness, i.e. it decreases in post perceptual content. We evoke the hypothesis of the gating mechanism [111, 3, 66]: after the perception process, the brain switches into a mode where a new perception is no longer possible before returning to a basal mode. Thus, as evoked by several authors [76, 47], consciousness would be a non-continuous phenomenon with discontinuous units, a bit like a movie and its 24 frames per second. Of course, these are only hypotheses, but to go further, these markers would have to be studied during longer resting states to analyze the dynamics of these fluctuations, but also in other perceptual modalities, with different neuroimaging markers (fMRI, MEG, PET) to confirm these results.

In the third study, interestingly, we do not find a correlation between HSR and CRS-R (state of consciousness of the patient) but we show a correlation with the fraction of anisotropy (anatomical connectivity). In this experiment, many cognitive functions are tested (consciousness, working memory, emotional valence, semantic understanding....).The fraction of anisotropy is the reflection of the cerebral lesion and of the neuronal networks' damage. This correlation shows the link that content and state of consciousness could

maintain between cardiac synchronization and the persistence of anatomical connectivity.

The question also arises as to how the state and content of consciousness are ordered in term of importance. What is the relationship between state and content of consciousness? If we accept the definition of the state of consciousness as a basic condition for the emergence of consciousness, which would be an appropriate level to "ensure adequate cortical excitability". The state of consciousness is then like the level of vigilance, a background condition for the emergence of consciousness. Bayne [12] proposes to study consciousness by means of a radar graph where each valence of consciousness would be studied. It would then be possible to deduce different patterns of MCS and VS patients. Another model that seems more reasonable for the study of patients is a hierarchical model [97, 82]. The first step would be to diagnose the state of consciousness using PET scan (metabolism marker), EEG, ERP and fMRI in resting state or passive paradigms. This allows the identification of spontaneous brain activity with or without stimulus but without the need for consciousness. In a second step to determine the conscious content, they propose using ERP and fMRI in active processes. In this sense many paradigms have been developed. In Owen's fMRI paradigm [98] for example (e.g., to imagine playing tennis), patients in MRI are asked to imagine playing tennis or walking around their house which activates certain brain areas when the patient has understood the instructions. By comparing the elicited blood oxygen level dependent (BOLD) signal changes in an unresponsive appearing patient to those seen in a group of healthy volunteers, it is possible to infer consciousness in those patients. Another method used in the detection of CMD (command motor dissociation, patients that show MRI or electrophysiologic evidence of command following) is recording an EEG during verbal motor command and comparing this EEG to a group of healthy volunteers [26].

In clinical practice, the diagnosis of the state of consciousness in brain-injured patients is important for therapeutic decisions, but identifying the state of consciousness at a specific point in time is not always relevant to determine the patient's prognosis [21]. This is due to the many fluctuations in the patient's clinical state, but also, for example, to frontal lesions that may decrease the patient's performance for motivational reasons, aphasia, etc.... Thus, when studying prognosis, the data of state of consciousness and content of consciousness are often combined.

3.5 Content and state of consciousness in the prognosis of neurological patients

The prognostic evaluation of patients is rather well coded in cardiorespiratory arrest [109] and more complex in TBI patients because the brain injury is uniform in cardiac arrest whereas the neurological evaluation of TBI patients can be over several years. Neurological evaluation in most intensive care units in France is based on clinical examination and repeated 30-minutes EEGs, checking reactivity, background rhythm analysis or the absence of specific abnormalities such as inter-critical or critical epileptic activity, periodic diffuse activity (anoxic, metabolic, diffuse) or focal abnormality (stroke, encephalitis). Finally, it is mainly the clinical examination that determines the patient's state of consciousness, i.e. coma, vegetative state or minimal state of consciousness. Obviously, the state of consciousness is related to prognosis, the higher the state of consciousness the better the prognosis [45]. However, the challenge is to detect patients who will have a good prognosis despite a clinical examination showing no obvious signs of consciousness.

In the second study, we show that the global effect in ERP is able to predict a good outcome. This could be the marker of the integrity of certain neural circuits before it can be detected with the clinical examination. Thus, we understand that separating the concept of state of consciousness and content of consciousness is difficult when talking about prognosis in these patients. Firstly, the diagnosis of the state of consciousness with clinical examination is complex because it requires significant neurological expertise, the examination is long, and it must be repeated several times due to the usual clinical fluctuations in these patients. Second, the content of consciousness in patients can only be probed through unrelated paradigms. The neuroimaging examinations cited above are not performed in routine practice. Finally, since some patients may have conscious content without us being able to really determine their state of consciousness, it is essential to link the results of imaging exams to the prognosis. Often, studies link neuroimaging data to the patient's state of consciousness using the clinic as a gold standard. It is essential to follow cohorts of neuroimaging patients and correlate neuroimaging results to prognostic data.

3.6 A new window to study not only the content but also the state of consciousness.

"The brain is not in a jar", this sentence illustrates wonderfully our third experiment. Indeed, the brain is not isolated and it communicates permanently with the rest of the body. The challenge here was to study the state and the content of consciousness without recording the brain. The originality of this article is recording the heart rate and to show a synchronization of these heartbeats between healthy volunteers during narrative stimuli. We were also able to find markers of conscious content and conscious state. For the conscious content, we showed a correlation between cardiac synchronization and memory in healthy subjects proving that the story had been listened to and more importantly had been encoded. Concerning the state of consciousness, we showed that modulating attention decreased the level of synchronization during a double task. In the neuro-injured patients, there was no synchronization with the group of healthy subjects, but there was a correlation with FA, which is a marker of the integrity of the neuronal networks. In the same way, in a recent study [20], heart evoked responses based on consciousness scores correlate with glucose metabolism (measured with PET) in the default mode network node (located in right superior temporal sulcus, right ventral occipito-temporal cortex). The level of cardiac synchronization therefore allowed us to investigate the content of consciousness but also the state of consciousness. How can we interpret this? Perhaps the fluctuation in the heart rates is a marker of state whereas the cardiac synchronization may be a marker of content. The other important question is the causality of this cardiac synchronization. The study does not allow us to answer this question but several hypotheses can be evoked. It is possible that synchrony can only be observed with very salient or complex stimuli (strong emotional valence, text, music, prosody but much less on simple perceptual presentation). The scientific literature on respiration and cognition [54, 106, 17, 2] gave us the intuition that the respiratory signal synchronizes between subjects but we could not show this effect. It is possible that the respiratory signal is too slow and the experiment was too short to study respiratory synchronization. It is also possible that cardiac synchronization is more important than respiratory synchronization because it depends on fewer factors, In particular, the heart rate is not potentially controlled voluntarily in contrast to breathing.

Part VI

Conclusion and
perspectives

Why focus so much on the distinction between state and conscious content when these two concepts seem ultimately artificial in relation to the concerns of the clinician and the families whose loved one has a brain injury? We believe that this distinction is important because we focus on the fact that a good prognosis is to recover functional communication, according to the definition of consciousness that we develop in the team "a conscious experience is one that can be related to the first person" but also "that can be shared". Thus, studying the state of consciousness would be a prerequisite to better understand the emergence of consciousness. The analysis of conscious content is crucial to probe the patient's experience.

From a theoretical point of view, the combined study of brain imaging markers that are more or less specific to the state and content of consciousness will allow us to better specify the networks involved in the content and states of consciousness. 1) This thesis consolidates the existence of a global network workspace. Indeed, it was previously shown that the global effect (P3b) corresponds to a large broadcast from the auditory areas to a large frontoparietal distributed network. By confirming that this signature predicts the return to consciousness, we hypothesize that it is at least a signature of conscious processes and that this large frontoparietal network is involved. 2) Furthermore, we assume the existence of a gating mechanism, where the conscious perceptual input closes the doors of connectivity and allows a higher stability of neuronal activity during conscious access. This theory will have to be tested by studying markers of connectivity in pre- and post-perceptual access. It highlights the possibility that consciousness is a discrete process and that the brain creates the illusion of continuous perception. 3) We explore the relationship between states/ content of consciousness and the embodied paradigm to cognition. We show that fluctuations in heart rate depend on top-down attention to the stimulus, predict memory performance and may represent a simple measure to assess conscious state and conscious content in patients. The link between these heartbeats and the brain remains to be defined.

From a clinical point of view, the brain-injured patient with disorder of consciousness is the main focus of our work. In this thesis, we have tried to predict the consciousness recovery with a simple EEG procedure, which adds to the set of tests already available. We also highlight the need to validate neuroimaging techniques with relevance to prognosis and not only to the initial diagnosis of consciousness. We also open a way of diagnosis and prediction of consciousness recovery with only body signal recording. These

recordings are performed at the bedside and are much easier to record than EEG or other neuroimaging methods.

Finally, we believe that the state of consciousness is important to define for diagnostic, prognostic and therapeutic issues in intensive care unit but that the first-person experience of patients, i.e. their consciousness content, is essential. The main goal is to be able to develop many applications such as designing efficient Brain Computer Interface tools to ease patients' lives and communication.

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