

Neural correlates of consciousness: what we know and what we have to learn!

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Abstract Consciousness is a multifaceted concept with two major components: awareness of environment and of self (i.e., the content of consciousness) and wakefulness (i.e., the level of consciousness). Medically speaking, consciousness is the state of the patient's awareness of self and environment and his responsiveness to external stimulation and inner need. A basic understanding of consciousness and its neural correlates is of major importance for all clinicians, especially those involved with patients suffering from altered states of consciousness. To this end, in this review it is shown that consciousness is dependent on the brainstem and thalamus for arousal; that basic cognition is supported by recurrent electrical activity between the cortex and the thalamus at gamma band frequencies; and that some kind of working memory must, at least fleetingly, be present for awareness to occur. New advances in neuroimaging studies are also presented in order to better understand and demonstrate the neurophysiological basis of consciousness. In particular, recent functional magnetic resonance imaging studies have offered the possibility to measure directly and non-invasively normal and severely brain damaged subjects' brain activity, whilst diffusion tensor imaging studies have allowed evaluating white matter integrity in normal subjects and patients with disorder of consciousness.

Keywords Consciousness · Disorders of consciousness · Ascending reticular activating system · Default mode network · Neuroimaging

Introduction

Consciousness is a multifaceted concept with two major components: awareness of environment and of self (i.e., the content of consciousness) and wakefulness (i.e., the level of consciousness).

Whereas the level of arousal reflects the overall state of activity in the brain, conscious awareness is a more dynamic and complex process involving various cerebral networks at any one time. There are several contrasting theories on how we become aware of environmental and internal stimuli, although it is widely believed to depend on interactions between the cortex and specific and non-specific (i.e., intralaminar) thalamic nuclei [1, 2].

Conscious awareness and arousal states also interact. Without arousal, there is no awareness, and in states of high arousal, awareness can be focused on one modality at the expense of others. Conversely, awareness also influences arousal, such as the abrupt increase in arousal when an alarm goes off [3].

Generally speaking, there are two opposing views about the extensiveness of neuronal involvement in consciousness, i.e., the holistic approach highlighting the perspective that all neurons in the brain collectively form the neural correlate of consciousness, and the neuronal specificity approach supporting the idea that consciousness depends on the formation of complex arrangements, which can be related to specific groups of neural cells. Thus, consciousness is believed to be a product of the processing of multiple brain regions, which in turn produce a high level

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of information integration [4]. In particular, the information integration theory of consciousness (IITC) suggests the idea that consciousness depends on the brain's ability to integrate complex patterns of internal communication [5, 6].

Neuronal circuitries and anatomical structures subserving consciousness

The initial discovery that specific brain areas could drive overall cerebral activity appeared for the first time in 1949 in a work by Moruzzi and Magoun, who proposed the existence of an ascending reticular activating system (ARAS)—situated in the upper brain stem tegmentum (reticular formation) and central thalamus—which promoted widespread cortical activation [7, 8].

Other brain regions, including the nuclei in the upper brain stem acting on the basal forebrain, thalamus, hypothalamus, striatum, and associative cortex are also involved in arousal but have a more modulatory role [9].

The consciousness system also comprises cortical regions important for higher-order integration including the lateral frontal and parietal association cortex, as well as the medial frontal, anterior, and posterior cingulate, and medial parietal (precuneus, retrosplenial) cortex. Indeed, stimuli are not acted on as reflexes, but typically require motivation to enter conscious awareness through a process called intention or goal-directed behavior. It has been suggested that dopaminergic modulation of glutamatergic inputs from the cortex and thalamus onto medium spiny neurons in the striatum contributes to cognition and the expression of consciousness [10].

Amusingly, lesion and functional brain imaging studies demonstrate that goal-directed behavior is primarily driven by the medial frontal and anterior cingulate cortices, such as supplementary eye field (SEF), supplementary motor area (SMA), and pre-SMA [11]. This sense of consciousness therefore throws a bridge between perception and action, the events we experience and the ones we bring about [4]. The aforementioned cortical regions are supported in producing goal-directed behavior by striato-pallidal-thalamic loops as well as the ventral tegmental area and the periaqueductal gray of the brain stem.

Behavioral inhibition system (BIS) activity plays an important role, instead, in the suppression of dominant behaviors, and reworking of risk-related mental processes, so BIS activity results in emotional states of anxiety and a sense of possible danger/loss. The neuroanatomical correlates of this system are not fully clear, although they are known to involve the amygdala, the septohippocampal system, and the prefrontal cortex [12, 13].

Herein, the main structures involved in maintaining alertness (Fig. 1) and consciousness (Fig. 2) are more specifically described, and summarized in Table 1.

ARAS The ARAS, made up of many neural circuits linking the brain stem to the cortex, and its activity on the cerebral cortex (depending on both specific sensory input and non-specific activating impulses from the brain stem) are the ground of the achievement of consciousness.

Although the ascending and descending reticular activating systems are well integrated, the latter tends to be centered in the medulla, whereas the former is found more in the pons and the midbrain. The reticular formation is essentially a heavily arranged network of neurons, which are distributed throughout the brain stem, wherever there are no specific neural tracts or nuclei. There is positive feedback between an awake mind and the reticular activating system. Neurochemically speaking, the brain stem monoaminergic nuclei including noradrenergic,

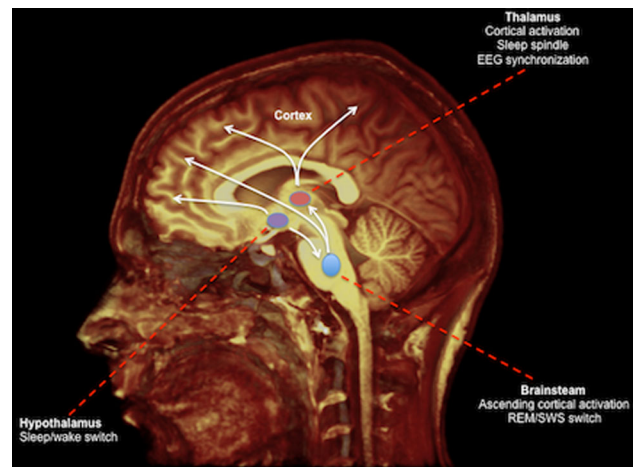


Fig. 1 Shows the reticular ascending system and the necessary projections in activating awareness

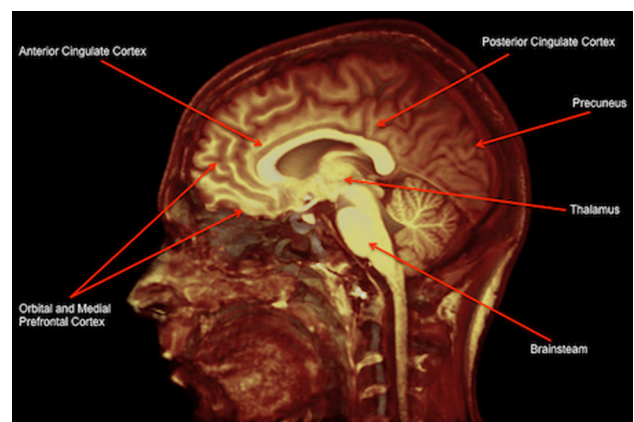


Fig. 2 Shows the main brain areas involved in consciousness

Table 1 Summarizes the main brain structures involving in wakefulness and awareness

Brain area	Correlation with states of consciousness
ARAS	It consists of ascending fibers to the thalamus and projecting to several thalamic nuclei from which they are distributed widely in the cerebral cortex. The ARAS is responsible for the level of consciousness and its changes. Damage to the reticular formation at the level of the rostral pons or caudal bulb can lead to coma or vegetative state
Thalamus	Close connections between the thalamus and the cerebral cortex ensure the maintenance of consciousness and particularly the modulation of arousal. The lack of the integrity of thalamus-cortical and cortical-basal ganglia-thalamus-cortical system can result in VS and MCS
Hypothalamus	It is linked to the brain stem and to the basal forebrain and is involved in the sleep-wake transition and in maintaining the awake state
Basal forebrain	It receives cholinergic projections from the ARAS and plays a major role in supporting arousal during REM sleep. The disconnection from specific brain stem arousal nuclei is present in traumatic coma
Amygdala	The amygdala is involved in emotional arousal and modulates the threshold for awareness of emotional stimuli
Basal ganglia	Diffuse disruption of the cortico-BG-thalamic-cortical loop is associated with impairment of emotional, motivational and cognitive processes, resulting also in coma state and DOC
Prefrontal cortex	The prefrontal cortex disconnects from the DMN during deep non-REM sleep and is one of the area with lower activity during propofol induced loss of consciousness. Impairment, decreased cerebral glucose metabolism and connectivity in the dorsolateral prefrontal cortex can lead to VS
Cingulate cortex	PCC and ACC are widely involved in maintaining the conscious state and, being part of the DMN, they show higher activity at rest than during attention-demanding tasks. Decreased connectivity in ACC is linked to altered state of consciousness, including VS
Precuneus	The precuneus is profoundly deactivated in pathophysiological altered states of consciousness, such as SWS, REM sleep, pharmacologically induced coma, general anaesthesia and PVS. Since during these state of consciousness its metabolism is much less active than other areas of the DMN, it could be considered a reliable criterion to distinguish VS from MCS patients

dopaminergic and serotonergic nuclei, project directly to the cortex, in order to modulate wakefulness and mood, as well as to the basal nuclei. Noradrenergic (locus coeruleus) and serotonergic (raphe) nuclei have been associated with attentiveness and behavioral responses to stimuli, while dopamine is, among others, associated with working memory by modulating excitatory and inhibitory transmission in the prefrontal cortex, and with motor control and reward. Moreover, although serotonergic neurons are silenced during REM sleep, they increase their activity during deep sleep. Spiking activity in cholinergic neurons increases during wakefulness and REM sleep and decreases during non-REM or deep sleep.

Acetylcholine is therefore believed to elevate arousal in the brain so as to allow the formation of consciousness, however fleeting. Histaminergic neurons of the posterior hypothalamus act like noradrenergic neurons in enforcing waking and are joined by neurons in the region that contain orexin, a neuropeptide recently shown to maintain waking and in absentia to be responsible for narcolepsy, or the inability to maintain wakefulness. These multiple arousal systems are grossly redundant, since no system is absolutely necessary for the occurrence of waking; yet they are differentiated, since each plays a special role in waking and sleep. During slow wave sleep (SWS), they are submitted to an inhibitory influence arising in part at least from particular GABAergic neurons co-distributed with many neurons of the arousal systems and also concentrated within the basal forebrain and adjacent preoptic region [14,

15]. Notably, lesions of ARAS may cause coma, i.e., the most severe disorder of consciousness [15], consisted in a state of continuous ‘eyes-closed’ unconsciousness in the absence of a sleep-wake cycle [4].

Thalamus It has been demonstrated that the connectivities of specific ARAS nuclei are implicated in arousal, and those of thalamic nuclei are implicated in modulation of arousal [16]. The intralaminar nuclei (non-specific nuclei) are the site of termination for the ascending reticular activating system. Central thalamic neurons appear to be both anatomically and physiologically specialized to support distributed network activity that maintains neuronal firing patterns across long-range cortico-cortical pathways and within cortico-striato-pallidal-thalamo-cortical loop connections. Recruitment of central thalamic neurons occurs in response to increasing cognitive demand, stress, fatigue, and other perturbations that reduce behavioral performance. In addition, the central thalamus receives projections from brain stem pathways evolved to rapidly generate brief shifts of arousal associated with the appearance of salient stimuli across different sensory modalities. Through activation of the central thalamus, neurons across the cerebral cortex and striatum can be depolarized and their activity patterns selectively gated by descending or ascending signals related to premotor attention and alerting stimuli. Moreover, the thalamic reticular nucleus is actually only a thin sheet of inhibitor neurons that are believed to function as a “gate” for signals directed to the cerebrum. Thus, the reticular complex may

control which sensory inputs are the subject of attention of the cerebral cortex [17]. Interestingly, the thalamic neurons sending projections to the cerebrum have specialized properties, which enable them to fire in synchronized bursts or with desynchronized single-spike firing. The former corresponds to the EEG desynchronization seen in REM sleep or in the alert, awakened state [18]. During SWS or wake state, only few correlations outside the thalamus have been shown, whilst, during REM sleep, strong correlations have been found between the thalamus and occipital and parietal cortices, hippocampus, motor areas, cerebellum and mesencephalic reticular formation [19].

Recent theoretical advances describing consciousness from information and integration have highlighted the unique role of the thalamo-cortical system in leading to integrated information and thus, consciousness [18]. Vegetative state (VS)/unresponsive wakefulness syndrome (UWS) patients seem to have lack of awareness due to the instability of the thalamus circuits. Although many clinicians tend to differentiate VS/UWS from minimally conscious state (MCS) patients (the latter showing some signs of conscious behavior), on account of properties of the thalamus it is clear that differences between MCS and VS/UWS patients are not so deep as expected. However, as regard the neural correlation of consciousness and the conscious awareness, the thalamus, being connected with cortical areas and belonging to the rich club, has certainly a great importance [20]. VS is a post-coma disorder which makes the patients be able to preserve wake-sleep cycle but unable to demonstrate any kind of awareness of self and environment. In this case, even if hypothalamic and brain stem autonomic functions work correctly, patients being in VS cannot show any voluntary response to external physical stimuli (noxious, visual or tactile) nor any language comprehension or expression. MCS is a post-coma condition in which patients, in spite of their neuronal damages, have partial preservation of conscious awareness of self and environment, showing a high threshold of responsiveness to internal and external stimuli [21].

Hypothalamus It has been shown that the hypothalamus is part of the neural network of consciousness since its histaminergic and orexinergic neurons help to maintain the awake state and regulate sleep-wake and emotional processing neuronal circuitries; in particular, their deactivation plays a major role in neuropsychiatric disorders and narcolepsy [15, 22].

Basal forebrain ARAS activates the central thalamus and basal forebrain through two different pathways, i.e., glutamatergic and cholinergic projections. Moreover, during REM sleep, the basal forebrain is active in order to support arousal [23]. In case of damage to the basal forebrain, it may be possible to find some problems regarding

the way the cholinergic neurons work, causing subsequent problems in the learning and plasticity processes (i.e., amnesia and confabulation). Many different factors can influence forebrain arousal, among them: ascending influences from brain stem/basal forebrain neuronal populations and signals descending from frontal cortical system. All these systems create an important converging network projection to the central thalamus, underlining their central role in the process of maintaining organized behavior during wakefulness [24, 25].

Amygdala Linked to the state of consciousness, the amygdala “chooses” the basic elements of a stimulus independently from the awareness. On this ground a new theory was recently born: some highly interactive cortical and subcortical structures are thought to be involved in the action of processing of motivationally relevant stimuli, and what is really important in this process is not the mere existence of two different systems, but the link and the correlation between them [26]. Emotional stimuli, including facial expressions, are thought to gain rapid and privileged access to processing resources in the brain. Despite this access, we are conscious of only a fraction of the myriad of emotion-related cues we face everyday. Considerable research supports the idea that contributions from the ventral visual system to consciousness vary in a category-selective manner [27, 28]. However, to date little evidence exists about the contribution from fronto-parietal areas that are considered critical for consciousness. A recent study by Amting et al. [29] has shown that activity in these regions can vary as a function of the emotion perceived and suppressed from awareness. Evidence is also provided that activity in regions of perigenual prefrontal cortex (pgPFC), previously implicated in extinguishing a fear-conditioned response and in explicit emotion regulation, is associated with the suppression of fearful faces from consciousness.

Basal ganglia (BG) Despite numerous suggestions that the basal ganglia are involved in a wide range of functions including perception, learning, memory, attention, many aspects of motor function, even analgesia and seizure suppression, increasingly evidence points to an underlying role in basic selection processes. In particular, the thalamus is a critical component of the frontal cortical-basal ganglia-thalamic circuits that mediate motivation and emotional drive, planning and cognition for the development and expression of goal-directed behaviors. Each functional region of the frontal cortex is connected with specific areas of each BG structure and of the thalamus. Tract-tracing and physiological experiments have indicated a general topographic organization of the cortical-BG-thalamic loops and supported a model of BG function based on parallel and segregated pathways. However, the learning and execution of appropriate behavioral responses require integration of

inputs related to emotional, cognitive, and motor cortical functions [17, 30, 31].

Prefrontal cortex According to Baars et al. [32] parietal and prefrontal cortical areas are part of a great network to which sensory information is largely spread, after conscious awareness is established. The most typical psychological term for functions carried out by the prefrontal cortex area is executive function. Executive function relates to the ability to differentiate among conflicting thoughts, determine good and bad, better and best, same and different, future consequences of current activities, working toward a defined goal, prediction of outcomes, expectation based on actions, and social “control” (the ability to suppress urges that, if not suppressed, could lead to socially unacceptable outcomes) [33]. Interestingly, a recent hypothesis sustains that the mental states commonly referred to as altered states of consciousness are principally due to transient prefrontal cortex deregulation. Indeed, it is proposed that transient hypofrontality is the unifying feature of all altered states and that the phenomenological uniqueness of each state is the result of the differential viability of various frontal circuits [23, 34].

The cingulate cortex It is usually considered part of the limbic lobe, involved in emotion formation and processing, selective attention (anterior cingulate cortex), learning, and memory (long term potentiation), and is also important for executive function [35]. It has been recently demonstrated the linkage of neural activity in the anterior cingulate cortex (ACC) during self-relatedness with the degree of consciousness patients with DOC. Most importantly, signal changes during self-relatedness in a caudal subregion of the ACC were correlated with the DOC patient’s level of consciousness. This may also suggest a useful neural, and thus diagnostic, marker of the dysfunction of consciousness in vegetative patients [36].

Precuneus It has been proposed that precuneus is involved in the wide network of the neural correlates of self-consciousness. Over the last years, fMRI studies revealed that the posteromedial parietal areas are amongst the brain structures displaying the highest resting metabolic rates (“hot spots”) and are characterized by transient decreases in the tonic activity during engagement in non self-referential goal-directed tasks (“default mode” of brain function) [37, 38]. Moreover, selective precuneal hypometabolism has been reported in a wide range of altered conscious states, such as sleep, hypnosis, drug-induced anaesthesia, vegetative state, and in neuropsychiatric conditions characterized by impaired consciousness (e.g., Alzheimer’s disease, epilepsy, schizophrenia). Taken together, these findings provide strong, albeit preliminary, evidence that this richly connected multimodal associative area belongs to the neural network subserving awareness and producing a conscious self-percept, a

process that possibly runs in the background (by default) during silent rest. In particular, a major challenge for theorists of the default mode of brain functioning is to determine how task-induced deactivations (TIDs) and selective hypometabolism in pathophysiological conditions affecting consciousness relate to resting-state mentation. One possibility is that when an individual is awake and alert and yet not actively engaged in particular cognitive task, the precuneus and interconnected posterior cingulate and medial prefrontal cortices subserve continuous information-gathering and representation of the self and external world [39, 40]. In other words, precuneus seems to contribute to the self-referential “thought” processing that humans experience during resting consciousness. Moreover, it has been shown that the functional connectivity of medial parietal regions is involved in distinguishing VS/UWS from MCS patients and that plays a major role in the process of recovery of consciousness [41].

Neurophysiology of consciousness: a brief overview

Consciousness entails desynchronized, low-amplitude brain activity ranging from 20 to 70 Hz. Embedded in this pattern of global desynchronization are phase-locked, synchronized areas, which progressively oscillate in unison at the gamma band frequency of 40 Hz, and are believed to be coordinated by the intralaminar nuclei of the thalamus. Nevertheless, the information flowing back and forth between the intralaminar thalamic nuclei and the cortex through the thalamo-cortical system is believed to set up the 40 Hz oscillating loop. The neurons of the definite thalamic nuclei have been shown to activate specific cortical pyramidal cells and silence other brain areas via activation of 40 Hz gamma-aminobutyric acid (GABA) inhibitory interneurons. In other words, consciousness is supposed to be possible only when the 40 Hz electrical hum is sustained among the brain circuits, with the recruitment of more cerebral networks allowing our consciousness to widen. Significant coupling in the gamma frequency has been demonstrated to take place in both wakefulness and REM sleep, although the variability of gamma cycle duration is larger during sleep. Sensory perturbation can reset this gamma rhythm in awake but not sleep states, signifying that, during sleep, the cortex activates itself from within. During deep sleep, however, the intralaminar thalamic nuclei are inactive, and no 40 Hz oscillations arise [42].

Notably, even at the lowest level of consciousness, the different areas considered essential for consciousness cannot function in isolation. Thus, it is logical to believe that consciousness involves widespread brain activity,

although this does not necessarily imply homogenous activity throughout the brain. Indeed, during consciousness, brain activity is distributed throughout diffuse regions of the brain, while in unconscious states activity is supposed to remain localized [43, 44].

To better understand the consciousness science, Miller has recently focused on the neural correlate/constitution distinction problem, arguing that no robust strategies are available to distinguish the correlates and constitution of consciousness. Particularly, he assumed that the stepwise inhibition strategy is able to identify the merely sufficient from the minimally sufficient neural correlates of consciousness, but not the constitutive status [45].

Neuroimaging studies and consciousness

Although bedside clinical examination remains the standard criterion for establishing diagnosis, recent studies suggest a number of potential clinical and rehabilitative applications of magnetic resonance (MR) techniques in diagnosing DOC. MR may provide an adjunctive diagnostic tool when behavioral findings are very limited or ambiguous. The futures of diagnostic and prognostic studies about DOC are based on functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), white matter fiber tractography and positron emission tomography (PET).

PET is the most sensitive method to image trace amounts of molecules *in vivo*, measuring biochemical and physiological processes in any organ with three-dimensional resolution. Moreover, it can provide an objective measure of the regional distribution of cerebral activity under various conditions. With the use of PET the consumption of glucose and oxygen is detectable, as well as regional cerebral blood flow (rCBF). The latest techniques allow the examination also of the deep brain structures, and the rCBF could be evaluated after stimulation or at rest, even in VS patients [46].

To this end, Laureys et al. [47] analyzed regional cerebral glucose metabolism (rCMRGlu) and cortical connectivity in patients in VS showing a common pattern of impaired rCMRGlu in the prefrontal, premotor, and parietotemporal association areas and posterior cingulate cortex.

fMRI is a new functional brain imaging method, which allows to examine the oscillating patterns reflected in the blood oxygenation level dependent (BOLD) fMRI signal. The technique is based on the paramagnetic properties of deoxyhemoglobin, as the blood flow variations and brain tissue oxygenation are strictly linked to the neural activity.

Normally, the same areas that presented an increasing consumption of glucose and oxygen during rest in PET

studies appear as resting state neuronal networks (RSN) in resting state fMRI (rs-fMRI) [48], since resting cerebral metabolism derived from quantitative glucose uptake, providing an indirect assessment of neuronal activity against which brain states may be compared quantitatively [49].

RSN activity can be outlined as an automatic condition in which the subject is in a state of absolute rest and does not carry out any physical or mental activity; definitely, it is not occupied in a particular task. The idea was developed after analyzing the functional implication among brain regions demonstrating spontaneous fMRI activity recorded in repose. Neuner et al. [50] studied, particularly, the default mode network (DMN), one of the most robustly measurable RSN, which includes the precuneus, ACC, posterior cingulate cortex (PCC) and lateral parietal inferior gyri, since it is thought to be linked to mental and emotional processing and introspection. In contrast with fMRI based on active tasks, it allows to easily study unresponsive patients or that cannot cooperate. For this reason, the rs-fMRI has begun to be used to investigate patients with DOC, ranging from VS to severe impairment [21], taking in consideration DMN connectivity integrity as a reliable marker of the level of consciousness in brain-injured patients [51]. Recently, important strides in the study of the complex and wide networks of neuronal activity associated with consciousness have been done on such DOC patients. Indeed, a dysfunctional DMN in patients in VS was found by a decreased connectivity in several brain regions, including the dorsolateral prefrontal cortex and anterior cingulate cortex, especially in the right hemisphere [52–55].

In addition, a noteworthy result has been recently obtained by using fMRI, since Naci and colleagues demonstrated a pattern of neural activation, in a patient in VS, similar to that of healthy subjects, while watching a movie by Alfred Hitchcock. The pattern of brain activity included the executive (frontal and parietal cortices) and sensory (auditory and visual cortices) brain areas, showing for the first time that a patient with altered state of consciousness was able to analyze and monitor information coming from his environment [56].

DTI is a new RM technique, which allows the analysis of the diffusive properties and of the direction of the flow of water molecules inside brain tissue (and not only) *in vivo*, and for this reason it seems to be an important tool to study the microstructural cerebral architecture both in physiological and pathological conditions (i.e., DOC). For example, Voss et al. [57] described two MCS patients with traumatic brain injury, and in both cases increased anisotropy was found in the bilateral medial parietal-occipital regions at their first evaluation, whereas it reduced to normal values 18 months later, in conjunction

with the raising of the metabolic activity, probably due to axonal regeneration in these regions. Although this is certainly a landmark finding in two high spectrum MCS patients, it remains to be evaluated whether DTI has any diagnostic or prognostic utility in a broader group of patients with DOC. To this end, Tollard et al. [58] and Perlberg et al. [59] have recently demonstrated that DTI measures in sub-acute severe traumatic brain injury may be a relevant biomarker for predicting the recovery of consciousness at 1 year. However, VS and MCS patients were classified in the same outcome category and potential differences between these two groups were not investigated.

In addition, DTI may be a valuable biomarker for the severity of tissue injury and a predictor for outcome, revealing changes in the white matter (WM) that are correlated with both acute GCS and Rankin scores at discharge. In fact, significant reduction of anisotropy was observed in WM structures, in particular in the internal and external capsule, corpus callosum, superior and inferior longitudinal fascicles, and the fornix in TBI patients [59, 60]. Moreover, Xu et al. [61] showed that fractional anisotropy (FA) and apparent diffusion coefficient (ADC) measurements offered superior sensitivity compared to conventional MRI diagnosis of diffuse axonal injury (DAI).

Studies of the ARAS in the human brain have been possible thanks to electrophysiological methods, conventional brain MRI, functional neuroimaging techniques, and MR spectroscopy [62–65]. However, accurate identification of the ARAS in the human brain can be problematic when using these methods, because the ARAS cannot be clearly discriminated from adjacent neural structures. In contrast, DTI has been used for assessing the entity of change in white matter fiber bundles [66, 67] and of connectivity of specific ARAS nuclei in altered states of consciousness [16]. In fact, Tollard et al. [58] and Perlberg et al. [59], performing DTI scanning in patients with severe TBI, revealed decreased FA values in supratentorial and infratentorial areas, including the midbrain, anterior pons and posterior pons, inferior longitudinal fasciculus, posterior limb of the internal capsule, and posterior corpus callosum.

Moreover, Laouchedi et al. [68], by using probabilistic tractography from diffusion tensor imaging data, showed lower density of thalamus-cortical and ponto-thalamo-cortical fiber bundles in TBI patients than in healthy controls, assuming that fiber tractography and density evaluation of cortical-subcortical networks could be major biomarkers for the DOC outcome.

In addition, more recently, constrained spherical deconvolution (CSD) tractography has proved to be a valuable technique allowing a reliable reconstruction of

long and short fiber from cortex to cortical and subcortical targets with subvoxel resolution pathways in brain regions with multiple fiber orientations [69]. This technique estimates the fiber orientation distribution function (fODF) directly from the DW signal by means of positive (avoiding the unreal negative regions) spherical deconvolution [70].

It is conceivable that such promising tool may further investigate ARAS connectivity and the neural correlates of consciousness, in order to better understand and clarify its complex physiological mechanisms and the related disorders.

Finally, it is important to stress the role of non-invasive brain stimulation as a valuable complement to neuroimaging tools. To this end, transcranial magnetic stimulation, transcranial direct current stimulation and transcranial alternating current stimulation have been recently used to better investigate the functional roles (neural prerequisites, neural consequences, and neural substrates) of empirical neural correlates of consciousness [71].

Conclusions

Consciousness is dependent on the brain stem and thalamus for arousal, whereas basic cognition is supported by recurrent electrical activity between the cortex and the thalamus at gamma band frequencies. Nevertheless, some kind of working memory, at least fleetingly, must be present for awareness to occur. It is generally accepted that the different features of objects are processed in different areas of the brain, and that the different qualities are cognitively bound together and experienced against the background of previous experiences—a process known as cognitive binding. However, for consciousness to be endowed with meaning that binds our perceptions into the seamless unity,—as suggested by Kant—, we require far-reaching explicit working memory which probably feeds on integrative circuits across the different domains of the prefrontal cortex.

Conversely, for the prefrontal structures to function properly in the generation of consciousness they must receive information from other brain areas such as other association cortices and the limbic system. Thus, consciousness may also depend on the multitude of unconscious processes that occurs in the brain, and that are, to date, far to be known. Further studies, using advanced neuroimaging tools, are needed in order to better investigate the amusing neural circuitries subserving consciousness and its several disorders.

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