

## **The self in disorders of consciousness**

Charlène Aubinet,<sup>\*1,2</sup> Audrey Vanhaudenhuyse,<sup>3,4</sup> Steven Laureys<sup>1</sup> & Athena Demertzi,<sup>2,5</sup>

<sup>1</sup> Coma Science Group, GIGA-Consciousness, University and University Hospital of Liège, Belgium

<sup>2</sup> Psychology and Neuroscience of Cognition Research Unit, University of Liège, Belgium

<sup>3</sup> Sensation and Perception Research Group, GIGA-Consciousness, University of Liège, Belgium

<sup>4</sup> Algology Interdisciplinary Center, University Hospital of Liège, Belgium

<sup>5</sup> Physiology of Cognition Research Lab, GIGA-Cyclotron Research Center, University of Liège,  
Belgium

\*Corresponding author

E-mail addresses:

[caubinet@uliege.be](mailto:caubinet@uliege.be)

[avanhaudenhuyse@uliege.be](mailto:avanhaudenhuyse@uliege.be)

[a.demertzi@uliege.be](mailto:a.demertzi@uliege.be)

[steven.laureys@uliege.be](mailto:steven.laureys@uliege.be)

## **ABSTRACT**

The clinical examination of residual (self-) consciousness in severely brain-damaged patients remains challenging. This is because patients in coma, vegetative/unresponsive wakefulness and minimally conscious states are by definition unable to communicate their subjective experiences. As a result, (self-) consciousness in this clinical population needs to be inferred. To date, this is feasible by presenting patients with attention-grabbing stimuli, such as their own name and own face, while measuring their brain activation with assisting technologies. Event-related potentials and functional neuroimaging studies using such stimuli are used to decipher the cognitive hierarchy of self-processing. Most studies show that brain responses are differential between unconscious and minimally conscious patients and that, an atypically high level of brain activity in response to self-referential stimuli can work as a marker of favorable clinical outcome. Brain function during resting state further sheds light on the subjective counterpart of “unconstrained” cognition and has paved the way towards single-patient differentiation. Taken together, the experimental exploration of the “self” in pathological unconsciousness surpasses the functional localization of self-related cognition and suggests a dynamic system-level approach to the phenomenological complexity of subjectivity.

## **KEYWORDS:**

Self-consciousness, coma, unresponsive wakefulness syndrome, minimally conscious state, event-related potentials, functional neuroimaging

## Introduction

Clinical practice indicates that it is particularly challenging to recognize unambiguous signs of conscious perception of the environment and of the self in patients with disorders of consciousness (DOC). This is because patients with DOC are by definition unable to communicate. Patients in coma, for example, lay with eyes closed and do not respond to any external stimulation. When they open their eyes but remain unresponsive to external stimuli they are considered to be in a vegetative state (VS; Jennett & Plum, 1972), renamed as unresponsive wakefulness syndrome (UWS; Laureys et al., 2010). When patients exhibit signs of fluctuating yet reproducible remnants of non-reflex behavior, such as tracking their face in a mirror, they are considered to be in a minimally conscious state (MCS; Giacino et al., 2002). In the absence of subjective reports from these patients, how can one know whether they experience something and what these experiences can be? In other words, can one claim that patients with DOC retain a type of “core consciousness” (Damasio and Meyer, 2009), which provides them with a sense of self about here and now?

We think that the study of patients with DOC offers a unique approach to tackle the neural correlates of self-consciousness. As patients with DOC are unable to communicate, we will here refer to self-consciousness as to its basic expression, i.e. as self-detection, when an organism can respond to stimuli with which it is directly implicated, or modify its behavior in ways which imply awareness of its own actions (Zeman, 2001). The underlying argument is that since clinical diagnosis shows that patients hold no subjective experience, the absence of subjective identity will be reflected on patients' brain function.

Next to the behavioral evaluation of consciousness, the employed experimental paradigms refer to the administration of self-referential stimuli (patients' own name and own face) and the subsequent measurement of brain responses to these stimuli with electrophysiology and neuroimaging (Magliacano et al., 2019a). However, it has been suggested that self-related processing can also be inferred by studying brain activity at rest, i.e. when patients do not receive any external stimulation. We will here review relevant experimental manipulations in the search of “self” in altered states of consciousness and we

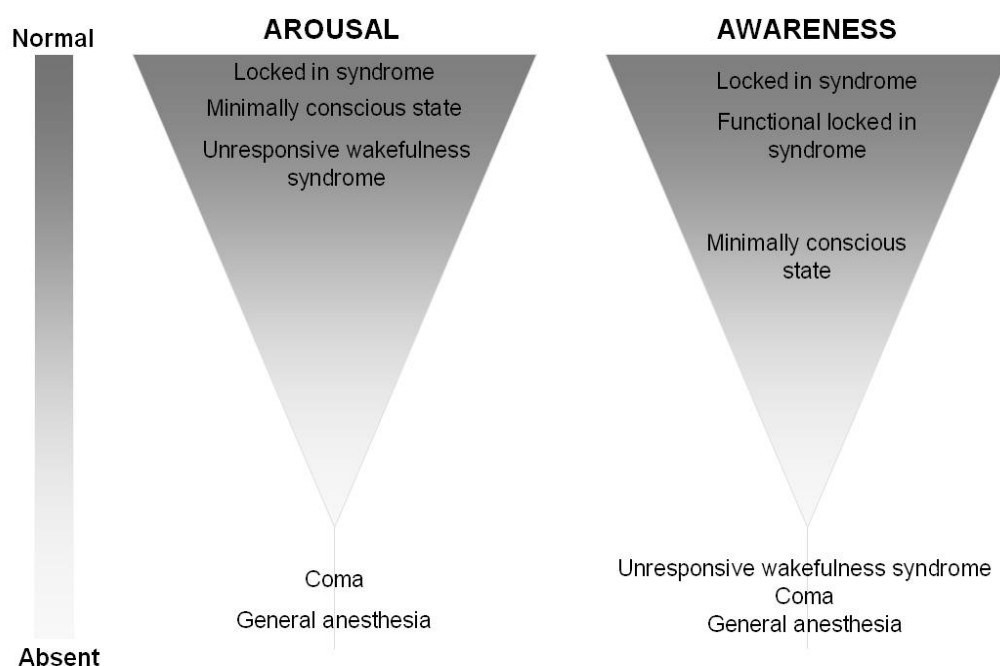
will see how such information can aid not only the clinics but also the neuroscientific quest of self-consciousness (Demertzi, Vanhaudenhuyse, et al., 2013).

### **Consciousness and its clinical conditions**

Consciousness is a multifaceted term which can mean different things to different people (Demertzi et al., 2009; Zeman, 2001). For the sake of clarity, we here define consciousness in an operational manner, namely that it consists of two components: *arousal* (i.e., the level of consciousness) and *awareness* (i.e., the content of consciousness) (Martial et al., 2020) (Figure 1). *Arousal* refers to the behavioral continuum that occurs between sleep and wakefulness, defined as the presence of prolonged periods of spontaneous or induced eye-opening. *Awareness* refers to the knowledge about the environment and the self. Compared to awareness of the environment (i.e., connectedness), awareness of self (i.e., internal awareness or self-consciousness) is an even more complex and ill-defined concept, requiring a representation of self versus other (Berrios and Markova, 2003; Morin, 2006; Martial et al., 2020). Awareness and arousal are linearly correlated, in the sense that the less aroused we get the less aware of our surroundings and ourselves we become (Laureys, 2005). Based on this definition, coma is characterized by the absence of arousal and thus of consciousness. It is a state of unarousable unresponsiveness in which the patient lies with eyes closed and has no awareness of self and surroundings (Posner et al., 2008). In general, comatose patients who survive begin to awaken and recover gradually within 2 to 4 weeks. This recovery may go no further than the VS/UWS or MCS, or these may be stages (brief or prolonged) on the way to more complete recovery of consciousness (Figure 2).

Patients in a VS/UWS are awake but are unaware of themselves and the environment (Jennett and Plum, 1972). These patients rarely recover consciousness after three months in case of non-traumatic VS/UWS, and after twelve months in case of traumatic VS/UWS. According to the recent practice guidelines recommendations on DOC, the term chronic VS/UWS should be applied after these time points (Giacino et al., 2018). When this diagnosis of chronic VS/UWS is established, ethical and legal issues around limitation of treatment can

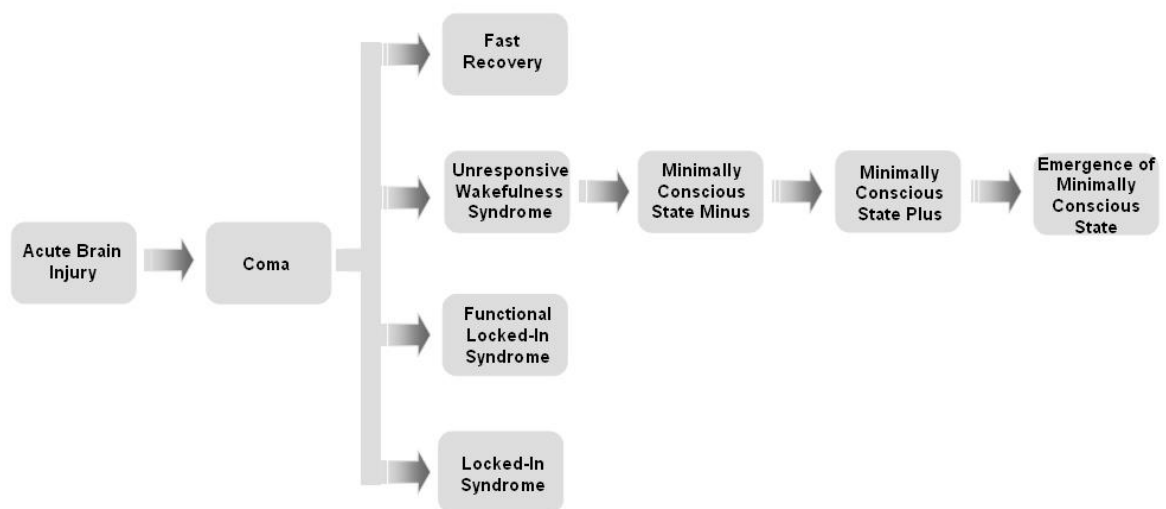
arise (Span-Sluyter *et al.*, 2018). In view, however, of spontaneous recoveries surpassing these temporal boundaries, an increasing number of clinicians remained uncomfortable when referring to patients as “vegetative” (e.g., (Shewmon, 2004), resulting in a number of papers reiterating the justification of the origins of the term (Coleman, 2015). This resulted in the introduction by the European Task Force on Disorders of Consciousness of the term “unresponsive wakefulness syndrome” (UWS), proposing a new terminology avoiding the unintended albeit persistent negative connotation of the term “vegetative” (Laureys *et al.*, 2010).



**Figure 1:** The 2 components of consciousness: arousal and awareness. Locked in syndrome is characterized by a preservation of both arousal and awareness while minimally conscious patient showed a preserved arousal level and decreased and fluctuating awareness. Unresponsive wakefulness syndrome (vegetative state) is defined as the dissociation of awareness (abolished) and arousal (preserved) systems. Coma and general anesthesia patients are totally unaroused and unaware.

To be considered as MCS, patients have to show limited but clearly discernible evidence of consciousness of self or environment, on a reproducible or sustained basis, by at least one

of the following behaviors: following simple commands, gestural or verbal yes/no response (regardless of accuracy), intelligible verbalization, purposeful behavior (including movements or affective behavior that occur in contingent relation to relevant environment stimuli and are not due to reflexive activity). The emergence of MCS is defined by the ability to use functional interactive communication or functional use of objects (Giacino et al., 2002). Further improvement is more likely in MCS than in VS/UWS patients (Magliacano *et al.*, 2022). However, some remain permanently in this state. In 2011, it was proposed to subcategorize the clinically heterogeneous “MCS entity” in minimally conscious PLUS (MCS+) and MINUS (MCS-) based on the presence or absence of language-related conscious behaviors (Bruno *et al.*, 2011) (Figure 2). MCS+ is indeed defined by the presence of command following, intelligible verbalization and/or gestural or verbal yes/no responses (Thibaut *et al.*, 2019). In contrast, patients in MCS- show only minimal levels of behavioral interaction characterized by the presence of non-reflex movements such as orientation of noxious stimuli and pursuit eye movements that occur in direct response to moving or salient stimuli (e.g., a moving mirror).



**Figure 2:** Classical evolution of patients after a traumatic or non-traumatic brain injury. After a coma, patients can quickly recover or evolve to an unresponsive wakefulness syndrome (vegetative state, unconscious) or in rare cases to a functional locked-in syndrome (consciousness detected only with paraclinical techniques such as active paradigms) or locked-in syndrome (normal consciousness with eyes movement communication). Unresponsive patients can progressively

recover consciousness by evolving through different states such as minimally conscious state minus (showing visual pursuit), plus (showing command following) to finally emerge from the minimally conscious state (showing functional communication).

The term "locked-in" syndrome (LIS) was introduced by Plum and Posner in 1966 to reflect the quadriplegia and anarthria brought about by the disruption of corticospinal and corticobulbar pathways, respectively (Posner *et al.*, 2008). LIS is defined by the presence of sustained eye-opening (bilateral ptosis should be ruled out as a complicating factor); preserved awareness of the environment; aphonia or hypophonia; quadriplegia or quadriparesis; a primary mode of communication that uses vertical or lateral eye movement or blinking of the upper eyelid to signal yes/no responses (Vidal, 2020). There are cases, however, where some LIS patients demonstrate a dissociation between their extreme behavioral motor dysfunction and the identified preserved higher cognitive functions as shown by functional imaging techniques (Gibson *et al.*, 2016; Naci *et al.*, 2018; Pan *et al.*, 2014; Schnakers *et al.*, 2008). For these LIS patients, the term of "functional LIS" has been proposed (Bruno *et al.*, 2011) (Figure 2).

### **Assessing (un)consciousness**

The estimation of consciousness or self-consciousness in patients with DOC is limited to the interpretation of motor responsiveness. The perception of self we are interested in is a conscious experience. As such, the wakeful unconsciousness of patients in VS/UWS by definition precludes this experience. There is of course the problem of evaluating subjective experience of self-consciousness (as any other conscious perception) in another person. This is one of the fundamental methodological problems confronting the phenomenology of subjective experience generally. As stated above, we can only infer the presence or absence of conscious experience in another person. For patients in VS/UWS and MCS, clinicians resort to various clinical scales to detect signs of awareness at the bedside (Bodien *et al.*, 2022). For instance, the Coma Recovery Scale-Revised (CRS-R; Giacino, Kalmar, & Whyte, 2004) and

Simplified Evaluation of CONsciousness Disorders (SECONDS; Sanz *et al.*, 2021) are sensitive tools to diagnose and differentiate between patients in VS/UWS and MCS because they assess the (most frequent) defining criteria for MCS, such as visual pursuit (Seel *et al.*, 2010; Aubinet, Cassol, *et al.*, 2021). Nonetheless, it is not only a certain behavior that needs to be detected, but the way this is assessed seems to be equally important. An illustrative example is that of visual pursuit. When visual pursuit was tested by means of a moving object, a moving person and a moving mirror, more patients tracked their image in the mirror compared to the other two stimuli, and were hence considered as in MCS (Thonnard *et al.*, 2014; Wannez, Vanhauzenhuysse, *et al.*, 2017; Trojano *et al.*, 2018). These studies imply that self-referential stimuli are effective to explore patients' responsiveness and can influence the diagnostic process (also see Laureys, Perrin, & Brédart, 2007). To what degree, however, can one claim that these paradigms also reflect the, indirect, assessment of residual self-consciousness in this non-communicating clinical population?

One way to approach the answer is to measure patients' brain responses and activation during sensitive experimental manipulations and compare them with that of healthy controls. If the cerebral pattern is indistinguishable between the two groups, then one has good reasons to believe that the extracted statistical maps reflect the same construct (Owen, 2013). Naturally, there are legitimate concerns about the degree of confidence one can have on electrophysiology or functional neuroimaging results, especially in the absence of subjective reports (e.g., Fins & Schiff, 2010). In addition, our limited understanding of the dynamic neural complexity underlying consciousness and its resistance to quantification in the absence of communication (Seth *et al.*, 2008) makes it difficult to establish strong claims about self-consciousness in non-communicating patients. Nevertheless, the use of these technologies have shed light on the grey zones between the different clinical entities of consciousness and have revealed that not all patients can be considered unresponsive (e.g., Laureys and Boly, 2008; Edlow *et al.*, 2017; Naci and Owen, 2022).



## **Self-referential stimuli**

Clinical practice shows that self-referential stimuli, such as the use of the patient's own name or the patient's own face, are more effective stimuli to explore patients' responsiveness when compared to non-self related stimuli (Perrin *et al.*, 2015). This is not accidental. In everyday social interactions, hearing our own first name captures our attention and gives rise to a sense of self-awareness, since it is one of the most socially self-related stimuli. Our own first name is intrinsically meaningful for each of us because of its personal significance, its emotional content and repetition throughout life. Beyond our day-to-day experience, the extreme salience of being presented one's own name or face has been highlighted in numerous experimental and clinical studies. Some of these suggest that self-referential stimuli are so potent that they can "capture attention and subsequently bring the stimulus into awareness" (Mack *et al.*, 2002). Before describing their application in assessing consciousness, we will first discuss the reasons that make our own names or faces so special.

### ***Own name***

Does one's own name capture attention? It seemingly does even if currently there is no strong consensus. For example, a first group of studies suggested that one's own name was a stimulus that could automatically capture attention and provoke distraction. Such studies employed dichotic listening (Moray, 1959; Mack *et al.*, 2002), unattended own name auditory stimulation (Wood and Cowan, 1995), or measured the effect of reducing inattention blindness<sup>1</sup> by means of own name presentation (Nakayama, 1999). Recently, Röer & Cowan (2021) replicated these results by showing that the own name attracted and captured attention of some individuals, whereas semantically unexpected words did not.

A second group of studies, however, suggested that even if it is easier to detect one's own name than other words, one's own name does not grab attention significantly more. This

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<sup>1</sup> Inattention blindness is the failure to notice a fully-visible but unexpected object because attention is engaged somewhere else.

is because it carries the same usual attentional capacity limitation that is found for other comparable words as well (Bundesen *et al.*, 1997; Harris and Pashler, 2004; Harris, Pashler and Coburn, 2004). In those studies that reported automatic capture of attention, the disruption effect was estimated from a small number of presentations of the participant's own name and small display loads were used. By contrast, in studies that did not find special attention-grabbing effect for own name, the display loads were more substantial and the distraction effect was evaluated from many presentations of the participant's own name. Therefore, the size of the display load and repetition of trials appear to be crucial experimental factors (Harris and Pashler, 2004). Altogether, the set of available results suggest that the *first* occurrences of one's own name, in a context where it is unexpected, provoke an involuntary shift of attention precisely when the perceptual load of the person's current activity is low and when there is enough available capacity for the one's own name to be perceived. Otherwise, one's own name does not seem to be a more potent distractor than other words. In sum, the distraction caused by the presentation of one's own name looks like a response of surprise that habituates very rapidly rather than the enduring ability of one's own name to attract attention. Finally, studies reported that when pronounced by a familiar person, the subject's own name elicits larger electrophysiological response than when the speaker is unknown to the subject (Holeckova *et al.*, 2006; Wang *et al.*, 2019).

Although one's own name is no more potent than other names as a distractor, most studies show that it is more readily detected as a target than other comparable stimuli (Bundesen *et al.*, 1997; Shapiro, Caldwell and Sorensen, 1997; Arnell, Shapiro and Sorensen, 1999; Harris and Pashler, 2004; Harris, Pashler and Coburn, 2004; Tateuchi, Itoh and Nakada, 2015; Holtze *et al.*, 2021; Ye *et al.*, 2021; Pinto *et al.*, 2022). This demonstrably easy detection in healthy participants is consistent with research that shows powerful detection of the own name in situations of reduced consciousness. For instance, auditory presentation of the participant's name during sleep may awaken the subject (Oswald, Taylor and Treisman, 1960) and sleepers show enhanced neural responses to their own names during sleep (Perrin *et al.*, 1999; Blume *et al.*, 2017). Robust responses are also found in demented patients whose

perception of their own name deteriorated well after perception of time, place and recognition (Fishback, 1977; Sun *et al.*, 2021). In addition, after general anesthesia, the patient's reactivity to her or his name occurs first, before reactivity to pain and noise (Kurtz *et al.*, 1977).

How may this easier detection of one's own name be interpreted? One's own name has particular properties: it is a very familiar stimulus with presumably high emotional charge. However, it remains to be shown whether these two properties explain the ease of detection of one's name in the environment. One's own name is a piece of information that we use to process in the auditory modality from infancy: 4-5 month-old infants are able to recognize the sound pattern of their own names (Parise, Friederici and Striano, 2010). Later in childhood, one's own name is also one of the first lexical items that we usually learn to write and read (Levin *et al.*, 2005). Some authors also argue that enhanced responses to familiar stimuli such as own name could be explained not by the recognition of these stimuli as being relevant, but because of pre-existing memories for these stimuli. The own name could benefit from a privileged processing at the cortical level and be processed differently because of past exposure (Andrillon and Kouider, 2020). Overall, we think that the extreme familiarity of one's name remains a plausible factor to explain its easier detection.

### **Own face**

Even if a direct link between one's own face and the assessment of self-awareness is still debated, several studies suggest that there is a relationship between self-recognition and self-awareness. Some researchers argue that the self-face is an ideal stimulus to investigate higher-order conscious processing, such as access to one's mental states or thoughts (for a review see Keenan, Rubio, Racioppi, Johnson, & Barnacz, 2005). Others think that self-face recognition may simply reveal a basic form of self-awareness such as the knowledge that one is a specific entity separate from others that also involves one's own physical appearance (for a discussion see Morin & Michaud, 2007). Studies demonstrate that faces constitute a class of stimuli that are especially prone to capture attention (Lavie, Ro and Russell, 2003; Bindemann *et al.*, 2005; Bindemann, Mike Burton and Jenkins, 2005; Theeuwes and Van der

Stigchel, 2006; Wolfe and Horowitz, 2017). Indeed, participants tend to respond faster to their own face than other familiar faces (Devue and Brédart, 2011; Alzueta *et al.*, 2019). Similarly to one's name, one's own face is easier to detect than other faces in visual search tasks (Tong and Nakayama, 1999) but one's own face does not "pop out" within a set of faces and is no more distractive than other faces in such tasks (Laarni *et al.*, 2000; Devue and Brédart, 2008; Devue, Van der Stigchel, *et al.*, 2009). Study of inattention blindness shows that if faces in general resist inattention blindness more than pictures or common objects, no differential resistance to blindness can be detected for the own face (Devue, Laloyaux, *et al.*, 2009). However, one's own face has been shown to disrupt a person classification task from names more strongly than another personally familiar face (Brédart, Delchambre and Laureys, 2006). This might indicate that the self-face elicits specific distraction effects only when its processing is somehow related to the task at hand but not when this processing is totally irrelevant to the task.

### **The "own name" paradigm in disorders of consciousness**

The own name paradigm has been particularly useful for the assessment of residual cognition in patients with DOC. At the behavioral level, patients' own names were used to evaluate sound localization as dictated by Coma Recovery Scale-Revised. According to the scale, sound localization is scored when patients orient their head or eyes toward the source of the sound. When the examiner presented orally the patient's own name, more patients oriented their head/gaze to them as compared to the meaningless sound of a ringing bell (Cheng *et al.*, 2013).

Using positron emission tomography, a study with one patient in MCS used the patient's own name next to baby cries and meaningless noise (Laureys *et al.*, 2004). It was found that passive listening to the own name recruited the activation of midline areas (such as precuneus and anterior cingulate/mesiofrontal cortex) next to lateral parietal areas (including language-related regions, such as Broca's and Wernicke's), suggesting a wide recruitment of cortical areas as a response to the own name.

As reported in Table 1, several studies investigated patients' cortical response to their own name by means of electrophysiology. In one of the first studies (Perrin *et al.*, 2006), healthy subjects and patients were exposed to listening to their own name and other unfamiliar first names without being asked to perform any particular task (passive condition). It was found that all healthy subjects showed a brain response (the so-called P300<sup>2</sup> event-related potential) to their own name. Interestingly, they observed such response in all six MCS patients and three out of five VS/UWS patients, but the latency was significantly delayed for DOC patients compared to healthy subjects. More recently, other studies found a significant P300 in this population (Sergent *et al.*, 2017), with significant latency differences in response to their own name compared to other names (Kempny *et al.*, 2018). Crivelli *et al.* (2019) further found, in a group of 21 VS/UWS patients, increased skin conductance, heart rate measures and alpha activity (over frontal areas) in response to their own name compared to other names. Interestingly, Li *et al.* (2018) compared passive listening of own name or music, as well as habit stimulation (i.e., alcohol for alcoholic patients or cigarette smell for smoking patients). The highest degree of electroencephalographic responses was found in the own name stimulation, revealing its highest ability to elicit patient arousal compared to habit or music stimulation. As regards patients' prognosis, it was further shown that the presence of mismatch negativity event-related potential (MMN)<sup>3</sup> in response to the own name correlated with recovery of consciousness of VS/UWS and coma patients: in the studied sample, three out of six VS/UWS and two out of four coma patients evolved to a MCS three months after the MMN was recorded, while the rest of the patients who did not demonstrate the MMN failed to show

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<sup>2</sup> The P300 event-related potential is a positive deflection in the electroencephalographic voltage with a latency between 250 to 500 ms after the presentation of a stimulus. It is typically elicited by means of "oddball" paradigms, where low-probability targets are mixed with high-probability or standard non-targets. The P300 is associated with cognitive processes of decision making.

<sup>3</sup> The mismatch negativity (MMN) is a negative deflection in the electroencephalographic voltage with a latency between 150-250 ms after the presentation of a stimulus. It is typically elicited by means of "oddball" paradigms, where low-probability targets are mixed with high-probability or standard non-targets. However, the MMN can be elicited regardless of whether the subject is paying attention to the deviant stimulus, and hence is considered an automatic response.

any clinical improvement (Qin *et al.*, 2008). Of note, a recent retrospective study on 251 DOC patients finally suggested that speech prosody of the own name stimuli should be standardized as it would be associated with P300 latency differences (Pruvost-Robieux *et al.*, 2022). Taken together, these studies suggest that automatic processes for speech are preserved in a great number of patients with DOC. However, the use of a passive paradigm is not sufficient to reliably disentangle patients in VS/UWS from those in MCS as they only require implicit cognitive abilities (Aubinet, Chatelle, *et al.*, 2021), and it is difficult to disentangle a conscious experience from an unconscious one by merely measuring responses to a presented stimulus.

Alternatively, the use of active paradigms can directly differentiate voluntary from automatic brain responses. This is because, during active paradigms, subjects are explicitly instructed to voluntarily direct attention to a target stimulus. By adding the command “listen carefully for pitch change” for instance, Schnakers *et al.* (2015) observed an enhanced P300 amplitude in nine DOC patients, including three MCS- and one VS/UWS who consequently showed covert cognition. In these patients, the amplitude of the response was lower in frontocentral electrodes compared with controls, but did not differ from that in the MCS+ group. Another similar study previously showed larger P300 response to the own name in the active compared to the passive condition for MCS patients, while no task-related P300 changes were observed for patients in VS/UWS (Schnakers *et al.*, 2008). These results suggest that at least patients in MCS would be able to voluntarily focus their attention on the target as a function of task requirements. Furthermore, time-frequency electroencephalographic analysis showed that both patients in MCS and in VS/UWS show theta synchronization<sup>4</sup> while actively counting their own name among other unfamiliar names (albeit the event-related responses were delayed in VS/UWS patients) (Fellinger *et al.*, 2011). However, only patients in MCS showed enhanced theta responses to own names when instructed to count as compared to passively listening. In this counting condition, other authors also reported higher P300 amplitudes

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<sup>4</sup> Theta synchronization underlies cognitive processes such as maintenance of information in short-term memory, sustained attention, and episodic encoding/retrieval (Klimesch, 1999).

compared to passive listening in several MCS patients (Risetti *et al.*, 2013; Hauger *et al.*, 2015).

Using functional magnetic resonance imaging (fMRI), studies showed that passive listening to the own name (compared to other names) in one patient in VS/UWS encompassed the activation of the medial prefrontal cortex bilaterally in parallel to temporoparietal and superior frontal cortices (Staffen *et al.*, 2006). Such widespread activation was further found in some exceptional patients in VS/UWS who exhibited an atypically high-level cortical activation in associative auditory cortices in response to their own name, similar to that observed in MCS patients (Di *et al.*, 2007). Interestingly, these patients in VS/UWS subsequently recovered to an MCS three months after the fMRI evaluation, whereas those VS/UWS patients who did not show mere activation of primary auditory cortex remained clinically unchanged. Therefore, activation of higher-order associative cortex in VS/UWS was proposed as a marker of good prognosis (for a review see Di, Boly, Weng, Ledoux, & Laureys, 2008). More recently, Wang *et al.* (2015) found that the response type and volume to own name in auditory cortex correlated with VS/UWS patients' prognosis, particularly with traumatic etiology. When the relationship between cortical activation and the presence of self in patients with DOC was investigated, fMRI signal changes were observed in medial cortical regions (i.e., anterior cingulate and supplementary motor areas) in all MCS and the majority of VS/UWS during the own name presentation. Furthermore, the signal changes in the anterior cingulate cortex during self-relatedness were correlated with the degree of consciousness in patients as assessed with the Coma Recovery Scale-Revised suggesting that this midline region is critically involved in linking self and consciousness patients with DOC (Qin *et al.*, 2010). Overall, these patients would show signal changes during self-relatedness in those medial cortical regions in which healthy subjects showed the strongest responses to self-related stimuli.

**Table 1:** Studies using of self-referential stimuli (own name, own face) in severely brain damaged patients with evoked potentials (ERPs), positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) techniques. UWS: Unresponsive Wakefulness Syndrome, MCS: Minimally Conscious State, LIS: Locked-In Syndrome, d: days, m: months, y: years, CRS-R: Coma Recovery Scale-Revised.

Reference	Technique	Number of patients	Diagnosis	Mean time since insult	Tasks	Results
Laureys et al. (2004)	PET ERPs	1	MCS	6 m	Passive listening of sound, baby cries and own name	PET: Widespread activation of bilateral inferior parietal lobules, right temporoparietal junction, left dorsal prefrontal, precuneal and anterior cingulate/mesiofrontal cortices, and inferior frontal gyrus, in response to the own name as compared to other stimulations. ERPs: P300 only evoked by the own name
Staffen et al. (2006)	fMRI	1	UWS	1 y	Passive listening of own name and other name.	Bilateral medial prefrontal, left temporoparietal and superior frontal cortices higher activity for own name as compared to other name.
Perrin et al. (2006)	ERPs	15	5 UWS 6 MCS 4 LIS	427 d	Passive listening of names	Presence of P300 in response to the own name compared to other non-familiar names in 4 LIS, 6 MCS and 3 UWS.
Di et al. (2007)	fMRI	11	7 UWS 4 MCS	10 m	Passive own name listening	4 MCS and 2 UWS: Primary auditory and higher order associative temporal cortices activation. These 2 UWS showed clinical improvement to MCS. 2 UWS: Primary auditory cortex activation only, no improvement. 2 UWS: None cerebral activation, no improvement.
Qin et al. (2008)	ERPs	12	4 COMA 6 UWS 4 MCS	> 1 m	Watching movie during oddball auditory paradigm with own name as novel stimulus	Recording of MMN in response to the own name was correlated with recovery of consciousness: 3 UWS and 2 COMA showed MMN response and evolved to a MCS 3 months later while others UWS and COMA patients failed to show any clinical improvement.
Schnakers et al. (2008)	ERPs	22	8 UWS 14 MCS	Range 12 d–23.7 y	Passive and active counting names tasks	Larger P300 to the patient's own name in MCS as compared to an unfamiliar name P300, with a significantly delayed latency in MCS as compared to controls.
Cavinato et al. (2009)	ERPs	34	8 UWS 26 MCS or EMCS	59 d	Oddball stimulation paradigm with own name as novel stimulus	Presence of P300 in 23 patients (88%) who recover and in none permanently UWS patients.



Fischer, Luaute, & Morlet (2010)	ERPs	27	16 UWS 11 MCS	45 m	Oddball stimulation paradigm with the own name as novel stimulus	3 UWS and 4 MCS showed a P300 to their own name. P300 less often present in anoxic patients than in others etiologies.
Qin et al. (2010)	fMRI	11	7 UWS 4MCS	Range 2-48 m	Own name listening	Signal changes in anterior cingulate cortex (ACC), caudal part of the ACC (cACC) and supplementary motor area (SMA) in all MCS and 6 UWS. Stronger signal changes in cACC in MCS as compared to UWS. Correlation between activation in cACC and the level of consciousness of patients (total CRS-R scores).
Cavinato et al. (2011)	ERPs	17	6 UWS 11 MCS	Range 1-16 m	Oddball stimulation paradigm with own name, other name or sine tone as novel stimulus	P300 tended to be higher (not significantly) to own name as compared to tone in UWS and MCS. No P300 response in 5 UWS. Prolongation in P300 latency in MCS patients in response to different level of stimulus complexity. Later P300 in MCS in response to own and other names.
Fellinger et al. (2011)	ERPs	21	8 UWS 13 MCS	55 m	Passive and active counting names tasks	Higher frontal theta event related synchronization (ERS), delayed as compared to controls, for the own name in the active task for UWS and MCS patients as compared to other name. Higher frontal theta-ERS for own name in the active vs passive condition in MCS and not in UWS. Delayed theta peak latencies in MCS and UWS. Alpha event related desynchronisation (ERD) in the active condition in MCS.
Sharon et al. (2013)	fMRI	4	UWS	17.8 m	Viewing pictures of non-familiar, personally familiar and own faces	UWS patients, similarly to healthy controls, exhibit limbic and salience activations in response to familiar face stimuli including their own face (specifically the amygdala and insula, respectively). Selective emotional processing can be elicited in UWS patients both by external emotionally salient stimuli and by internal cognitive processes, suggesting the ability for covert emotional awareness of self and the environment in UWS patients.
Schnakers et al. (2015)	ERPs	26	10 UWS 16 MCS	39.9 m	Own name passive listening, added command "try to listen attentively your own name"	In 5 MCS+, 3 MCS- and 1 UWS patients, enhanced P300 amplitude was observed in the active versus passive condition. Relative to controls, patients showed a response that was widely distributed over frontoparietal areas, and not present in all blocks. In patients with covert cognition, the amplitude of the response was lower in frontocentral electrodes compared with controls but did not differ from that in the

						MCS+ group. Volitional top-down attention would thus be impaired in patients with covert cognition.
Wang et al. (2015)	fMRI	66	39 UWS 25 MCS 2 EMCS	8.5 m	Own name (said by a familiar voice) listening	The activation patterns were correlated with the clinical outcome assessed with the CRS-R revised scale performed at 3, 6, and 9 months after scanning. BOLD signal in auditory cortex elicited by the own name could statistically reliably predict the outcome in VS/UWS, particularly in traumatic patients.
Sergent et al. (2017)	ERPs	13	4 UWS 8 MCS 1 EMCS	19.6 m	Own name recognition, as part of a protocol including 8 dimensions of cognitive processing	The time window of interest for “own name” versus “other name” was –550 to 0 ms. A significant P300 effect was observed in most but not all control subjects (9/15). The effect was present in 4/8 MCS patients, and 1/4 UWS patients. It was absent in the conscious patient. For most patients showing the effect, the latency of the P300 to own name was shifted in time.
Kempny et al. (2018)	ERPs	16	5 UWS 11 MCS	17.3 m	Own name listening	Four DOC patients (3 MCS and 1 UWS) showed a statistically significant difference in EEG response to their own name versus other peoples' names with ERP latencies (~300 ms and ~700 ms post stimuli). Some of these differences were similar to those found in a control group of healthy subjects. This study shows the feasibility of using self-relevant stimuli such as a subject's own name for assessment of brain function in prolonged DOC patients.
Li et al. (2018)	ERPs	19	10 UWS 9 MCS	UWS: 4 m MCS: 3.1 m	Own name, music listening and habit stimulation	The EEG response under habit stimulation (cigarette smell or alcohol taste) was higher than that under music listening, but lower than that under the own name listening.
Crivelli et al. (2019)	ERPs (skin conductance and heart rate)	21	UWS	37.2 m	Own name listening	A consistent pattern of increased skin conductance and heart rate measures was highlighted in response to patients' own name with respect to other names. An increased delta and decreased alpha activity was observed over frontal areas in response to their own name with respect to other names. Own-name stimuli might call on residual attention orientation and preferred coding resources, suggesting the existence of partly preserved information-processing pathways that extends beyond basic auditory sensory processing.
Pruvost-Robieux et al. (2022)	ERPs	251	/	/	Own name listening	The difference in the prosody of recorded names (i.e. whether names were pronounced with a rising or falling intonation) correlate with differences in P300 latencies of 66.13 ms among patients for whom these responses were observed. This association appeared despite the huge variability between patient conditions (e.g., various DOC etiologies, various delays between the onset of DOC and the neurophysiological assessment, etc.), and some overlap due to namesakes.

## **The “own face” paradigm in disorders of consciousness**

Visual pursuit of a moving or salient stimulus is the most frequent clinical sign revealing consciousness in patients with DOC (Wannez, Gosseries, *et al.*, 2017). Clinically, it can be assessed with different stimuli according to the behavioral scales used by the examiner: a moving finger in the Full Outline of UnResponsiveness scale (FOUR; Wijdicks *et al.*, 2005), a moving person in the Wessex Head Injury Matrix (WHIM; Shiel *et al.*, 2000) and in the Sensory Modality Assessment and Rehabilitation Technique (SMART; Gill-Thwaites and Munday, 2004), a moving mirror in the CRS-R (Giacino *et al.*, 2004) and SECONDS (Aubinet, Cassol, *et al.*, 2021).

Due to the difficulty of controlling voluntary opening of eyes in patients with DOC, very few studies have investigated the effect of own face in this clinical population. In behavioral studies, we first showed that the clinical assessment of visual pursuit in patients improves when evaluated with a moving mirror rather than a neutral object or a moving person (Vanhaudenhuyse *et al.*, 2008). The importance of using a mirror to assess visual functions in MCS patients was further confirmed, and these patients (especially in MCS- and in chronic setting) preferentially track on the horizontal rather than the vertical plane (Thonnard *et al.*, 2014). The use of a mirror also showed higher positive response rate, compared to a ball or a flash light, in eliciting a visual fixating response (Di *et al.*, 2014). We could however not confirm the hypothesis that the efficiency of the mirror to objectify visual pursuit capacity in this population was related to its self-aspect (Wannez, Vanhaudenhuyse, *et al.*, 2017). In this study, the mirror was compared: (1) to the patient’s picture and to the picture of a famous face in 22 MCS patients, and (2) to the patient’s picture and a fake mirror (i.e., dynamical and bright aspect without face reflection) in 26 other MCS patients. According to our results, the mirror was significantly more efficient than the patient’s picture (which showed no statistical difference compared to the famous face), while it could not induce more responses than the fake mirror. Trojano *et al.* (2018) finally reported a similar proportion of on-target fixations elicited by a picture of patient’s own face and a picture of an unfamiliar face in 44 DOC patients.

Nevertheless, MCS+ patients showed more fixation responses on these pictures compared to other neutral stimuli, suggesting that human faces definitely represent one of the most salient class of stimuli for DOC patients (Magliacano *et al.*, 2019b). Of note, according to a fMRI study (Sharon *et al.*, 2013), DOC patients could display face selective brain responses with further limbic and cortical activations elicited by familiar faces (including their own face), and connectivity would be observed between emotional, visual and face specific areas, suggesting emotional perception.

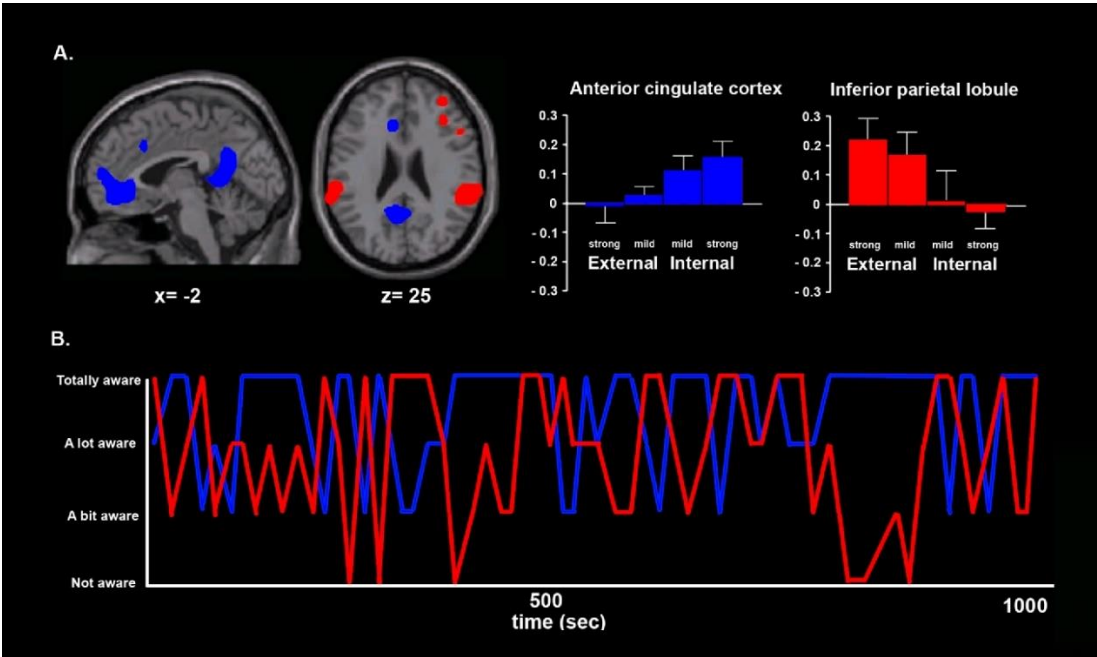
Obviously, more research is needed to understand the attentional properties of one's face own and their significance in terms of self-awareness perception. However, the use of the patients' face/own reflection as stimulus seems promising for the study of residual self-awareness in non-communicating patients.

### **The “self” in the resting brain**

In addition to brain activation in response to self-referential stimuli, increasing attention has been paid to the study of spontaneous brain activity. The resting state paradigm is particularly appealing because it does not require sophisticated experimental setup to administer external stimuli and surpasses the need for subject's collaboration (Soddu *et al.*, 2011). As such, it is suitable for the study of subjects who are unable to communicate in a functional manner, such as babies, neuropsychiatric and neurologic patients. Using fMRI, the brain's activity at rest is characterized by spontaneous low-frequency fluctuations in the blood-oxygen-level-dependent (BOLD) signal, in the range of 0.01–0.1 Hz (mean 20 sec). These spontaneous BOLD fluctuations cannot be attributed to peripheral noise, like cardiac and respiratory fluctuations or motion of the subject. Rather, they show synchronized activity with other functionally related brain regions (Fox and Raichle, 2007) in a way that the brain can be organized in large-scale cerebral networks (Damoiseaux *et al.*, 2006).

To date, such functional neuroimaging studies point to the critical recruitment of anterior and posterior midline cerebral areas in experimental paradigms using self-referential conditions. In a combined fMRI-behavioral experiment, it was shown that behavioral ratings

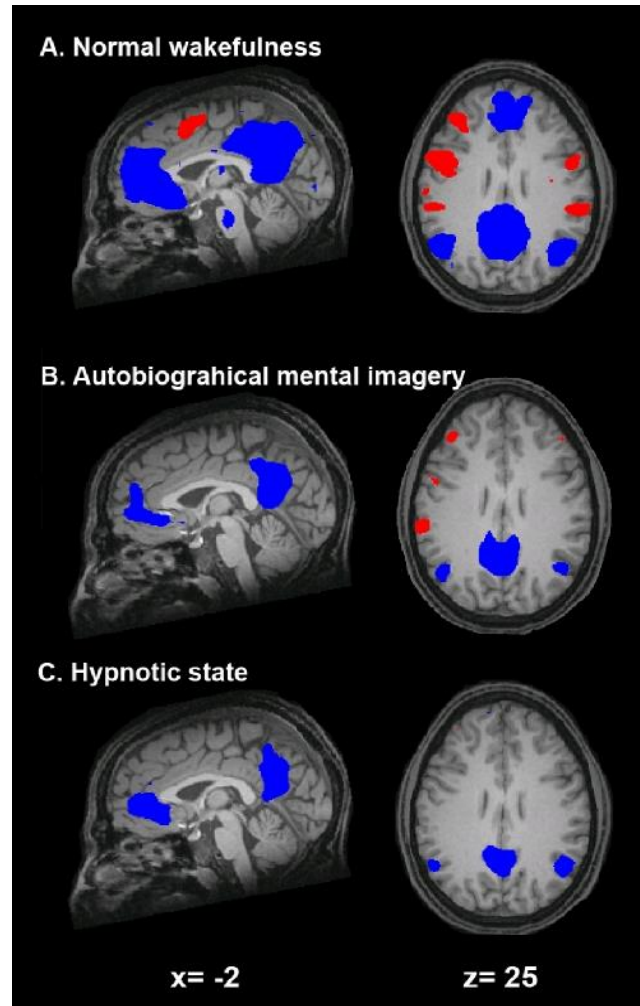
about one’s state of awareness had a cerebral correlate (Vanhaudenhuyse et al., 2011). In that study, the phenomenological complexity of conscious awareness was considered as having two components: external awareness, i.e. everything we perceive through our senses (what we see, hear, feel, smell and taste), and internal awareness or self-related mentation (Demertzi, Soddu, & Laureys, 2013). When subjects rated their awareness as “strongly external”, their responses correlated with the activity of a lateral fronto-parieto-temporal set of regions; conversely, behavioral reports of awareness being “strongly internal” were linked to the activity of midline anterior cingulate/mesiofrontal areas as well as posterior cingulate/precuneal cortices (Figure 3, panel A). In addition, at the behavioral level these two components of awareness were found to anticorrelate, switching their dominance on average every 20 sec (Figure 3, panel B). These findings highlight that the anticorrelated pattern between the internal and external awareness system may be of functional relevance to subjective awareness (Demertzi, Soddu, et al., 2013).



**Figure 3:** The cognitive-behavioral counterpart of “resting state”. External (red) and internal (blue) awareness anticorrelate at the behavioral level (panel B) and correspond to distinct cerebral patterns as a function of intensity of subjective reports (panel A). Data taken from Vanhaudenhuyse et al. (2011).

Interestingly, such anticorrelated activity is also observed in the BOLD fMRI signal of resting state acquisitions so that the brain's baseline can be organized in two widespread brain networks: an "extrinsic" and an "intrinsic" network (Fox *et al.*, 2005; Fransson, 2005; Golland *et al.*, 2006; Tian *et al.*, 2007; Buckner and DiNicola, 2019). These anticorrelated networks have been shown to be robust and reliable (Damoiseaux *et al.*, 2006; Shehzad *et al.*, 2009; Van Dijk *et al.*, 2010; Zuo *et al.*, 2010). Although currently it remains unclear how these competing brain systems are exactly regulated, it has been shown that the degree to which they are anticorrelated significantly associates with cognitive function (Kelly *et al.*, 2008; Whitfield-Gabrieli *et al.*, 2009; Hampson *et al.*, 2010; Keller *et al.*, 2015). For example, greater anticorrelation has been linked with superior task performance, suggesting that stronger anticorrelations reflect a more effective capacity to switch between internal and external modes of attention. Also, functional connectivity between these two systems has been shown to be mediated by the level of awareness (Heine *et al.*, 2012). Indeed, in a non ordinary conscious state like hypnosis, where subjects report awareness modulations but remain fully responsive, hypnosis-related reductions in functional connectivity were shown in the external awareness system parallel to subjective ratings of increased sense of dissociation from the environment and reduced intensity of external thoughts (Demertzi *et al.*, 2011) (Figure 4). Similar reductions in external awareness systems have been also shown for non-responsive conditions, such as deep sleep and anesthesia (for a review see Heine *et al.*, 2012). Taken together these studies indicate that the two awareness networks mediate (at least partially) conscious ongoing under the functions of a wide "global neuronal workspace" (Baars, Ramsøy and Laureys, 2003; Dehaene and Changeux, 2011). From a theoretical perspective, the anticorrelation between the extrinsic and the intrinsic systems can be viewed as an alternating balance between the external and the internal milieu (Demertzi, Soddu, *et al.*, 2013). According to a suggested framework taking the external and internal awareness systems into account, two complementary states of system imbalance are possible, where one system can be in a hyperfunctional state, while the other is hypoactive. Extrinsic system hyperfunction is expected to lead to a state of total sensorimotor absorption or "lost self". In contrast, intrinsic or default

system hyperfunction is expected to lead to a state of complete detachment from the external world. A state where both extrinsic and intrinsic systems are hypofunctional is predicted to lead to markedly impaired consciousness as seen in DOC patients (Soddu *et al.*, 2009).



**Figure 4:** Functional connectivity decreases of resting state acquisitions as we move from normal wakefulness to autobiographical mental imagery and hypnotic state. The connectivity values are profoundly decreased in the extrinsic system (areas in red) during hypnotic state. This could possibly reflect decreased sensory awareness in combination with a subjective experience of self-centered absorption. Data taken from Demertzi *et al.* (2011).

These two systems are also known as “task positive” and “task negative” networks (Fox *et al.*, 2005) to describe the dampening of activation of the default mode network (DMN) during task performance (Shulman *et al.*, 1997; Mazoyer *et al.*, 2001). The DMN encompasses mainly midline anterior cingulate/mesiofrontal and posterior cingulate/precuneus as well as lateral

parietal areas (Figure 4, panel A in blue). An immediate challenge is to decipher the functional role of the systems-level intrinsic connectivity. To date, considerable evidence supports the view that the DMN mediates consideration of one's own thoughts and feelings, or self-referential processing (Gusnard and Raichle, 2001; Johnson, 2002; Kelley *et al.*, 2002; Northoff and Bermpohl, 2004; D'Argembeau *et al.*, 2005; Moran *et al.*, 2006; Whitfield-Gabrieli *et al.*, 2011; Raichle, 2015; Davey, Pujol and Harrison, 2016; Yeshurun, Nguyen and Hasson, 2021). In these studies, people typically make judgments about their own feelings or about their own characters. Although self-referential tasks involve stimulus presentation and task performance rather than rest, they engage two medial core components of the DMN, namely the medial prefrontal and the posterior cingulate cortex (Davey, Pujol and Harrison, 2016). Indeed, these midline regions have been thought to be involved not only with self-referential processing, but also with remembering one's past, planning one's future, and forming one's beliefs (Raichle and Snyder, 2007; Buckner, Andrews-Hanna and Schacter, 2008). As illustrated in Figure 4 (panel B), they are particularly activated in autobiographical mental imagery tasks. The frequent activation of these DMN components in memory retrieval can be interpreted as a sort of time travel to one's own past to retrieve memory for a prior experience. What appears to be shared across the kinds of tasks that activate these DMN midline regions is a focus on oneself—one's feelings, one's character, one's memories, and one's aspirations. Note that components of the DMN have also been activated in social cognition—thinking about other people or what other people are thinking about (theory of mind) (Saxe, Carey and Kanwisher, 2004; Schilbach *et al.*, 2008; Mars *et al.*, 2012; Hughes *et al.*, 2020). The overlap in brain regions between areas engaged in reflection about oneself and reflection about other people raises the possibility that thinking about other minds involves a sort of simulation of the same processes that are engaged in thinking about oneself. Therefore, as people are at rest, it may be hypothesized that they are spontaneously engaged in self-reflection because the same brain regions are activated.

With regards to patients with DOC, connectivity in the DMN posterior cingulate was shown to be indistinguishable between controls and LIS patients (i.e. conscious but severely



paralyzed), relatively preserved in MCS patients and significantly reduced in VS/UWS patients (Demertzi et al., 2014; Vanhaudenhuyse et al., 2010) and could not be identified in brain death (i.e. irreversible coma with absent brainstem reflexes; Boly *et al.*, 2009). As long as the clinical utility of this paradigm is concerned, it was found that single patients could be discriminated from healthy controls with 85% accuracy based on information about “neuronality” of the DMN and the auditory resting state network (Demertzi et al., 2014). The presence of anticorrelations between the DMN and the task-positive network was also shown in conscious subjects (either EMCS patients or healthy subjects), but not in DOC patients (either in VS/UWS or MCS), suggesting that switching between the two networks is crucial for conscious cognition (Di Perri *et al.*, 2016). Of note is that negative DMN connectivity in VS/UWS or MCS patients may be characterized by positive values, showing a pathological between-network hyperconnectivity in these patients. Mäki-Marttunen et al. (2016) additionally investigated DMN and attention network activity in DOC patients during the performance of a task involving only self-referential and sustained attention processes, as well as during resting state. They observed a disrupted relationship between the two networks during the task in DOC patients, which was gradually recovered with consciousness. At rest, these patients also showed an altered pattern of functional connectivity within the DMN and between the DMN and the attention network. The authors finally suggest that more than one area of these networks have to be taken into account to evaluate the hypothesis of the required efficient switching between those networks for peak cognitive performance. Overall, a growing number of studies show disruption of DMN functional connectivity in DOC patients, which could be used as a prognostic marker for consciousness recovery (Wu *et al.*, 2015; Bodien, Chatelle and Edlow, 2017; Luppi *et al.*, 2019; Zhang *et al.*, 2022). Taken together, these changes in the DMN functional connectivity could reflect restricted abilities for self-referential processing.

## **Conclusions**

Assessing self-consciousness in coma survivors who remain unable to verbally or non-verbally express their thoughts and feelings is difficult by means of behavioral observation

only. Self-referential stimuli such as the patient's own name and own face are clinically valuable attention-grabbing emotional stimuli, the use of which increases the chances to obtain non-reflex (i.e., "willed" or "voluntary") motor responsiveness in DOC. Behavioral data demonstrate that the use of self-referential stimuli such as the own reflection of the patient in a mirror is a significant help to detect consciousness in non-communicative patients. Electrophysiology and neuroimaging studies using such stimuli show the interest to record brain activity in response to self-referential stimuli to help in differentiating unconscious VS/UWS from fluctuating MCS patients. Residual brain response could also be a potential marker of good prognosis of recovery of consciousness in VS/UWS patients. Finally, brain function during resting state sheds light on the subjective counterpart of these data and paves the way towards single-patient differentiation. Taken together, the experimental exploration of the "self" in pathological unconsciousness surpasses the functional localization of self-related cognition, and suggests a dynamic system-level approach to the phenomenological complexity of subjectivity.

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