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ADVANCES IN THE ASSESSMENT OF DISORDERS OF CONSCIOUSNESS: THE ROLE OF BEDSIDE ASSESSMENT AND NEUROIMAGING TECHNIQUES IN THE DIAGNOSTIC PROCESS

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El estado vegetativo se define clínicamente por la falta de conciencia de uno mismo y el entorno, junto con el mantenimiento de funciones básicas como la respiratoria, cardiaca, o los ciclos de sueño y vigilia. Se trata de pacientes incapaces de reaccionar de un modo intencional a la estimulación externa y que no manifiestan ninguna capacidad comunicativa. Estudios recientes han demostrado que en torno al 40% de estos pacientes han sido incorrectamente diagnosticados y se encuentran, en realidad, conscientes. Sin embargo, en los últimos años se ha producido una revolución en las herramientas disponibles para evaluar a estos pacientes. El presente artículo tiene como objetivo discutir el papel de las escalas de evaluación clínica estandarizadas, así como técnicas avanzadas de neuroimagen, en la reducción del alarmante error diagnóstico. Se revisarán el alcance y las limitaciones de cada aproximación para identificar signos de conciencia externos o encubiertos, y se presentará evidencia a favor de una evaluación multimodal, combinando la información clínica, estructural y funcional para garantizar el diagnóstico correcto en cada caso individual.
Palabras clave: *Alteraciones de conciencia, Evaluación clínica, Resonancia magnética.*

Patients in a vegetative state are considered to lack awareness of themselves or the environment, but preserve respiratory and cardiac functions, as well as sleep/wake cycles. These patients are incapable of producing intentional responses to external stimulation and do not demonstrate any communication skills. Recent studies have shown that around 40% of vegetative state patients have been misdiagnosed. However, in recent years there has been a revolution in the tools that are available for the assessment of these patients. The objective of this article is to discuss the role of behavioural scales, as well as advanced neuroimaging techniques, in reducing the misdiagnosis rate. We review the scope and limitations of these approaches for the identification of overt and covert signs of awareness, and we present evidence to support a multimodal assessment that combines information from behavioural, structural, and functional imaging tools to ensure an accurate diagnosis for each individual patient.
Key words: *Disorders of consciousness, Clinical assessment, Magnetic resonance imaging.*

Defining consciousness and understanding its nature is one of the great challenges of contemporary neuroscience. Although the scientific community does not have a universally accepted definition of consciousness, the field of clinical neuroscience uses an operational definition that can be utilised in the bedside examination of the patient (Laureys, Perrin, & Bredart, 2007). In this context, consciousness is considered to be a complex system with two key dimensions: the level of consciousness or alertness (known as 'wakefulness' in the literature), and the content of consciousness or consciousness *per se* (known as 'awareness' in the literature) (Plum & Posner, 1982). The former refers to a state in which the eyes are open and there is a motor response. The latter encompasses both self-awareness and awareness of the environment, and refers to the ability to have subjective experiences of any kind. These two dimensions are related to very different brain mechanisms and networks. The level of consciousness depends on the ascending reticular activating system and its cortical connections (Parvizi & Damasio, 2001), while the content of consciousness depends on complex cortical-cortical and subcortical-cortical networks, which are not yet fully understood (Schiff, 2008). Because of the hierarchical relationship between these two systems, it is considered that a patient must have some preservation of the structures of wakefulness in order to have subjective experiences (awareness). Conversely, a patient may be alert but it should not be assumed that they are therefore aware of

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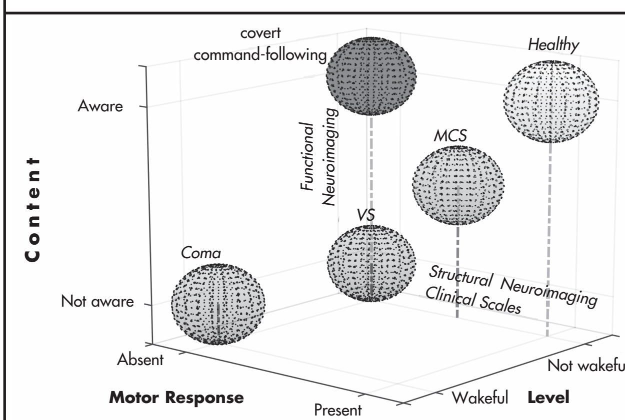
FIGURE 1
DIMENSIONS IN ASSESSING DISORDERS OF CONSCIOUSNESS, AND TECHNIQUES OF CHOICE FOR THE DIFFERENTIAL DIAGNOSIS ON EACH AXIS



* Figure based on Monti, Coleman, & Owen, 2009 (with important modifications and including additional information).

themselves and their environment. This dissociation is crucial in understanding altered states of consciousness in patients who have suffered a severe brain injury (see Figure 1).

The most common causes of such injuries are traumatic brain injury (TBI) and hypoxic-ischemic encephalopathy (HIE) (The Multi-Society Task Force on PVS, 1994*)*. The TBI that lead to severe consciousness disorders are often related to traffic accidents, although also, to a lesser extent, to falls or assaults. HIE, however, occurs after a prolonged lack of oxygen, in most cases after cardiorespiratory arrest, but also after drowning, carbon monoxide poisoning, etc. (The Multi-Society Task Force on PVS, 1994). Thanks to advances in emergency medical care, the widespread use of assisted ventilation and the presence of defibrillators in public places, a large number of patients survive both types of accidents today (Fernandez-Espejo & Owen, 2013). However, because of the extreme gravity of the accidents, many patients sustain severe brain injuries and enter a phase of coma.

A coma is an acute state (usually lasting a few days or weeks), in which the patient shows no signs of wakefulness or awareness: there is no spontaneous eye opening and the patient cannot be awakened with the application of vigorous sensory stimulation (Plum & Posner, 1982). Once the phase of the coma has passed, some of the patients regain consciousness and evolve favourably (albeit with cognitive sequelae of varying severity). A significant percentage of them, however, come out of the coma (open their eyes) but do not regain consciousness and fall into what is known as a **vegetative state** (VS).

Unlike the coma, the VS is defined by the preservation of wakefulness, manifested by the presence of sleep-wake cycles in the absence of consciousness (Jennett & Plum, 1972). These patients regain their autonomic function, the ability to regulate their breathing and heart rate without the aid of mechanical ventilation, but they do not react intentionally to stimulation, they do not respond to simple commands, and they do not have any communication skills (Royal College of Physicians, 2003). It is therefore considered that they are not aware of themselves or their surroundings. The VS is considered persistent when the patient remains unchanged one month after the accident, and permanent when no improvement has been recorded after 12 months after the TBI, or 3/6 months (according to American and British standards, respectively) in cases of HIE (Royal College of Physicians, 2003; The Multi-Society Task Force on PVS, 1994). Once the diagnosis of a permanent VS has been reached, it is considered that this state is irreversible and there is no possibility of recovery.

Before reaching the criterion of permanent, some patients begin to show fluctuating but clear signs of awareness and progress to what is known as a **minimally conscious state** (MCS) (Giacino et al., 2002). This category includes a heterogeneous group of patients, who at the bottom of the spectrum are able to follow a moving object with their eyes, and at the top are able to follow simple commands. In cases where there are no concomitant pathologies that reduce life expectancy, the patient may survive in a VS or MCS for decades. Some patients begin to be able to use everyday objects such as a cup, or a comb, or they manifest functional communication skills (i.e., they are able to respond to basic situational questions correctly). It is considered in this case that the patient has emerged from the MCS (Giacino et al., 2002), and would go on to receive a complete neuropsychological examination to determine the profile of the cognitive sequelae and, in cases where it is deemed appropriate, to design the rehabilitation program (Rosenbaum & Giacino, 2015; Royal College of Physicians, 2013).

At present there are no official statistics on the incidence or prevalence of disorders of consciousness partly because, with the exception of the coma, these clinical conditions are not listed in the International Classification of Diseases (ICD-10-ES, 2016 version[1]). In 2005, it was estimated that there were 46 new cases of VS patients per million inhabitants in the United States; and 14 per million inhabitants in the UK (Jennett, 2005). However, these data are based solely on trauma cases, since non-trauma cases have a more varied etiology and are referred to different specialists, making them difficult to identify. Although in Spain we do not have official figures for VS or MCS, in 2003 the *Institut de Neurorehabilitació Guttmann* estimated an annual incidence of TBI resulting in severe disability of 20 cases per 100,000 inhabitants/year (Alberdi Odriozola, Iriarte Ibarrán, Mendía Gorostidi, Murgialdai, & Marco Garde, 2009). With regards to the prevalence, several studies in Austria, the Netherlands and France have recently described the existence of between 0.2 and 6.1 VS patients, and 1.5 MCS patients per 100,000 inhabitants (Lavrijsen, van den Bosch, Koopmans, & van Weel, 2005; Pisa, Biasutti, Drigo, & Barbone, 2014; Saout et al., 2010). These figures are useful as a reference, but they cannot be easily extrapolated to other countries, among other reasons because there are important differences in the decisions concerning the termination of life in the acute phase, in cases such as these where the patient has catastrophic injuries. Although the incidence and prevalence are relatively low, the social, family and economic impact associated with the care of these patients is extremely high (Moretta et al., 2014), so it is necessary to carry out a proper assessment to identify the cognitive functions that the patient has preserved or lost, in order to ensure a good allocation of the resources. In the sections below, a critical review will be presented of the options available for diagnosing patients with disorders of consciousness in the areas of clinical assessment, as well as structural and functional neuroimaging. The most important contributions of each area will be discussed as well as the scope and limitations for identifying both overt and covert signs of awareness. Finally, this paper will argue the need for a multimodal assessment of patients with disorders of consciousness in order to ensure a correct diagnosis in each individual case.

CLINICAL ASSESSMENT OF DISORDERS OF CONSCIOUSNESS

Currently there are no objective biomarkers or laboratory analysis to determine whether a patient is or is not aware of themselves or their environment. The differential diagnosis of VS and MCS is based solely on the clinical examination of the patient, and observing the behavioural repertoire that they are capable of displaying; both spontaneously

[1] http://eciemaps.mspsi.es/ecieMaps/browser/index_10_mc.html

and in response to external stimulation provided by the examiner (Royal College of Physicians, 2003). The main function of the clinician is to determine whether the behaviours the patient displays are reflexes or whether they in fact indicate that the patient is able to interact intentionally with the environment. It is extremely complex to determine whether a behaviour is a reflex or voluntary, and in many cases the diagnostic process is further complicated by the presence of concomitant motor or language deficits that hinder the assessment (Majerus, Bruno, Schnakers, Giacino, & Laureys, 2009; Majerus, Gill-Thwaites, Andrews, & Laureys, 2005; Schnakers et al., 2015). In two studies in specialised neurorehabilitation centres in the US and the UK in the 90s, it was found that, due to these difficulties, 37% and 43% (respectively) of patients admitted with a diagnosis of VS had been incorrectly diagnosed. When these patients were re-evaluated by qualified personnel with experience in the diagnosis of disorders of consciousness, signs of partial consciousness were identified, or in some cases even complete consciousness (Andrews, Murphy, Munday, & Littlewood, 1996; Childs, Mercer, & Childs, 1993). The authors pointed to a lack of familiarity with the diagnostic criteria, and a lack of standardised assessments as being primarily responsible for these errors.

After these studies, the scientific and clinical communities agreed in recommending that the classic bedside examination is not sufficient to diagnose these patients, and it is necessary to use standardised batteries and to incorporate family and caregivers into the process (Bernat, 2006; Gill-Thwaites, 2006). In 2010, The Brain-Injury Interdisciplinary Special Interest Group, Disorders of Consciousness Task Force was established during the American Congress of Rehabilitation Medicine, with the aim of reviewing the scientific literature and formalising a recommendation of diagnostic scales, based on their content validity, diagnostic validity, reliability and prognostic value (American Congress of Rehabilitation Medicine, Brain Injury-Interdisciplinary Special Interest Group, Disorders of Consciousness Task Force et al., 2010). The main conclusions were that the only scales that were adequate for diagnosing patients with disorders of consciousness are the following: the Coma Recovery Scale-Revised (CRS- R) (Giacino, Kalmar, & Whyte, 2004), the Sensory Stimulation Assessment Measure (SSAM) (Rader & Ellis, 1994), the Wessex Head Injury Matrix (WHIM) (Shiel et al., 2000), the Western Neuro Sensory Stimulation Profile (WNSSP) (Ansell & Keenan, 1989), the Sensory Modality Assessment Technique (SMART) (Gill-Thwaites, 1997) and the Coma/Near-Coma Scale (CNC) (Rappaport, 2005) although the recommendation of this latter scale was with reservations. At the same time, they spoke out against the use of other scales that are widely used in neurological practice, such as the Full Outline of UnResponsiveness Score (FOUR) (Wijdicks, Bamlet, Maramattom, Manno, & McClelland, 2005), the Comprehensive Levels of Consciousness Scale (CLOCS) (Stanczak et al., 1984), the Innsbruck Coma Scale (INNS) (Benzer et al., 1991), the Glasgow-Liege Coma Scale (Born, 1988), the Swedish Reaction Level Scale-1985 (Johnstone et al., 1993), and the Loewenstein Communication Scale (Borer-Alafi, Gil, Sazbon, & Korn, 2002) due to their lack of content validity, standardisation or reliability (see Table 1).

Among the recommended scales, the two most complete ones, which contain specific elements for the differential diagnosis between VS and MCS, and which have received the most support in the scientific literature, are the SMART and CRS-R scales. The SMART scale was developed by occupational therapists at the Royal Hospital for

TABLE 1
RECOMMENDATIONS OF THE DISORDERS OF CONSCIOUSNESS TASK FORCE ON SCALES FOR THE DIAGNOSIS OF DISORDERS OF CONSCIOUSNESS. ***(American Congress of Rehabilitation Medicine, Brain Injury-Interdisciplinary Special Interest Group, Disorders of Consciousness Task Force*, 2010)**

Scale	Complete Name	Reference	Recommendation
CRS-R*	*Coma Recovery Scale-Revised*	Giacino, Kalmar & Whyte, 2004 (Spanish version: Noé et al., 2012)	Yes
CNC	*Coma/Near-Coma Scale*	Rappaport, 2005	With reservations
CLOCS	*Comprehensive Levels of Consciousness Scale*	Stanczak et al., 1984	No
INNS	*Glasgow-Liege Coma Scale* *Innsbruck Coma Scale (INNS)* *Loewenstein Communication Scale*	Born, 1988 Benzer et al., 1991 Borer-Alafi, Gil, Sazbon, & Korn, 2002	No No No
MATADOC	*Music Therapy Assessment Tool for Awareness in Disorders of Consciousness*	Magee, Siegert, Daveson, Lenton-Smith, & Taylor, 2013	Not studied
SMART*	*Sensory Modality Assessment Technique*	Gill-Thwaites, 1997	Yes
SSAM	*Sensory Stimulation Assessment Measure*	Rader & Ellis, 1994	Yes
FOUR	*Swedish Reaction Level Scale-1985* *The Full Outline of UnResponsiveness Score*	Johnstone et al., 1993 (Wijdicks, Bamlet, Maramattom, Manno, & McClelland, 2005	No No
WHIM	*Wessex Head Injury Matrix*	Shiel et al., 2000	Yes
WNSSP	*Western Neuro Sensory Stimulation Profile*	Ansell & Keenan, 1989	Yes

* Most widely accepted scales in the scientific community

Neuro-disability in London, as a tool for assessing and planning a rehabilitation program and monitoring its effects on the patient (Gill-Thwaites & Munday, 2004). It contains 29 sub-scales that allow a full exploration of the five sensory modalities, the motor function, functional communication and level of alertness. The patient's responses are classified hierarchically according to the functional level they represent (no response, reflex response, withdrawal response, localising response, or differentiating response). In order to access this scale, specific training by the team that developed it must be received, which, together with its high cost, in practice makes it inaccessible to most clinicians and researchers who are not resident in the UK (American Congress of Rehabilitation Medicine, Brain Injury-Interdisciplinary Special Interest Group, Disorders of Consciousness Task Force et al., 2010).

With a similar emphasis on rehabilitation, in this case based on music therapy, the Royal Hospital for Neuro-disability recently published the Music Therapy Assessment Tool for Awareness in Disorders of Consciousness scale (MATADOC) (Magee, Siegert, Daveson, Lenton-Smith, & Taylor, 2013). In the first standardisation study, the scale showed good internal validity and diagnosis consistent with that obtained using the SMART and CRS-R scales (Magee et al., 2013). As it does not rely on linguistic stimulation, this scale is especially useful in patients with aphasia (Schnakers et al., 2015), or paediatric patients (Magee, Ghetti, & Moyer, 2015). However, it suffers from access problems similar to those of the SMART scale, so its use is not yet widespread.

The CRS-R scale specifically evaluates all behaviours described by the Aspen Workgroup for the differential diagnosis of VS and MCS (Giacino et al., 2002), and has excellent content validity (American Congress of Rehabilitation Medicine, Brain Injury-Interdisciplinary Special Interest Group, Disorders of Consciousness Task Force et al., 2010). In addition, unlike the previous two scales, it is free to access and no formal training is required to administer it (Giacino et al., 2004). This has become the most widely used scale in the specialised scientific literature. It consists of 25 items hierarchically ordered and distributed in 6 subscales that assess the following different functions: auditory, visual, motor, oromotor/verbal, communication and arousal. The score for each subscale is based on the presence or absence of specific behaviours in response to sensory stimulation that the assessor presents in a standardised way. Low scores reflect reflex behaviours, while higher scores represent cognitively mediated behaviours (Giacino et al., 2004). This scale has recently been adapted to Spanish by the team of Enrique Noé at the Neuro-rehabilitation and Brain Damage Service of the NISA Hospital in Valencia (Noé et al., 2012).

Despite the high availability of these assessment scales (particularly the easy access to the CRS-R), the publication of differential diagnostic criteria (Giacino et al., 2002), and the recommendation to carry out standardised tests that appears in the clinical practice guidelines for dealing with patients with disorders of consciousness (*Royal College of Physicians*, 2003), a recent study, in which 103 patients were evaluated in Belgium, found a diagnostic error rate similar to the rate described in the 90s (Schnakers et al., 2009). The authors compared the diagnosis reached by clinical consensus in the medical team with that obtained after repeated assessments by qualified personnel using the CRS-R scale. The study found that 41% of patients with a clinical diagnosis of VS were actually in MCS, 10% of patients diagnosed with MCS had emerged from this state, and 89% of patients about whom the medical staff had not reached a consensus diagnosis were in MCS.

THE ROLE OF NEUROIMAGING

Diagnostic errors like those described in the previous section can have serious consequences. Firstly, the MCS has a more favourable prognosis than the VS (Giacino & Kalmar, 1997; Luauté et al., 2010), so misdiagnosis could influence the resources made available to the patient to facilitate recovery. Likewise, patients in MCS retain a higher cognitive processing capacity, which reaches more complex brain areas, than patients in VS (Boly et al., 2004; Laureys et al., 2000; 2002; Silva et al., 2010). For example, several studies have suggested that patients in MCS are capable of experiencing pain (Boly, Faymonville, et al., 2008a; Laureys et al., 2002), which must be taken into account when administering invasive clinical procedures. Finally, at present and in most jurisdictions in Western countries, legal proceedings relating to the withdrawal of life support (in this case artificial nutrition and hydration) are only initiated in cases where the patient has a diagnosis of VS (Andrews, 2004; Fernandez-Espejo & Owen, 2013).

In order to reduce this alarming misdiagnosis rate, several research groups have begun to use advanced structural neuroimaging techniques to identify objective biomarkers that provide complementary information to the clinical assessment. The foundations for this line of work were established in neuropathological studies carried out in the 90s, before the explosion of modern neuroimaging. After analysing 178 cases published in the scientific literature to date, Kinney and Samuel (1994) identified three general patterns of brain damage: diffuse axonal injury in trauma cases, destruction of the cortical rim in cases with hypoxic-ischemic etiology and thalamic lesions in both etiologies. These findings were confirmed in a series of successive studies (Adams, Graham, & Jennett, 2000; Adams, Jennett, McLellan, Murray, & Graham, 1999; Jennett, Adams, Murray, & Graham, 2001), which also reported a greater severity of diffuse axonal injury and traumatic lesions in VS patients than in those in MCS (Jennett et al., 2001).

The first morphometric studies based on magnetic resonance imaging (MRI) confirmed the previous findings (Ammermann et al., 2007; Juengling, Kassubek, Huppertz, Krause, & Els, 2005; Kampfl, Franz, et al., 1998a; Kampfl, Schmutzhard, et al., 1998b). However, it was not until 2011 that the first study was published in which it was possible to identify diagnostic biomarkers *in vivo*, by diffusion tensor imaging analysis (Fernandez-Espejo et al., 2011). This type of imaging allows us to characterise the microstructure of the brain tissue by observing the movement of the water molecules, and is particularly sensitive in detecting subtle changes that are not observable with other conventional forms of MRI (Bruno et al., 2011; Le Bihan et al., 2001). Firstly, this study confirmed differences in the severity of damage to the white matter and the thalamus between patients in VS and MCS. However, the real importance of this study is that, using only objective indices of the damage in these areas, it was possible to correctly diagnose 95% of the patients analysed (Fernandez-Espejo et al., 2011).

The thalamus is a structure of tremendous structural and functional complexity, with connections distributed across multiple cortical areas (Morel, Magnin, & Jeanmonod, 1997). Several studies have attempted to determine whether there is regional specificity in the thalamic damage in patients with disorders of consciousness (Fernandez-Espejo, Junque, Bernabeu, et al., 2010a; Lutkenhoff et al., 2015; 2013; Maxwell, MacKinnon, Smith, McIntosh, & Graham, 2006; Maxwell et al., 2004; Schiff, 2008). It has been shown that this atrophy particularly affects the central body (the dorsomedial nucleus and the internal medullary lamina), and is more pronounced in VS patients than in those in MCS (Fernandez-Espejo, Junque, Bernabeu, et al., 2010a; Maxwell et al., 2004; 2006), and in patients with TBI than those with HIE (Lutkenhoff et al., 2015). In trauma cases, the degree of acute atrophy present in the dorsomedial and anterior-medial nuclei has also been linked with prognosis at 6 months (Lutkenhoff et al., 2013).

Similar to the case of the thalamus, the regional distribution of white matter damage was profiled in a recent study of 52 patients of varying severity (Fernandez-Espejo et al., 2012). It was found to affect specifically the tracts connecting the cortical regions that make up part of the default mode network (medial prefrontal cortex, posterior cingulate/precuneus and inferior parietal lobes), as well as those connecting the posterior cingulate/precuneus with the thalamus. Numerous studies have found activation of this network in periods when we are resting, daydreaming or letting the mind wander (Buckner, Andrews-Hanna, & Schacter, 2008; Mason et al., 2007), and its functional integrity has been suggested as a prerequisite for the existence of conscious experience (Boly, Phillips, et al., 2008b; Laureys et al., 2007; Vanhaudenhuyse et al., 2010). In the previous study (Fernandez-Espejo et al., 2012), the severity of damage in the connections between the posterior and lateral nodes of this network as well as with the thalamus, correlated with the severity of the disorder of consciousness and the patient diagnosis.

Together, these findings open the way for the potential identification of more specific diagnostic biomarkers within the white matter and the thalamus. Although to date there have been no formal attempts in this direction, it is to be expected that this increased specificity will improve the diagnostic accuracy obtained previously (95%) (Fernandez-Espejo et al., 2011). The potential for clinical application of these techniques is clear, given that, as highlighted by the Royal College of Physicians in its latest guide (Royal College of Physicians, 2013), they do not require the participation of the patient and they can easily be performed in centres that are not specialised and that do not have research experience. Thus, if adopted as part of routine clinical assessment, they can help facilitate the identification of patients in MCS in cases where the diagnosis is not clear, or when the patient cannot be evaluated by teams of specialists (Schnakers et al., 2009).

In parallel, thanks to advances in *functional* neuroimaging techniques, a new group of conscious patients has been discovered whose detection is not possible even with assessments by teams of experts (Owen, 2013), or structural techniques. These patients retain complex cognitive skills but are unable to show them with external behaviour and, therefore, are incorrectly diagnosed as VS (see Figure 1). It is only possible to identify these cases through the use of techniques such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), which enable us to relate changes in brain activation after presenting sensory stimuli with specific cognitive processes, without needing the patient to produce external verbal or motor responses (Owen, Epstein, & Johnsrude, n.d.). The early studies of brain activation in patients in VS or MCS were based on the presentation of passive stimulation, and showed that some of these patients retain emotional processing capabilities and are able to react, for example, to their own name (Di et al., 2007; Fischer, Luaute, & Morlet, 2010; Qin et al., 2010; 2008; Staffen, Kronbichler, Aichhorn, Mair, & Ladurner, 2006), familiar voices (Bekinschtein et al., 2004; de Jong, Willemsen, & Paans, 1997; Machado et al., 2007), familiar faces (Menon et al., 1998), or music with personal emotional content (O'Kelly et al., 2013; Okumura et al., 2014; Varotto et al., 2012). Successive studies have also found evidence of sensorimotor (Moritz et al., 2001; Schiff et al., 2005), visual (Monti, Pickard, & Owen, 2013; Moritz et al., 2001; Zhu et al., 2009), and linguistic processing (Bekinschtein et al., 2005; Fernandez-Espejo, Junque, Cruse, et al., 2010b; Fernandez-Espejo et al., 2008; Moritz et al., 2001; Owen et al., 2005; Schiff et al., 2005).

Several authors have stressed the need to carry out passive stimulation tasks hierarchically, starting with studying the simplest cognitive processes and progressively increasing their complexity (Laureys, Owen, & Schiff, 2004; Owen & Coleman, 2008a). Following this reasoning, Rodd and collaborators developed an auditory paradigm which proceeds from the basic acoustic processing of non-linguistic stimuli to semantic processing and linguistic comprehension (Rodd, Davis, & Johnsrude, 2005). In 2009, Coleman and colleagues used this paradigm in a group of 41 patients (22 VS, 19 MCS) (Coleman et al., 2009), revealing that 19 of them (7 VS 12 MCS) showed evidence of recognising linguistic stimuli (compared to other sounds) and 4 patients (2 VS, 2 MCS) showed evidence of linguistic comprehension, despite what might be inferred from their diagnosis. It is worth noting that the 7 patients in VS that showed linguistic responses in this paradigm progressed to MCS at 6 months, which suggests that the information obtained in fMRI tasks may have prognostic value. In fact, in a review of 15 studies published up to 2008 on fMRI and positron emission tomography in VS patients, Di and colleagues found that the presence of activation in association areas predicts a favourable outcome with 93% specificity and 69% sensitivity (Di, Boly, Weng, Ledoux, & Laureys, 2008). In a linguistic study similar to the previous one but carried out in Spain, it was also found that the only VS patient that showed linguistic responses in the fMRI (Fernandez-Espejo et al., 2008) had a favourable progression and regained consciousness one year after the initial injury (Fernandez-Espejo, Junque, Cruse, et al., 2010b).

The main advantage of passive fMRI paradigms is that they do not require the voluntary participation of the patient, so they can provide information about specific cognitive processes, regardless of the patient's ability or intention to collaborate. However, despite the fact that they can find cognitive functions contrary to diagnosis (e.g., linguistic comprehension), these types of paradigm do not allow us to make inferences about the state of consciousness of the patient. The only exception is the paradigm recently published by Naci and colleagues

(Naci, Cusack, Anello, & Owen, 2014), in which it was shown that when several people watch a movie (in this case a fragment of a short film by Hitchcock) their brain activity synchronises with that of the other spectators, and correlates with the film's executive demands. The same fragment was presented to a VS patient and it was shown that the patient's brain activity was highly correlated with those of the healthy volunteers, which was interpreted as evidence that the patient shared the conscious experience of the film with the healthy individuals.

Other attempts to overcome this limitation have been based on the use made in clinical practice of following simple commands (e.g., 'open your mouth', 'look at the ceiling', etc.) as definitive proof of consciousness (Giacino et al., 2004). With this idea in mind, active fMRI paradigms, in which the patient is asked, rather than to respond to these orders externally, to do so by voluntarily modulating their neuronal activity (Fernandez-Espejo & Owen, 2013). This approach is based on the fact that certain mental imagery tasks are associated with specific patterns of brain activation. Thus, the presence of these patterns can be used to determine that the patient followed the instructions and did the visualisation when asked to do so (Owen & Coleman, 2008b). Specifically, the paradigm that has proven most successful in identifying the following of orders in VS patients is based on motor imagery and spatial navigation. The patient is instructed to imagine moving their hand to hit a tennis ball repeatedly every time they hear the word 'tennis', or to imagine that they are going around the different rooms of their house and to try to visualise the objects that they would find every time they hear the word 'house' (Boly et al., 2007). In healthy volunteers, the two tasks elicit a very similar brain activation to that which would be obtained if the participant were actually moving his hand (supplementary motor area), or performing a spatial navigation task (parahippocampal cortex, posterior parietal lobe, and lateral premotor cortex) (Boly et al., 2007).

In 2006, Owen and colleagues used this task with a VS patient and found that the patient's brain activity was indistinguishable from that obtained with healthy volunteers, which showed that the patient was able to understand and follow instructions and therefore was not actually in a VS (Owen et al., 2006). Several subsequent studies have successfully used this paradigm to identify the following of orders in unresponsive patients (Fernandez-Espejo & Owen, 2013; Gibson et al., 2014; Monti et al., 2010). For example, Monti and colleagues studied a group of 23 VS patients and found evidence of following orders in 17% of them (Monti et al., 2010). What is even more important, one of these patients successfully managed to use activation in these two tasks (motor and spatial imagery) to communicate with the researchers; i.e., the patient used one type of visualisation to answer 'yes' and the other to answer 'no', and answered 5 autobiographical questions correctly (e.g., "Is your father's name Alexander?") (Monti et al., 2010). Recently, this technique allowed another patient, who had been in a VS for 12 years, to answer questions with important implications for his quality of life (e.g., whether he was suffering any pain) (Fernandez-Espejo & Owen, 2013). This patient also showed he knew the name of the person who had been his primary caregiver since the accident, whom he did not know before, showing that he was able to create memories of events that had occurred while he was diagnosed as being in a VS. Although so far this paradigm is only available in specialised research centres (Royal College of Physicians, 2013), it has been proven that it can be successfully performed on a clinical MRI scanner (Fernandez-Espejo, Norton, & Owen, 2014).

Other active tasks that have been applied to evaluate the following of orders in VS and MCS patients using fMRI include visualising motor activities such as swimming (Bardin et al., 2011; Forgacs et al., 2014), motor preparation (Bekinschtein, Manes, Villarreal, Owen, & Della-Maggiore, 2011), or attention directed to specific stimuli presented aurally (Monti et al., 2015; Naci & Owen, 2013; Naci, Cusack, Jia, & Owen, 2013), or visually (Hampshire et al., 2013; Monti et al., 2013). To date, the only one of these tasks that has been successfully used to communicate with patients in VS or MCS, is based on selective attention to the words 'yes' or 'no' (depending on the response) presented aurally (Naci & Owen, 2013).

Despite the great success of fMRI in this field, it is an expensive technique, it is not available in many hospitals, and it cannot be performed on patients with, for example, excessive agitation, certain metallic implants, or those who are unable to lie supine on a flat surface. Therefore, several research groups have developed active paradigms similar to the above, but based on the EEG (Coyle, Stow, McCreadie, McElligott, & Carroll, 2015; Cruse et al., 2011; Cruse, Chennu, Chatelle, et al., 2012a; Cruse, Chennu, Fernandez-Espejo, et al., 2012b; Gibson et al., 2014; Horki et al., 2014; Lulé et al., 2013; Pan et al., 2014; Schnakers et al., 2008). For example, Cruse and colleagues succeeded in identifying responses in two tasks of motor imagery (imagining that you close your hand and open it again, and imagining that you are moving your toes) in 19% of 16 VS patients (Cruse et al., 2011). This technique is portable, so the patient does not need to be transferred. The technique can be performed with the patient lying down or sitting up, and it has a much lower cost. However, to date, no patients in VS or MCS have managed to use EEG to communicate.

CONCLUSIONS

Three main conclusions can be drawn from the studies discussed here:

Firstly, the clinical assessment for the diagnosis of patients with disorders of consciousness should include the repeated administration of standardised scales by qualified personnel, to ensure the identification of subtle signs of consciousness that the patient is capable of displaying.

Secondly, structural MRI techniques have shown great potential for assisting in the diagnostic process through the objective identification of markers that enable us to differentiate between patients in VS and MCS. Their contribution is vital in cases where the clinical assessment does not provide a clear diagnosis, or when there is no team of experts available to evaluate the patient.

Finally, functional neuroimaging techniques (fMRI and EEG) are necessary in identifying covert cognitive functions, which some patients are not able to show externally. These functions can range from the basic processing of sensory stimuli to language comprehension, executive functions, or even the ability to follow simple orders in some cases. In fact, it is estimated that at least 17-19% of patients in VS are able to follow orders in fMRI or EEG tests, and therefore have been diagnosed incorrectly.

Achieving a correct diagnosis and appropriately identifying the cognitive abilities of the patient has profound clinical implications, but also ethical and moral ones (Weijer et al., 2014). Because of this, and given that to date these tests are only available as part of research studies, there is a need to share the findings from these studies with the medical staff responsible for the patient and the family. To this end, and in collaboration with professionals of bioethics, we researchers in this area have recently developed an ethical framework for the disclosure of information obtained in our studies (Graham et al., 2014).

On the other hand, the evidence gathered to date, and discussed in this article, advocates the urgent need to re-evaluate the existing diagnostic categories to include this new group of patients, who are still conscious, but completely non-responsive externally (Fernandez-Espejo & Owen, 2013). It also points to the need to incorporate into the routine assessment of patients with disorders of consciousness functional and structural neuroimaging tests such as the ones reviewed here. To make this possible, first progress must be made in adapting the tasks and acquisition protocols so they are compatible with the equipment normally available in nonspecialised clinical centres (e.g., less powerful MRI machines, limited equipment for presenting stimulation to the patient, etc.). This will facilitate access to a greater number of patients and the realisation of future studies of validation and standardisation of neuroimaging tests in large samples, so that they may be included in the clinical practice guidelines for the management of patients with disorders of consciousness.

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