JNNP Online First, published on July 2, 2015 as 10.1136/jnnp-2015-310958

REVIEW

Preserved consciousness in vegetative and minimal conscious states: systematic review and meta-analysis

Daniel Kondziella,[1,2] Christian K Friberg,[3] Vibe G Frokjaer,[4] Martin Fabricius,[3] Kirsten Møller[5]

▸ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jnnp-2015-310958).

[1]Department of Neurology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[2]Institute of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway
[3]Department of Clinical Neurophysiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark
[4]Neurobiology Research Unit, Copenhagen University Hospital and Center for Integrated Molecular Brain Imaging, Copenhagen, Denmark
[5]Department of Neuroanesthesiology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Correspondence to
Dr Daniel Kondziella, Department of Neurology, Rigshospitalet, Copenhagen University Hospital, Copenhagen DK-2100, Denmark; daniel_kondziella@yahoo.com

Received 31 March 2015
Revised 5 June 2015
Accepted 18 June 2015

ABSTRACT

Active, passive and resting state paradigms using functional MRI (fMRI) or EEG may reveal consciousness in the vegetative (VS) and the minimal conscious state (MCS). A meta-analysis was performed to assess the prevalence of preserved consciousness in VS and MCS as revealed by fMRI and EEG, including command following (active paradigms), cortical functional connectivity elicited by external stimuli (passive paradigms) and default mode networks (resting state). Studies were selected from multiple indexing databases until February 2015 and evaluated using the Quality Assessment of Diagnostic Accuracy Studies-2. 37 studies were identified, including 1041 patients (mean age 43 years, range 16–89; male/female 2.1:1; 39.5% traumatic brain injuries). MCS patients were more likely than VS patients to follow commands during active paradigms (32% vs 14%; OR 2.85 (95% CI 1.90 to 4.27; $p<0.0001$)) and to show preserved functional cortical connectivity during passive paradigms (55% vs 26%; OR 3.53 (95% CI 2.49 to 4.99; $p<0.0001$)). Passive paradigms suggested preserved consciousness more often than active paradigms (38% vs 24%; OR 1.98 (95% CI 1.54 to 2.54; $p<0.0001$)). Data on resting state paradigms were insufficient for statistical evaluation. In conclusion, active paradigms may underestimate the degree of consciousness as compared to passive paradigms. While MCS patients show signs of preserved consciousness more frequently in both paradigms, roughly 15% of patients with a clinical diagnosis of VS are able to follow commands by modifying their brain activity. However, there remain important limitations at the single-subject level; for example, patients from both categories may show command following despite negative passive paradigms.

INTRODUCTION

Probing consciousness in non-communicating patients by clinical examination is essential yet challenging. In patients with disorders of consciousness (DoC), the origin of many clinical signs is not entirely clear and their significance as to whether or not the patient is conscious is even less certain. Perhaps even more important is the fact that consciousness may wax and wane in the short term (seconds to hours) and long term (days to months). For instance, although visual pursuit suggests a minimally conscious state (MCS), it may only be elicited by certain powerful stimuli, for example, the patient's own eyes reflected by a mirror, and only in certain situations, for example, when the presence of relatives boosts arousal[1 2] (figure 1). Consequently, as many as 40% of non-communicating patients with DoC are erroneously classified as being in the vegetative state (VS).[3] This has significant ethical and practical implications for patients and their caregivers, including prognosis, treatment, resource allocation and end-of-life decisions.

Technologies based on functional MRI (fMRI) and EEG (including cognitive event-related potentials (ERPs)) have been developed during the past two decades to assist in the clinical evaluation of patients in VS and MCS. Although these patients may not show any signs of consciousness at the bedside because of lost motor output, some are able to wilfully modulate their brain activity on command, even answering yes or no questions by performing mental imagery tasks. This can be detected by fMRI and EEG paradigms.[4] There are three main approaches to test for preserved consciousness in patients with DoC: (1) active paradigms in which patients are required to execute cognitive tasks as outlined above, (2) passive paradigms relying on the documentation of preserved large-scale functional cortical connectivity, following an external stimulus, and (3) resting state conditions in which assumptions about the patient's conscious state are made by extrapolation from patterns of spontaneous brain activity, including (but not limited to) the default mode network.[5] Theoretically, whereas active paradigms of consciousness may suggest a higher degree of certainty, passive and resting state paradigms should also allow detection of signs of consciousness in patients who are not able to cooperate in cognitive tasks because of aphasia, neglect, executive dysfunction, major depression or deafness.

We performed a systematic review and meta-analysis of the literature in order to assess whether the clinical diagnosis (ie, VS vs MCS) is accurately reflected by the presence or absence of signs of consciousness as revealed by fMRI and/or EEG. To this end, we calculated ORs for command following (active paradigms), preserved cognitive ERPs or cortical activation (passive paradigms) and presence of a default mode network (resting state conditions). We hypothesised that active paradigms, despite their obvious benefits, may underestimate the degree of preserved consciousness in patients with DoC as compared to passive and resting state paradigms.

To cite: Kondziella D, Friberg CK, Frokjaer VG, *et al.* *J Neurol Neurosurg Psychiatry* Published Online First: [*please include* Day Month Year] doi:10.1136/jnnp-2015-310958

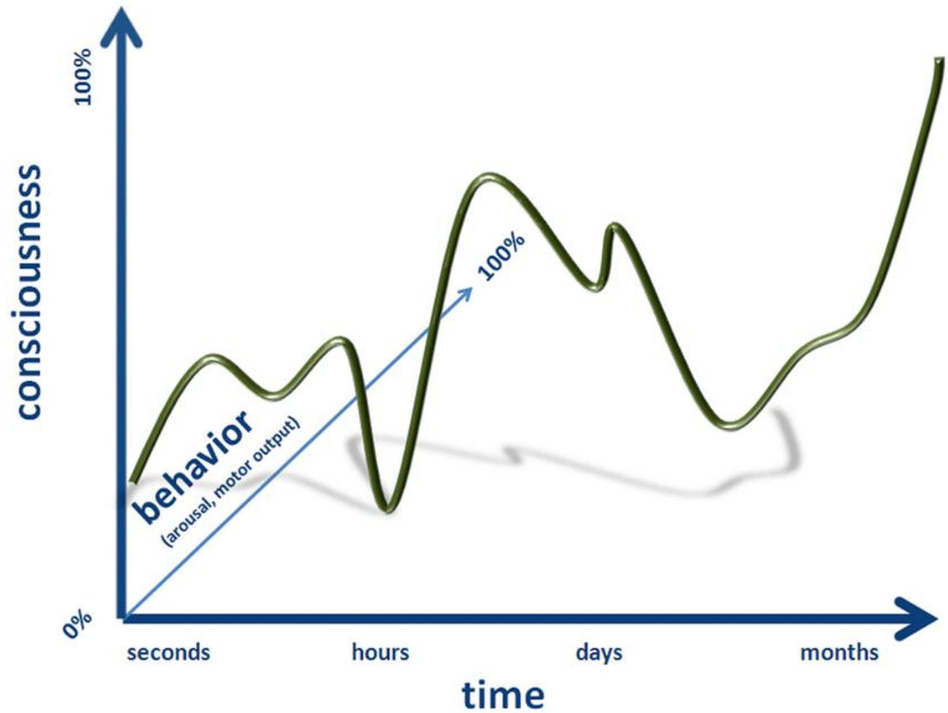

Figure 1 This figure depicts a 3D-model of consciousness in non-communicating patients, including those with a diagnosis of vegetative or minimal conscious states. The degree of consciousness typically fluctuates with time (x-axis) both in the short term (seconds to hours) and long term (days to months). The correct evaluation of consciousness (y-axis) depends on the patient's behaviour (z-axis), which is typically conceptualised as a product of arousal and motor output. Whereas clinical evaluation at the bedside is indeed critically reliant on measurable motor activity, active, passive and resting state paradigms also allow assessment of consciousness in patients who have lost all motor output. These paradigms, however, are still dependent on a sufficient degree of arousal.

METHODS

We performed a systematic review and meta-analysis using standardised methods. The review protocol can be accessed from the online supplementary files.

Primary and secondary objectives

Using the PICO approach (Patients, Intervention, Comparison, Outcomes),[6] we phrased the following primary research question: In unresponsive patients with DoC (P), does a clinical diagnosis of VS (I), as compared to MCS (C), indicate absence of or a lower level of consciousness as reflected by poorer performance in active paradigms and/or less preserved neuronal connectivity during passive or resting state conditions (O)?

In addition, we phrased a secondary research question:

In unresponsive patients with DoC (P), does testing of consciousness using passive paradigms and resting state conditions (I), as compared to active paradigms requiring patient cooperation (C), more frequently suggest preserved consciousness (O)?

Criteria for considering studies for this review

Types of studies

We included all cross-sectional or longitudinal, retrospective or prospective observational studies as well as interventional trials, reporting on active, passive and resting state paradigms of consciousness in patients diagnosed with VS or MCS. Notably, we included only original articles allowing assessment of patient data at the single-subject level. In order to reduce the influence of convenience sampling, studies with n <5 were excluded.

Participants

Adults (age ≥16 years) presenting in intensive care units, specialist units (ie, stroke units, neurological and neurosurgical departments), step-down units, rehabilitation facilities or nursing homes were included if they fulfilled the established criteria for VS or MCS (see below) and if they had been evaluated by active, passive and/or resting state paradigms of consciousness, comprising fMRI and/or EEG, at any time point following the acute injury (ie, at least 10 days after ictus).

Index tests

The index tests comprised fMRI and EEG used in active, passive or resting state paradigms of consciousness. In addition, we included studies on EEG in combination with transcranial electromagnetic stimulation (TMS). Notably, paradigms were only classified as 'active' if the authors explicitly made assumptions of whether or not patients had followed their instructions. For instance, instructions such as 'pay attention' or 'listen carefully' prior to auditory oddball tests were not regarded per se as indicating active paradigms. Further, papers focusing on structural MRI, MR spectroscopy, positron emission tomography, single-photon emission CT and/or magnetoencephalography were excluded. We also excluded studies assessing the EEG background reactivity or the presence of ERPs for wholly prognostic reasons (ie, if authors made assumptions about the clinical outcome but not the present conscious states of their patients). Recent theories of consciousness suggest that early ERPs correspond to unconscious processing stages, whereas late ERPs with a wide topographical cortical representation are associated with conscious processes.[7] Specifically, long-latency or 'cognitive' ERPs involving fronto-temporo-parietal connective pathways (such as P300, N400, P600 and late positive complex (LPC)) are regarded as EEG markers for neuronal conscious perception.[8 9] In addition, EEG complexity and the 'global' EEG response to external stimuli can be used as a substrate of conscious perception.[7 10–12] For the purpose of this study the mismatch negativity (MMN) was not regarded as late cognitive ERP and excluded from analysis, since MMN seems to reflect unconscious integration of the auditory environment.[10]

Target conditions

The target condition was defined as signs of preserved consciousness in patients with VS or MCS due to traumatic brain injury (TBI), cerebrovascular disorders (CVA; including

Kondziella D, *et al*. *J Neurol Neurosurg Psychiatry* 2015;**0**:1–8. doi:10.1136/jnnp-2015-310958

ischaemic and haemorrhagic stroke, subarachnoid haemorrhage and cerebral venous sinus thrombosis), anoxic-ischaemic encephalopathy (eg, due to cardiac arrest) and similar critical brain disorders. We applied the classical definition of consciousness as a "state of full awareness of the self and one's relationship to the environment".[13] The VS, or unresponsive wakefulness syndrome, is a condition of wakefulness without awareness.[14] Patients in this condition may open their eyes but exhibit only reflex behaviours and are therefore considered unaware of themselves and their surroundings. In contrast, patients in MCS show unequivocal signs of non-reflex behaviours occurring inconsistently, yet reproducibly, in response to environmental stimuli. By definition, although some may follow commands to a certain degree, accurate communication is not possible. VS and MCS most likely exist on a spectrum rather than being categorically distinct.[15 16] Thus, patients may be classified into MCS plus (ie, if they are able to obey commands) or minus (ie, if they only localise pain, exhibit visual pursuit or show appropriate emotional expressions).[17] Traditionally, VS has been considered permanent 3 months after non-traumatic injuries and 12 months following TBI, although late recovery is increasingly recognised.[14] Patients may evolve from VS into MCS (or better), and they may or may not relapse. It follows that signs of preserved consciousness can wax and wane. Therefore, we assessed if studies had employed serial testing of consciousness.

Reference standards

We considered clinical bedside evaluation for signs of consciousness using standardised scales as reference standards. Of these, the Coma Recovery Scale-Revised (CRS-R) is widely regarded as the most sensitive and specific instrument.[18]

Search methods for identification of studies

Electronic searches

We searched the following databases for relevant literature from 1 January 1990 to 28 February 2015: Cochrane Central Register of Controlled Trials (Cochrane Library), Medline (PubMed), and clinicaltrials.gov. The search terms are listed in the review protocol (see online supplementary files). The references of relevant articles were manually searched to identify additional articles. Papers were cross-referenced using the 'cited by' function on PubMed.

Data collection and analysis

Selection of studies, data extraction and management

Titles were reviewed first, followed by evaluation of the abstracts with titles suggesting that a study was of relevance. Eligible studies were identified on the basis of their full text. The initial selection was undertaken by one author (DK), whereas quality assessment and data extraction were performed blinded by two assessors (DK, CKF). The review was reported following the PRISMA criteria (see online supplementary files).[19]

Assessment of methodological quality

Using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2), a recent modified version of QUADAS,[20] two of the authors (DK, CKF) independently assessed the methodological quality of each included study. QUADAS-2 comprises four domains: (1) participant selection, (2) index test, (3) reference standard and (4) flow of participants through the study and timing of the index tests and reference standard (flow and timing). Each domain is assessed for risk of bias, and the first three domains are also assessed for concerns regarding applicability. Risk of bias and concerns about applicability are judged as 'low', 'high' or 'unclear'. See online supplementary files for details. Disagreement between the two reviewing authors was resolved by consensus or an independent referee (MF) if required.

Statistical analysis and data synthesis

We conducted a meta-analysis on the available numerical data by calculating ORs and CI for patients in VS or MCS for command following (active paradigms), cortical connectivity (passive paradigms) and presence of an intact default mode network (resting state conditions), using standardised statistical methods. We considered a p value below 0.05 as statistically significant.

RESULTS

Systematic literature search and quality assessment

The initial literature search yielded 718 citations. We included 44 original publications for meta-analysis, reporting on 37 studies.[7 9–11 15 21–55 12 56–58] For a flow diagram of the literature review, the reader is referred to online supplementary figure S1. The majority of studies were prospective single-centre case series in which active and/or passive paradigms were used to assess consciousness at one given time point; hence, systematic serial or continuous testing of all included patients was not performed. Only eight studies (22%) included (infrequently) repeated testing sessions, and just one study employed systematic serial assessments in a limited number of patients (12 patients, twice a day, morning and afternoon, for 2 days[30]). Roughly one half of all publications reported on fMRI-based paradigms and the other half on EEG-based paradigms. Just two papers on resting state paradigms allowed extrapolation of data at the single subject level and were deemed suitable for inclusion. See tables 1 and 2 and online supplementary tables S1 and S2 for details.

Using QUADAS-2, we found that most studies were affected by a rather high risk of bias related to patient selection, index test and the flow and timing of patient evaluation. In contrast, there were no or only a few concerns regarding applicability (figure 2). See online supplementary files for detailed results.

Patient population

We identified eligible data on 1041 patients (mean age 43 years, range 16–89 years; 68% males). Of these, 54.1% were clinically classified as VS and 45.9% as MCS. The most common diagnosis was TBI (39.5%), followed by CVA (25%) and anoxia (25%). A minority of patients (10.5%) were diagnosed with a large variety of different disorders; including CNS malignancy, autoimmune encephalitis, metabolic encephalopathy, fat embolism and neurodegenerative disease (tables 1 and 2; and online supplementary tables S1 and S2).

Active, passive and resting state paradigms

Compared to patients with a clinical diagnosis of VS, MCS patients were more likely to follow commands during active paradigms (32% vs 14%; OR 2.85 (95% CI 1.90 to 4.27; $p<0.0001$)) and to show preserved cortical connectivity during passive paradigms (55% vs 26%; OR 3.53 (95% CI 2.49 to 4.99; $p<0.0001$)). Data on resting state paradigms were deemed insufficient for statistical evaluation due to low numbers.

Passive paradigms were more often compatible with signs of preserved consciousness than active paradigms (38% vs 24%; OR 1.98 (95% CI 1.54 to 2.54; $p<0.0001$)). EEG-based and

Table 1 This table shows results from a systematic review of studies on active paradigms of consciousness testing in VS and MCS (n≥20 patients)

Source	Site	Modality	Design	Clinical rating	Serial testing	Task	N (VS, MCS)	Aetiology TBI, CVA, anoxia, other	Command following
Bekinschtein *et al*[56]	Buenos Aires, Argentina	fMRI	Single (p)	CRS-R	No	Motor imaginary	24 (24, 0	ns	2/24 VS
Monti *et al*[34]	Cambridge, UK	fMRI	Single (p)	CRS-R	No	Speech	24 (8, 16)	16 TBI, 12 non-TBI	3/8 VS; 6/16 MCS
Monti *et al*[21]	Cambridge, UK; Liège, Belgium	fMRI	2 centres (p)	CRS-R	No	Motor, spatial imagery	54 (23, 31)	32, 3, 15, 4	2/23 VS, 3/31 MCS
Stender *et al*[33]	Liège, Belgium	fMRI	Single (p)	CRS-R	No	Motor, spatial imagery	70 (28, 42)	ns	3/28 VS, 19/42 MCS
Chennu *et al*[53 54]	Cambridge, UK	fMRI	Single (p)	CRS-R	No	Motor imaginary	32 (13, 19)	23, 0, 9, 0	4/13 VS, 11/19 MCS
Forgacs *et al*[43]	New York, New York, USA	fMRI	Single (p)	CRS-R	Limited	Motor, spatial imagery	20 (6, 14)	13, 3, 3, 1	0/6 VS, 3/14 MCS
Cruse *et al*[48 49]	Cambridge, UK; Liège, Belgium	EEG	2 centres (p)	CRS-R	No	Motor imaginary	39 (16, 23)	20 TBI, 19 non-TBI	3/16 VS, 5/23 MCS
Faugeras *et al*[7 11]	Paris, France	EEG	Single (p)	CRS-R	Limited	Auditory (local-global)	41 (22, 19)	11, 14, 17, 7	2/22 VS, 4/19 MCS
King *et al*[39 40]	Paris, France	EEG	Single (p)	CRS-R	Limited	Auditory (local-global)	95 (56, 39)	20, 33, 30, 21	9/56 VS, 9/39 MCS
Kotchoubey *et al*[37]	Tübingen, DE	EEG	Single (p)	DRS	No	Speech	88 (50, 38)	31, 27, 27, 3	11/50 VS, 10/38 MCS
Rohaut *et al*[27]	Paris, France	EEG	Single (p)	CRS-R	No	Auditory (local-global)	29 (15, 14)	7, 9, 8, 5	0/15 VS, 5/14 MCS
Schnakers *et al*[28]	Liège, Belgium	EEG	Single (p)	CRS-R	No	Speech	22 (8, 14)	10, 2, 8, 2	0/8 VS, 9/14 MCS

For studies with n<20, please see online supplementary table S1.
CRS-R, Coma Recovery Scale-Revised; CVA, cerebrovascular accident (including cerebral infarction, parenchymal haemorrhage, subarachnoid bleeding); ns—not specified; DRS, Disability Rating Scale; fMRI, functional MRI; MCS, minimal conscious state; P, prospective; TBI, traumatic brain injury; VS, vegetative state.

Table 2 This table shows results from a systematic review of studies on passive and resting state paradigms of consciousness testing in VS and MCS (n≥20 patients)

Source	Site	Modality	Design	Clinical rating	Serial testing	Paradigm	N (VS, MCS)	Aetiology TBI, CVA, anoxia, other	Cortical connectivity
Bekinschtein *et al*[56]	Buenos Aires, Argentina	fMRI	Single (p)	CRS-R	No	Speech	24 (24, 0)	5 TBI, 19 non-TBI	5/24 VS
Coleman *et al*[51 52]	Cambridge, UK	fMRI	Single (p)	CRS-R	No	Speech	41 (22, 19)	26, 4, 11, 0	2/22 VS, 2/19 MCS
Crone *et al*[50]	Salzburg, Austria	fMRI	Single (p)	CRS-R	No	Speech	25 (17, 8)	12, 0, 13, 0	6/17 VS, 2/8 MCS
Chennu *et al*[53]	Cambridge, UK	EEG	Single (p)	CRS-R	No	Speech	21 (9, 12)	7, 0, 4, 0	1/9 VS, 3/12 MCS
Boly *et al*[9]	Liège, Belgium	EEG	Single (p)	CRS-R	No	Auditory	21 (8, 13)	7, 7, 7, 0	1/8 VS, 4/13 MCS
Fischer *et al*[44]	Lyon, France	EEG	Single (p)	CRS-R	No	Speech	27 (16, 11)	4, 4, 18, 1	3/16 VS, 4/11 MCS
Kotchoubey *et al*[37]	Tübingen, DE	EEG	Single (p)	DRS	No	Auditory	88 (50, 38)	31, 27, 27, 3	16/50 VS, 14/38 MCS
Rohaut *et al*[27]	Paris, France	EEG	Single (p)	CRS-R	No	Speech	29 (15, 14)	7, 9, 8, 5	2/15 VS, 7/14 MCS
Schnakers *et al*[28]	Liège, Belgium	EEG	Single (p)	CRS-R	No	Speech	22 (8, 14)	10, 2, 8, 2	VS 0/8, MCS 14/14
Schoenle and Witzke[29]	Magdeburg, DE	EEG	Single (p)	Author's definition	No	Speech	66 (43, 23)	28, 21, 17, 0	5/43 VS, 18/23 MCS
Sitt *et al*[31]	Paris, France	EEG	Single (r)	CRS-R	Limited	Auditory (local-global)	100 (59, 41)	24, 35, 24, 17	20/59, 31/41
Demertzi *et al*[46]	Liège, Belgium	fMRI	Single (p)	CRS-R	No	Resting state	48 (24, 24)	21, 13, 12, 2	9/24 VS, 9/24 MCS (DMN)

For studies with n<20, please see online supplementary table S1.
CRS-R, Coma Recovery Scale-Revised; CVA, cerebrovascular accident (including cerebral infarction, parenchymal haemorrhage, subarachnoid bleeding); DMN, default mode network; DRS, Disability Rating Scale; fMRI, functional MRI; MCS, minimal conscious state; ns, not specified; p, prospective; r, retrospective; TBI, traumatic brain injury; VS, vegetative state.

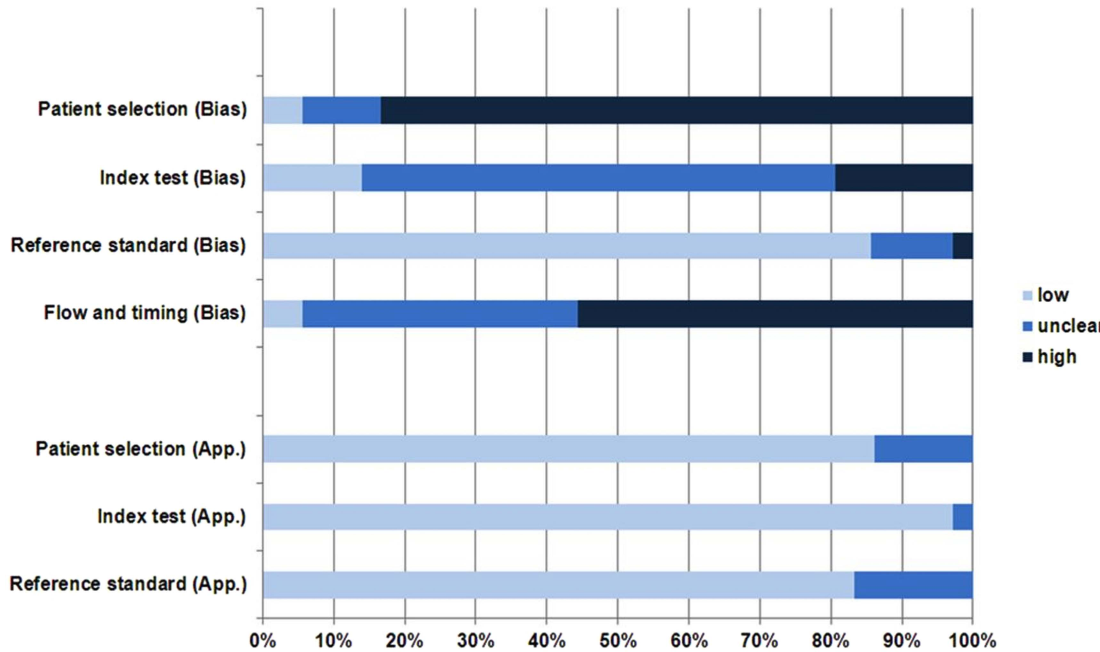

Figure 2 Graphic overview of the systematic evaluation with respect to risk of bias and concerns of applicability of 37 original studies on active, passive and resting state consciousness paradigms using QUADAS-2, a revised tool for the Quality Assessment of Diagnostic Accuracy Studies.[20] A high risk of bias is noted for the majority of studies, in particular concerning the selection of patients and the flow and timing of their evaluations, whereas few or no concerns are seen with respect to applicability. See the Methods section and online supplementary files for details. App., applicability.

fMRI-based active paradigms were not significantly different in terms of command following, but EEG-based evaluation was more likely to reveal cognitive ERPs than fMRI to show cortical activation during passive paradigms (40% vs 28%; OR 1.78; (95% CI 1.16 to 2.74; p=0.008)). Results are depicted in table 3.

TBI versus non-traumatic aetiologies

Twenty-seven studies allowed assessment at the single subject level with respect to evaluation of consciousness paradigms according to DoC aetiology (traumatic vs non-traumatic; n=657). Compared to patients with non-traumatic disorders, patients with TBI were significantly more likely to follow commands on active paradigms (32% vs 19%; OR 2.00 (95% CI 1.44 to 3.50; p=0.015)). There was no statistically significant difference regarding passive paradigms (33% vs 36%; OR 0.86 (95% CI 0.56 to 1.32; p=0.495).

DISCUSSION

Detecting consciousness in non-communicating patients by clinical examination requires that patients are awake, that they possess the voluntary drive to mobilise motor function, that this motor function is preserved to a degree that is readily measurable, and that all these requirements are fulfilled at the time of examination. In contrast, EEG-based and fMRI-based paradigms also allow the assessment of consciousness in patients who have lost their motor output. In this meta-analysis, the first of its kind, we assessed the frequency of preserved consciousness in patients with a clinical diagnosis of VS or MCS as revealed by fMRI and EEG.

Active and passive paradigms

Of 292 patients with a clinical diagnosis of VS, 42 (14.4%) were able to wilfully modify their brain activity on demand, strongly suggesting that they were fully conscious. This figure might be an overestimate, given that the majority of included studies were single centre convenience samples. However, Bekinschtein *et al*[56] assessed 24 consecutively admitted VS patients and found 2 patients (8.3%) with command following during an fMRI motor imaginary task; it therefore seems reasonable to assume that the true incidence of consciousness in patients fulfilling the clinical criteria for VS, as detected by active paradigms, is between 5% and 15%. Extrapolating from the present analysis, the incidence of command following in MCS patients is probably 2–3 times as high. Most MCS patients are therefore *not* able to sufficiently participate in active consciousness paradigms despite unambiguous bedside signs of non-reflex, intentional behaviour. It follows that, in line with our primary research hypothesis, active paradigms have the advantage of high specificity (ie, command following as revealed by EEG or fMRI represents evidence of conscious understanding and an appropriate mental response), but they appear not to be very sensitive. This is corroborated by the two times greater likelihood of passive paradigms yielding results compatible with preserved consciousness as compared to active paradigms. Of course, it is reasonable to assume that false positive results can occur with passive paradigms, but at present their frequency is unknown. However, serial assessments, although rarely performed, may increase the diagnostic yield and reveal signs of consciousness in passive and active paradigms in patients who initially are without such signs.[11 15 25 40]

In the absence of a gold standard for consciousness, precise estimates of the sensitivity and specificity of active and passive paradigms are futile. It is noteworthy, however, that in active paradigms EEG-based and fMRI-based technologies yielded positive results with similar frequency, whereas in passive paradigms, EEG protocols were nearly two times more likely to be interpreted as compatible with preserved consciousness than

Table 3 Results are listed from a meta-analysis of 37 studies on active, passive and resting state paradigms of consciousness testing in VS and MCS, comprising 1041 patients

Active paradigms

	Command following	No command following	Total	Per cent		Command following	No command following	Total	Per cent
VS	42	250	292	14.4%	fMRI	66	180	246	26.8%
MCS	98	205	303	32.0%	EEG	74	275	349	21.2%
			595					595	
MCS vs VS: OR 2.85 (95% CI 1.9 to 4.27; p<0.0001)*					EEG vs fMRI: OR 0.73 (95% CI 0.50 to 1.07; p=0.112)				

Passive paradigms

	Cortical connectivity	No cortical connectivity	Total	Per cent		Cortical connectivity	No cortical connectivity	Total	Per cent
VS	91	261	352	25.6%	fMRI	35	92	127	27.6%
MCS	134	109	243	55.1%	EEG	192	283	475	40.4%
			595					602	
MCS vs VS: OR (3.53; 95% CI 2.49 to 4.99; p<0.0001)*					EEG vs fMRI: OR (1.78; 95% CI 1.16 to 2.74; p=0.008)*				

Resting state paradigms (fMRI)

	DMN preserved	DMN not preserved	Total	Per cent
VS	9	23	32	28.1%
MCS	10	15	25	40.0%
			57	
MCS vs VS: OR 1.70 (95% CI 0.56 to 5.17) p=0.35				

Active versus passive paradigms

	Signs of consciousness	No signs of consciousness	Total	Per cent
Active	140	455	595	23.5%
Passive	225	370	595	37.8%
			1190	
Passive vs active: OR 1.98 (95% CI 1.54 to 2.54; p<0.0001)*				

For details, please see Methods and Results sections.
*Statistically significant.
DMN, default mode network; fMRI, functional MRI; MCS, minimal conscious state; VS, vegetative state.

fMRI studies. As to EEG paradigms, the wider the topographical distribution and the longer the latency of an ERP, the more likely it is to represent a conscious response to an external stimulus.[7 8] In analogy to the clinical definition of MCS,[15–17] this is most likely a matter of gradual function (rather than all or none). Late and spatially distributed ERPs include P300, N400, P600 and LPC, and these most likely represent EEG markers for conscious perception.[8 9] In addition, EEG complexity suggestive of large-scale cortical neuronal connectivity represents a substrate of consciousness.[7 10 11] A promising new development in this regard is the perturbational complexity index (PCI). By measuring the complexity of the brain's response to TMS, the PCI reflects the amount of information (spectral content of brain signals) and the integration of the overall corticothalamic system output (spatial extent of brain activations).[12] In the present review, however, the majority of EEG studies involved a P300 response which is the earliest and least widely distributed cognitive ERP. Excluding P300 from our analysis would obviously have increased specificity but at the expense of decreased sensitivity. It follows that EEG-based and fMRI-based technologies, at least in passive paradigms, are not interchangeable but rather complementary. EEG allows consciousness to be monitored in real time and, at least in theory, continuously; in that respect, EEG monitoring may better reflect the fluctuating states of VS and MCS patients than a single fMRI scan. Ideally, however, consciousness in these patients should be assessed serially using both techniques. Standardised clinical rating scales, such as the CRS-R, and EEG-based and fMRI-based technologies could then be integrated into a composite reference standard.[59]

Although it appears that enough evidence has emerged for EEG-based and fMRI-based consciousness paradigms to be recommended for clinical implementation, there remain several important caveats at the single-subject level. As to clinical aspects, we noted that patients believed to be in VS may show command following, whereas MCS patients may not; patients from both categories may follow commands even though passive paradigms are negative;[53] and VS patients with initially preserved cognitive ERPs or command following may progress clinically to MCS but subsequently fail to show ERPs or command following during serial testing.[40] In addition, and of special concern, healthy volunteers may not necessarily be able to cooperate in active paradigms; for instance, in one study, only 9 (75%) of 12 healthy controls produced EEG data that could be classified significantly above chance.[48] As to EEG-based paradigms, it seems important to be aware that the absence of some ERPs does not exclude the presence of others;[47] that the latency of ERPs can be increased and their amplitude decreased;[28] and that serial ERP testing may reveal inconsistent results.[30] Notably, the stability of auditory information processing in VS and MCS patients, for example, as indicated by a preserved P300 response, is the prerequisite for other even more demanding tasks and cognitive potentials.[30] EEG may be prone to movement and electromyographic artefacts, but postprocessing often allows removal of these artefacts, leaving the underlying EEG intact.[60] As to fMRI-based paradigms, pattern classification of the blood oxygenation level-dependent (BOLD) response during mental imagery may yield positive results more often than traditional general linear model-based univariate analysis methods.[57] fMRI is also subject to movement artefacts but, unlike EEG, patient movements of even a few millimetres can make an entire data set useless.[60]

Resting state paradigms

The default mode network is believed to reflect non-goal oriented cognitive processes (or mind-wandering) and to implicate self-referential thoughts, for example, autobiographic memory.[61] Somewhat surprisingly, we identified only two studies on resting state paradigms that allowed evaluation of data at the single-subject level.[32 46] A recent systematic review and meta-analysis on resting state paradigms in patients with DoC assessed a total of 36 studies.[62] However, the included studies referred exclusively to group level data and were insufficient to allow assumptions about whether the clinical diagnosis (ie, VS vs MCA) was correctly reflected by these activity patterns or not. It follows that resting state paradigms of consciousness, in contrast to the active and passive paradigms which we have analysed in the present paper, are not yet well established to extrapolate information about the presence of consciousness in individual patients. It should be further noted that classical resting state conditions are largely uncontrolled stimulation conditions and therefore susceptible to confounding effects such as drowsiness. Also, when assessing resting-state connectivity in non-communicating patients, it is especially important to ensure motion artefact removal and spatial normalisation in order to prevent non-neuronal signal contributions due to head motion, respiration or cardiac artefacts. In addition, the two main approaches employed in the analysis of resting state functional connectivity data (ie, data-driven independent component analysis as opposed to hypothesis-driven seed-voxel) present multiple methodological difficulties, in particular in non-collaborative VS and MCS patients.[32 46 63 64] Previous work has shown that patients with DoC evaluated by resting state fMRI exhibit reduced activity within midline cortical and subcortical sites linked to the default-mode network.[62] Future studies must examine the relation between activation (and deactivation) within these structures and their significance for the emergence of conscious awareness in non-communicating patients both at the group and single patient levels.

Systematic literature quality assessment

Using QUADAS-2, a quality assessment tool designed specifically for diagnostic accuracy studies, we found that the literature on consciousness paradigms in non-communicating patients with DoC is subject to a relatively high risk of bias. This was mainly related to the selection of patients and methodology. Most studies were single-centre case series using convenience sampling, often without a clear statement about the number of excluded patients and the reasons for their exclusion (eg, due to logistic reasons), and patient numbers were in general low. Concerns about the index test were mainly related to the lack of blinding of the examiners with respect to the reference standard (ie, clinical evaluation). In addition, the flow and timing of the study might have introduced bias because time intervals between reference standards and index tests were not always clearly stated and because serial testing was not performed in the majority of studies. In contrast, there were no or very few concerns about the reference standard since the vast majority of studies used the CRS-R, the most robust clinical scale for the assessment of DoC.[18] Likewise, there were no or only a few concerns regarding applicability; hence, the conduct and interpretation of the index tests in the identified studies were in line with our review question.

CONCLUSIONS

Active paradigms may underrate the degree of consciousness as compared to passive paradigms, but the former have the advantage of greater specificity. While MCS patients are more likely to show signs of preserved consciousness in both paradigms, a significant number of patients with a clinical diagnosis of VS can modify their brain activity on command, strongly supporting the notion that these patients are indeed conscious. Further, patients with TBI seem more likely to follow commands on active paradigms than their counterparts with non-traumatic disorders, probably reflecting the greater potential for preserved cognition because of trauma as compared to cardiac arrest and other non-traumatic causes.[65] Nonetheless, there remain significant limitations at the single-subject level. Unresolved dilemmas further include the lack of a gold standard for consciousness, and hence, at the present moment it is impossible to precisely estimate the sensitivity and specificity of EEG-based and fMRI-based technologies for the evaluation of consciousness. Large-scale systematic multicentre studies are needed to assess the robustness of active, passive and resting state paradigms in evaluating consciousness in individual patients. Notably, repeated probing is of the essence because consciousness fluctuates with time.

Contributors DK was involved in the study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content. CKF, VGF MF KM were involved in the acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Di H, Nie Y, Hu X, *et al*. Assessment of visual fixation in vegetative and minimally conscious states. *BMC Neurol* 2014;14:147.
2 Rohaut B, Faugeras F, Naccache L. Neurology of consciousness impairments. In: Stevens RD, Sharshar T, Ely EW, eds. *Brain disorders in critical illness*. New York, NY: Cambridge University Press, 2013:59–67.
3 Schnakers C, Vanhaudenhuyse A, Giacino J, *et al*. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. *BMC Neurol* 2009;9:35.
4 Naci L, Owen AM. Making every word count for nonresponsive patients. *JAMA Neurol* 2013;70:1235–41.
5 Vanhaudenhuyse A, Noirhomme Q, Tshibanda LJ, *et al*. Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. *Brain* 2010;133:161–71.
6 Schardt C, Adams MB, Owens T, *et al*. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med Inform Decis Mak* 2007;7:16.
7 Faugeras F, Rohaut B, Weiss N, *et al*. Probing consciousness with event-related potentials in the vegetative state. *Neurology* 2011;77:264–8.
8 Vanhaudenhuyse A, Laureys S, Perrin F. Cognitive event-related potentials in comatose and post-comatose states. *Neurocrit Care* 2008;8:262–70.
9 Boly M, Garrido MI, Gosseries O, *et al*. Preserved feedforward but impaired top-down processes in the vegetative state. *Science* 2011;332:858–62.
10 Bekinschtein TA, Dehaene S, Rohaut B, *et al*. Neural signature of the conscious processing of auditory regularities. *Proc Natl Acad Sci USA* 2009;106:1672–7.
11 Faugeras F, Rohaut B, Weiss N, *et al*. Event related potentials elicited by violations of auditory regularities in patients with impaired consciousness. *Neuropsychologia* 2012;50:403–18.
12 Casali AG, Gosseries O, Rosanova M, *et al*. A theoretically based index of consciousness independent of sensory processing and behavior. *Sci Transl Med* 2013;5:198ra105.
13 Posner J, Plum F, Saper C. *Plum and Posner's diagnosis of stupor and coma*. New York, NY: Oxford University Press, 2007.
14 Laureys S, Celesia GG, Cohadon F, *et al*. Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. *BMC Med* 2010;8:68.
15 Rosanova M, Gosseries O, Casarotto S, *et al*. Recovery of cortical effective connectivity and recovery of consciousness in vegetative patients. *Brain* 2012;135:1308–20.
16 Liberati G, Hünefeldt T, Olivetti Belardinelli M. Questioning the dichotomy between vegetative state and minimally conscious state: a review of the statistical evidence. *Front Hum Neurosci* 2014;8:865.
17 Bruno MA, Vanhaudenhuyse A, Thibaut A, *et al*. From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness. *J Neurol* 2011;258:1373–84.
18 Gerrard P, Zafonte R, Giacino JT. Coma Recovery Scale-Revised: evidentiary support for hierarchical grading of level of consciousness. *Arch Phys Med Rehabil* 2014;95:2335–41.
19 Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions:

explanation and elaboration. *BMJ* 2009;339:b2700. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2714672&tool=pmcentrez&rendertype=abstract (accessed 4 Feb 2015).
20 Whiting PF, Rutjes AW, Westwood ME, *et al*. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155:529–36.
21 Monti MM, Vanhaudenhuyse A, Coleman MR, *et al*. Willful modulation of brain activity in disorders of consciousness. *N Engl J Med* 2010;362:579–89.
22 Okumura Y, Asano Y, Takenaka S, *et al*. Brain activation by music in patients in a vegetative or minimally conscious state following diffuse brain injury. *Brain Inj* 2014;9052:1–7.
23 Perrin F, Schnakers C, Schabus M, *et al*. Brain response to one's own name in vegetative state, minimally conscious state, and locked-in syndrome. *Arch Neurol* 2006;63:562–9. http://archpedi.jamanetwork.com/article.aspx?articleid=791093 (accessed 6 Jan 2015).
24 Ragazzoni A, Pirulli C, Veniero D, *et al*. Vegetative versus minimally conscious states: a study using TMS-EEG, sensory and event-related potentials. *PLoS ONE* 2013;8:e57069.
25 Risetti M, Formisano R, Toppi J, *et al*. On ERPs detection in disorders of consciousness rehabilitation. *Front Hum Neurosci* 2013;7:775.
26 Rodriguez Moreno D, Schiff ND, Giacino J, *et al*. A network approach to assessing cognition in disorders of consciousness. *Neurology* 2010;75:1871–8.
27 Rohaut B, Faugeras F, Chausson N, *et al*. Probing ERP correlates of verbal semantic processing in patients with impaired consciousness. *Neuropsychologia* 2015;66:279–92.
28 Schnakers C, Perrin F, Schabus M, *et al*. Voluntary brain processing in disorders of consciousness. *Neurology* 2008;71:1614–20.
29 Schoenle PW, Witzke W. How vegetative is the vegetative state? Preserved semantic processing in VS patients–evidence from N 400 event-related potentials. *Neuro Rehabilitation* 2004;19:329–34. http://www.ncbi.nlm.nih.gov/pubmed/15671587 (accessed 6 Dec 2014).
30 Schorr B, Schlee W, Arndt M, *et al*. Stability of auditory event-related potentials in coma research. *J Neurol* 2014;262:307–15.
31 Sitt JD, King JR, El Karoui I, *et al*. Large scale screening of neural signatures of consciousness in patients in a vegetative or minimally conscious state. *Brain* 2014;137:2258–70.
32 Soddu A, Vanhaudenhuyse A, Bahri MA, *et al*. Identifying the default-mode component in spatial IC analyses of patients with disorders of consciousness. *Hum Brain Mapp* 2012;33:778–96.
33 Stender J, Gosseries O, Bruno MA, *et al*. Diagnostic precision of PET imaging and functional MRI in disorders of consciousness: a clinical validation study. *Lancet* 2014;384:514–22.
34 Monti MM, Rosenberg M, Finoia P, *et al*. Thalamo-frontal connectivity mediates top-down cognitive functions in disorders of consciousness. *Neurology* 2015;84:167–73.
35 Manganotti P, Formaggio E, Storti SF, *et al*. Effect of high-frequency repetitive transcranial magnetic stimulation on brain excitability in severely brain-injured patients in minimally conscious or vegetative state. *Brain Stimul* 2013;6:913–21.
36 Lulé D, Noirhomme Q, Kleih SC, *et al*. Probing command following in patients with disorders of consciousness using a brain-computer interface. *Clin Neurophysiol* 2013;124:101–6.
37 Kotchoubey B, Lang S, Mezger G, *et al*. Information processing in severe disorders of consciousness: vegetative state and minimally conscious state. *Clin Neurophysiol* 2005;116:2441–53.
38 Kremer S, Nicolas-Ong C, Schunck T, *et al*. Usefulness of functional MRI associated with PET scan and evoked potentials in the evaluation of brain functions after severe brain injury: preliminary results. *J Neuroradiol* 2010;37:159–66.
39 King JR, Sitt JD, Faugeras F, *et al*. Information sharing in the brain indexes consciousness in noncommunicative patients. *Curr Biol* 2013;23:1914–9.
40 King JR, Faugeras F, Gramfort A, *et al*. Single-trial decoding of auditory novelty responses facilitates the detection of residual consciousness. *Neuroimage* 2013;83:726–38.
41 Huang Z, Dai R, Wu X, *et al*. The self and its resting state in consciousness: an investigation of the vegetative state. *Hum Brain Mapp* 2014;35:1997–2008.
42 Heelmann V, Lippert-Grüner M, Rommel T, *et al*. Abnormal functional MRI BOLD contrast in the vegetative state after severe traumatic brain injury. *Int J Rehabil Res* 2010;33:151–7.
43 Forgacs PB, Conte MM, Fridman EA, *et al*. Preservation of electroencephalographic organization in patients with impaired consciousness and imaging-based evidence of command-following. *Ann Neurol* 2014;76:869–79.
44 Fischer C, Luaute J, Morlet D. Event-related potentials (MMN and novelty P3) in permanent vegetative or minimally conscious states. *Clin Neurophysiol* 2010;121:1032–42.
45 Fernández-Espejo D, Junqué C, Vendrell P, *et al*. Cerebral response to speech in vegetative and minimally conscious states after traumatic brain injury. *Brain Inj* 2008;22:882–90.
46 Demertzi A, Gómez F, Crone JS, *et al*. Multiple fMRI system-level baseline connectivity is disrupted in patients with consciousness alterations. *Cortex* 2014;52:35–46.
47 De Tommaso M, Navarro J, Ricci K, *et al*. Pain in prolonged disorders of consciousness: laser evoked potentials findings in patients with vegetative and minimally conscious states. *Brain Inj* 2013;27:962–72.
48 Cruse D, Chennu S, Chatelle C, *et al*. Bedside detection of awareness in the vegetative state: a cohort study. *Lancet* 2011;378:2088–94.
49 Cruse D, Chennu S, Chatelle C, *et al*. Relationship between etiology and covert cognition in the minimally conscious state. *Neurology* 2012;78:816–22.
50 Crone JS, Ladurner G, Höller Y, *et al*. Deactivation of the default mode network as a marker of impaired consciousness: an fMRI study. *PLoS One* 2011;6:e26373.
51 Coleman MR, Rodd JM, Davis MH, *et al*. Do vegetative patients retain aspects of language comprehension? Evidence from fMRI. *Brain* 2007;130:2494–507.
52 Coleman MR, Davis MH, Rodd JM, *et al*. Towards the routine use of brain imaging to aid the clinical diagnosis of disorders of consciousness. *Brain* 2009;132:2541–52.
53 Chennu S, Finoia P, Kamau E, *et al*. Dissociable endogenous and exogenous attention in disorders of consciousness. *NeuroImage Clin* 2013;3:450–61.
54 Chennu S, Finoia P, Kamau E, *et al*. Spectral signatures of reorganised brain networks in disorders of consciousness. *PLoS Comput Biol* 2014;10:e1003887.
55 Cavinato M, Volpato C, Silvoni S, *et al*. Event-related brain potential modulation in patients with severe brain damage. *Clin Neurophysiol* 2011;122:719–24.
56 Bekinschtein TA, Manes FF, Villarreal M, *et al*. Functional imaging reveals movement preparatory activity in the vegetative state. *Front Hum Neurosci* 2011;5:5.
57 Bardin JC, Schiff ND, Voss HU. Pattern classification of volitional functional magnetic resonance imaging responses in patients with severe brain injury. *Arch Neurol* 2012;69:176–81.
58 Bardin JC, Fins JJ, Katz DI, *et al*. Dissociations between behavioural and functional magnetic resonance imaging-based evaluations of cognitive function after brain injury. *Brain* 2011;134:769–82.
59 Reitsma JB, Rutjes AW, Khan KS, *et al*. A review of solutions for diagnostic accuracy studies with an imperfect or missing reference standard. *J Clin Epidemiol* 2009;62:797–806.
60 Harrison AH, Connolly JF. Finding a way in: a review and practical evaluation of fMRI and EEG for detection and assessment in disorders of consciousness. *Neurosci Biobehav Rev* 2013;37:1403–19.
61 Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci* 2008;1124:1–38.
62 Hannawi Y, Lindquist MA, Caffo BS, *et al*. Resting brain activity in disorders of consciousness: a systematic review and meta-analysis. *Neurology* 2015;84:1272–80.
63 Bruno MA, Soddu A, Demertzi A, *et al*. Disorders of consciousness: Moving from passive to resting state and active paradigms. *Cogn Neurosci* 2010;1:193–203.
64 Soddu A, Vanhaudenhuyse A, Demertzi A, *et al*. Resting state activity in patients with disorders of consciousness. *Funct Neurol* 2011;26:37–43. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3814510&tool=pmcentrez&rendertype=abstract (accessed 7 Dec 2014).
65 Katz DI, Polyak M, Coughlan D, *et al*. Natural history of recovery from brain injury after prolonged disorders of consciousness: outcome of patients admitted to inpatient rehabilitation with 1–4 year follow-up. *Prog Brain Res* 2009;177:73–88.

JNNP

Preserved consciousness in vegetative and minimal conscious states: systematic review and meta-analysis

Daniel Kondziella, Christian K Friberg, Vibe G Frokjaer, Martin Fabricius and Kirsten Møller

J Neurol Neurosurg Psychiatry published online July 2, 2015