Resting brain activity in disorders of consciousness

A systematic review and meta-analysis

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ABSTRACT

Objective: To quantitatively synthesize results from neuroimaging studies that evaluated patterns of resting functional activity in patients with disorders of consciousness (DOC).

Methods: We performed a systematic review and coordinate-based meta-analysis of studies published up to May 2014. Studies were included if they compared resting-state functional neuroimaging data acquired in patients with DOC (coma, minimally conscious state, emergence from minimally conscious state, or vegetative state) with a group of healthy controls. Coordinate-based meta-analysis was performed in studies that included voxel-based comparisons at the whole-brain level and if analysis was accomplished with data-driven approaches.

Results: A total of 36 studies (687 patients, 637 healthy controls) were included in the systematic review. Reported DOC were vegetative state (43.2%), coma (23.4%), minimally conscious state (22.8%), and emergence from minimally conscious state (1.6%); the most common etiologies of DOC were traumatic brain injury (37.7%) and anoxic brain injury (36.9%). Functional neuroimaging was accomplished using fMRI (16 studies), PET (15 studies), SPECT (4 studies), and both PET and SPECT in one study. Meta-analysis in 13 studies (272 patients, 259 healthy controls) revealed consistently reduced activity in patients with DOC in bilateral medial dorsal nucleus of the thalamus, left cingulate, posterior cingulate, precuneus, and middle frontal and medial temporal gyri.

Conclusions: In patients with DOC evaluated in the resting state, functional neuroimaging indicates markedly reduced activity within midline cortical and subcortical sites, anatomical structures that have been linked to the default-mode network. Studies are needed to determine the relation between activation (and coherence) within these structures and the emergence of conscious awareness. *Neurology*® 2015;84:1272-1280

GLOSSARY

ALE = activation likelihood estimate; **ALFF** = amplitude of low-frequency fluctuations; **BOLD** = blood oxygen level-dependent; **CRS-R** = Coma Recovery Scale-Revised; **DMN** = default mode network; **DOC** = disorders of consciousness; **EMCS** = emergence from minimally conscious state; **FDG** = fluorodeoxyglucose; **HC** = healthy control; **ICA** = independent component analysis; **MCS** = minimally conscious state; **MNI** = Montreal Neurological Institute; **PCC** = posterior cingulate cortex; **ReHo** = regional homogeneity; **ROI** = region of interest; **TBI** = traumatic brain injury; **VS** = vegetative state.

Coma is a cardinal sign of brain injury resulting from trauma, stroke, cardiac arrest, infection, or metabolic causes. While coma is a transient state from which the majority of subjects awaken, a subset of patients develop a more prolonged impairment in consciousness, such as the vegetative state (VS) or minimally conscious state (MCS). Despite considerable research, states such as coma, VS, and MCS—collectively termed disorders of consciousness (DOC)—remain poorly understood regarding their neural basis, clinical recognition, and long-term outcome.^{1,2} Neurophysiologic and functional neuroimaging evaluations indicate that behaviorally unresponsive brain-damaged patients may retain patterns of higher-order cerebral processing analogous to those seen in conscious patients.³ These results suggest that functional brain mapping is a valuable paradigm to characterize severe brain injury.⁴

Supplemental data
 at Neurology.org

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Analysis of resting fMRI time courses reveals a distributed brain network architecture that is dynamic and reproducible, and appears homologous to known task-activated and anatomical systems.⁵ Changes in resting-state fMRI activity have been reported in development, aging, and in a range of neurologic and psychiatric disorders.⁶ Resting functional neuroimaging in general is appealing in patients with DOC since it does not require direct cooperation and is not subject to variances or bias introduced by task execution and observation. Understanding patterns of functional activity in patients with severe brain injury could generate important insight on the neural basis of conscious awareness and on targets for therapeutic intervention. We therefore conducted a systematic review and coordinate-based meta-analysis of studies comparing resting-state brain activity in patients with DOC and in controls without DOC.

METHODS Article selection. We conducted a systematic review and meta-analysis in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline.⁷ Table e-1 on the *Neurology*[®] Web site at

Neurology.org shows the Patient/Intervention/Comparison/Outcome statement. To be included in the systematic review, reports had to meet the following criteria: (1) observational study conducted in human subjects with DOC (coma, VS, MCS, or emergence from MCS [EMCS]), (2) comparison group of healthy control (HC) subjects; (3) subjects were evaluated with fMRI, PET, SPECT, or magnetoencephalography; and (4) scans were acquired in the absence of a predefined stimulus or task. Articles were excluded if they involved nonhuman subjects or were case reports or case series with fewer than 5 subjects per group. In instances where the same study population was reported on in more than one article, the data were included only once for meta-analysis. Criteria used for inclusion in the meta-analysis are provided in the next section. Details of the literature search strategy and data extraction process are provided in appendix e-1 and figure 1.

Coordinate-based meta-analysis. We used GingerALE (version 2.3.2, available at brainmap.org), a program that applies the activation likelihood estimate (ALE) method.^{8–10} A detailed account of the ALE approach has been published elsewhere.^{8,11} In brief, coordinates in 3-dimensional stereotactic space (e.g., Talairach or Montreal Neurological Institute [MNI]) are pooled from different studies and spatially normalized to a single template. ALE model coordinates using a gaussian kernel, with a full width at half maximum value corresponding to the sample size of the study, to accommodate for spatial uncertainty associated with the reported coordinates. The smoothed values are then treated as probabilities, and their union is computed to give the activation likelihood. This is interpreted as the probability that at least one of the peak activations lies within this voxel.¹² ALE can detect consistencies

Figure 1 Flow diagram of the systematic literature search

Flow diagram showing the results of the systematic search for the selected studies in the systematic review and meta-analysis.

across different studies in a more objective and quantitative manner than descriptive analysis.¹¹

Articles were selected for meta-analysis if (1) voxel-based comparisons were made at the whole-brain level between patients with DOC and controls, and (2) differences in voxel signal intensity between patients and controls were reported in Talairach or MNI space (if the coordinates were not available in the published report, missing data were requested by e-mailing corresponding authors), and (3) signal analysis was performed using data-driven approaches, i.e., independent component analysis (ICA), amplitude of low-frequency fluctuations (ALFF), or voxel-wise general linear model applied at the whole-brain level. Studies were excluded if they used seed-based or region-of-interest (ROI)-based correlational analysis (a concise description of these methods is provided in appendix e-2). Given intrinsic differences between ICA and ALFF, we performed 2 separate analyses, one including the ALFF studies and another without. We included data acquired with different neuroimaging techniques (e.g., fMRI, PET) as has been done successfully in other meta-analyses.^{13,14} Coordinates in Talairach space were transformed to MNI space using Lancaster transformation available on BrainMap.¹⁵ We used false discovery rate of 0.05 and minimum cluster volume of 200 mm³.⁸ Meta-analysis was first performed using data acquired in patients with different types of DOC (VS and MCS) and in HCs. Then, we performed separate analyses of the patients in VS and MCS alone, followed by a contrast analysis to compare peak voxel signal activity between MCS and VS. In addition, we performed separate analyses of studies that grouped patients according to the etiology of DOC (traumatic brain injury [TBI] or anoxic brain injury). Finally, we analyzed studies that reported peak voxel activity that correlated with Coma Recovery Scale-Revised (CRS-R) score. We used Mango software version 3.1.2 (rui.uthscsa.edu/mango/) to visualize the results that were registered on a standardized MNI anatomical template.

RESULTS Systematic review. Population characteristics.

The systematic review included 36 studies whose characteristics are provided in table e-2.^{16–51} In 2 instances, the same patient samples were reported in more than one article.^{17,32,34,36} In these cases, only data from one study were used for quantitative synthesis; however, because different analytical methods were used, results of all 4 articles are presented in the systematic review. Thus, a total of 34 studies reporting on 687 patients (431 males [62.7%], mean age 47.7 years) and 637 HCs were included. The most frequent DOC was VS, noted in 297 patients (43.2%), followed by coma in 161 (23.4%), MCS in 157 (22.8%), and EMCS in 11 (1.6%). Etiologies of DOC included TBI identified in 259 patients (37.7%) followed by anoxia in 254 (36.9%), ischemic stroke in 71 (10.3%), intracerebral hemorrhage in 46 (6.6%), and subarachnoid hemorrhage in 19 (2.7%). Anoxia was the sole cause of DOC in 8 studies, while TBI was the sole cause of DOC in 6 studies (table e-2). Sedation was reported in 7 studies (78 subjects) and included propofol, fentanyl, phenobarbital, midazolam, and diazepam.^{16,17,19,30,43,48,49}

Resting-state image acquisition and analysis. Resting-state brain activity was evaluated with fMRI in 16 studies (292 subjects, 295 HCs).^{16–25,27,28,30,33,34,40}

Fourteen studies (282 subjects, 289 HCs) were accomplished with ¹⁸F fluorodeoxyglucose (FDG)-PET, 4 (87 subjects, 36 HCs) used SPECT with different tracers (^{99m}Tc, ¹²³I, or ¹³³Xenon),^{47,48,50,51} one (10 subjects, 10 HCs) used ¹⁵O H₂O PET, and one (16 subjects, 7 HCs) used both SPECT and ¹⁸F FDG-PET. The median duration of resting-state fMRI acquisition was 7 minutes, 45 seconds (interquartile range, 6–10 minutes). Other details of image acquisition are provided in table e-2. ROI-based comparisons of patients and HCs were done in 9 studies (174 subjects, 127 HCs) including 5 PET and 4 SPECT studies. Voxel-based comparisons at whole or regional brain level were performed in 27 studies (513 patients and 510 HCs) including 11 PET studies and 16 fMRI studies. Analytical approaches included ICA in 9 studies, seed-based correlative analysis in 5, ALFF in 3 studies, graph theory in 3, and regional homogeneity (ReHo) in one (table e-3; see also appendix e-2 for details on these methods).

PET and SPECT findings. While PET and SPECT studies measure a signal correlated to regional brain metabolism and/or perfusion, for the purposes of this study, we refer to this signal as cerebral “activity” in a manner analogous to fMRI (blood oxygen level-dependent [BOLD]) recordings. Five studies reported global reductions in activity in all ROIs of DOC patients when compared with HCs.^{44–46,49} Two studies reported that patients had decreases in activity that were most pronounced in frontal lobe ROIs.^{50,51} One study found lower activity in ROIs placed in the brainstem, striatum, thalamus, and cerebellar cortex in comatose patients compared with HCs,⁴³ while differences in regional activity were minimal in another study across preselected ROIs.⁴⁷

Voxel-based comparisons of resting-state activity in DOC subjects and HCs with either ¹⁸F FDG-PET or ¹⁵O PET yielded similar results. These studies showed widespread reductions in activity in parietal, occipital, frontal, insular and cingulate cortices, and in the thalamus (findings of each study are listed in detail in table e-3).^{26,29,31,32,35,36,38,41,42} In several studies, when compared with subjects in the MCS, patients in VS had proportionally greater reductions in activity in the precuneus and in the posterior cingulate cortex (PCC).^{26,35,39} This reduction in activity in the precuneus was coupled with increased activity in brainstem arousal centers in one study.³⁹ In patients with VS, widespread reductions in activity were noted within exteroceptive (left and right lateral parietal and lateral prefrontal cortices) and interoceptive systems (midline precuneus/posterior cingulate and mesiofrontal/anterior cingulate cortices), while in MCS, reduced activity was observed in interoceptive systems only, and in EMCS, reduced activity was noted only in the PCC.²⁹

Two SPECT and 4 PET studies evaluated patients with TBI separately (table e-2).^{32,36,41,43,47,48} In one study of comatose patients with TBI, a global reduction in activity was noted with minimal variation across ROIs compared with HCs.⁴⁷ This reduction was noted to be highly significant in the brainstem, striatum, and thalamus in another coma TBI study.⁴³ Elsewhere, patients with TBI in VS or MCS were found to have decreased activity in the thalamus and medial prefrontal and cingulate cortices.^{32,36,41}

One SPECT and 5 PET studies evaluated subjects with anoxic brain injury separately (table e-2), revealing widespread decreases in activity across the brain^{26,31,42,45,46,51}; in 3 of these studies, activity reductions were more pronounced in bilateral PCC, insula, and thalamus.^{26,31,42}

fMRI findings. Three studies using ALFF or ReHo showed that patients with DOC had decreased activity in the PCC,^{16,21,25} precuneus,²¹ thalamus, orbitofrontal cortex, and medial prefrontal cortex^{16,25}—structures that have been linked to the default mode network (DMN). A reciprocal increase in activity was noted in the supplementary motor area and the insula, sites linked to external awareness and task activation.¹⁶

Resting functional connectivity was evaluated using seed-based correlations, ICA, or graph theoretical approaches (table e-3). ICA was used in 9 studies, and the most frequently analyzed network was the DMN. DMN resting functional connectivity and size (number of voxels inside the DMN) were significantly reduced in patients with DOC compared with HCs.^{16,18,19,21,23,24,30,33,40} Two of these studies exclusively evaluated patients with anoxic brain injury; both demonstrated decreased connectivity within the DMN.^{19,30} Studies demonstrated a relationship between the degree of impaired consciousness and DMN connectivity, with greater reductions in connectivity in VS compared with MCS.^{23,33,40} In one study, functional connectivity of the PCC and precuneus was linked to the severity of consciousness impairment, differentiating among VS, MCS, coma, and HC.⁴⁰ Other neuronal systems in which decreased functional connectivity was noted in patients with DOC included left and right executive control, auditory, and attention networks.^{18,21} Six studies evaluated functional connectivity using seed-based correlative analysis^{22–24,28,34,40} (table e-3). Intrinsic connectivity of the DMN was found to be decreased in patients with MCS and VS,^{23,40} while extrinsic connectivity between DMN and limbic structures was increased.²³ Interhemispheric connectivity was reduced when seeds were set in the precuneus, postcentral gyrus and intraparietal sulcus, or across the brain.^{22,28} In a study in which seeds were placed in the thalamus, patients in VS demonstrated a

greater reduction in connectivity of the nonspecific thalamic connections of the intralaminar nuclei associated with the ascending reticular activating system than in the specific thalamic connections related to the thalamic sensory and motor relay functions.³⁴

Brain network topology was assessed through graph theoretical approaches in several studies.^{17,20,27} In patients with acute postanoxic coma, fundamental network characteristics were preserved,²⁷ but a restructuring of hubs (nodes with high degree of connectivity) was noted: anatomical sites that were hubs in HCs were nonhubs in comatose patients.²⁷ However, patients in MCS and VS showed impaired network properties, such as clustering (connections between the nearest neighbors of a node) and modularity (nodes with higher connections to each other compared with the remainder of the network).²⁰ One report indicated that scale-free distribution of node size and node degree were absent in patients with VS but maintained in HCs (even under sedation), suggesting that sustained self-organization is a fundamental characteristic distinguishing pharmacologically induced loss of consciousness from DOC.¹⁷

Outcome assessment. The relationship between functional neuroimaging data and outcome was assessed in a small number of studies (table 1).^{19,30,47,49,51} Among reports using an ROI-based analysis, one found no correlation between regional activity and recovery of consciousness in VS and comatose patients,⁴⁹ a second study found more pronounced frontal lobe hypoperfusion in comatose patients who died than in those who awoke,⁵¹ and a third study indicated that an increase of global cerebral blood flow between 1 and 3 days and a decrease in total cerebral blood flow between 14 and 42 days postinjury were correlated with unfavorable 3-month Glasgow Outcome Scale score.⁴⁷ Two studies evaluated the predictive value of functional connectivity in comatose patients after cardiac arrest.^{19,30} In the first of these, preservation of intrinsic DMN connectivity accurately discriminated comatose patients who regained consciousness from those who did not.³⁰ In the second, a significant association was noted between connectivity strength in the PCC and precuneus and functional status at hospital discharge.¹⁹

Coordinate-based meta-analysis findings. A total of 13 studies including 272 patients with DOC and 259 HCs and reporting on 164 foci in 16 experiments were included in the meta-analysis.^{16,18,19,25,26,29–31,35,38,40–42} (table 2). Coordinate-based meta-analysis indicated reduced activity in patients with DOC compared with HCs in the following areas: left cingulate gyrus, medial temporal gyrus, middle frontal gyrus, PCC, precuneus, and right and left medial dorsal nucleus of the thalamus (table 2, figure 2A). Seven studies

Table 1 Studies evaluating the relationship between resting functional activity and outcome

Reference	Time delay postinjury for outcome determination	Outcome assessment	Reported outcome	Functional activity–outcome relationship
Koenig et al., ¹⁹ 2014	At hospital discharge (36.3 ± 41.7 d)	CPC	Good outcome (CPC 1–2) 47%; poor outcome (CPC 3–5) 53%	PCC connectivity reduced in patients with unfavorable outcome
Norton et al., ³⁰ 2012	3 mo	GOS	Good outcome 15.4%; poor outcome 84.6%	DMN not identifiable in patients who remained unconscious
Shiina et al., ⁴⁷ 1998	3 mo	GOS	NA	Patients with poor outcome had increased global metabolism at 1–3 d postinjury and decreased global metabolism 14–42 d.
Tommasino et al., ⁴⁹ 1995	NA	NR	Coma outcome: 40% dead, 40% VS, 20% regained consciousness. VS outcome: 10% dead, 70% remained VS, 20% regained consciousness	No correlation between brain metabolism and recovery of consciousness
Roine et al., ⁵¹ 1991	12 mo	GOS	Good outcome (GOS 4–5) 53.2%; poor outcome 46.8%	Frontal hypoperfusion was more pronounced in patients who remained comatose vs those who regained consciousness. The degree of hypoperfusion did not correlate with GOS.

Abbreviations: CPC = cerebral performance category; DMN = default mode network; GOS = Glasgow Outcome Scale; NA = not available; NR = none reported; PCC = posterior cingulate cortex; VS = vegetative state.

(85 subjects, 52 foci)^{26,29,35,38,41,42} reported peak voxel activity differences in patients in VS compared with HCs and were analyzed separately; meta-analysis demonstrated consistently decreased activity in left cingulate gyrus and right and left medial dorsal nucleus of the thalamus. Three studies (68 subjects and 30 foci)^{29,31,41} reported peak voxel activity differences in patients in MCS compared with HCs; meta-analysis showed decreased activity in the right medial dorsal nucleus of the thalamus and right cingulate gyrus. A contrast analysis of studies reporting on patients in MCS and VS showed the right medial dorsal nucleus of the thalamus to be a conjunction area of decreased activity, but failed to show a statistically significant difference (likely because of the small number of available studies). Coordinate-based meta-analysis of patients with DOC who had anoxic brain injury (5 studies, 62 subjects, and 48 foci)^{19,26,28,38,42} revealed significantly decreased activity in the precuneus, middle frontal gyrus, and bilateral medial dorsal nuclei of the thalamus. Only one study of DOC related to TBI met inclusion criteria, hence meta-analysis of patients with TBI was not possible. Finally, areas that correlated with CRS-R score (4 studies, 119 subjects and 36 foci)^{26,29,31,40} included the left superior and middle frontal and cingulate gyri (table 2, figure 2B). Two studies using the ALFF methodology met our inclusion criteria^{16,25}; meta-analysis with and without ALFF studies yielded similar results (table 2).

DISCUSSION The systematic review indicates widespread decreases in activity in bilateral cerebral cortices and thalamus when contrasting DOC patients with HCs. Reduced activity is most consistently observed in midline structures, and is more pronounced in

patients in VS compared with MCS. Activity appeared even more reduced in coma patients than in other DOC in the small number of studies that allowed for these comparisons.^{40,49} A coordinate-based meta-analysis identified statistically significant decreases in activity in the left cingulate gyrus, PCC, precuneus, medial temporal lobe, middle frontal lobe, and bilateral medial dorsal nuclei of the thalamus when comparing patients with DOC with controls. These effects were noted consistently using different functional neuroimaging approaches in patients with a range of DOC etiologies (appendix e-3).

ALE allows coordinate-based meta-analysis but it does not provide information regarding the degree of impairment in cerebral activity. To further explore this, we analyzed data on patients in the VS and MCS separately. When comparing these 2 groups, ALE indicated reduced activity in the cingulate gyrus in all subjects; however, this involved bilateral medial dorsal thalamic nuclei in patients in VS compared with the right medial dorsal nucleus alone in MCS. When considering subjects with anoxia alone, the results showed decreased activity in the bilateral medial dorsal thalamic nuclei, precuneus, and middle frontal gyrus. These findings are in concordance with the systematic review, and support a central role of the thalamus in the generation of conscious processing. We also assessed anatomical sites that correlated with CRS-R score in the meta-analysis. The CRS-R score is a neuro-behavioral sum score that evaluates auditory, visual, verbal, motor, arousal, and communication domains of responsiveness.⁵² Sites in which activity correlated positively with CRS-R were the left middle and superior frontal gyrus and the cingulate gyrus.

The anatomical structures whose activity was found to be reduced in subjects with DOC are

Table 2 Anatomical breakdown of alterations in resting activity identified in patients with DOC

Cluster	Anatomical region	Brodmann area	MNI coordinates			Volume, mm ³
			x	y	z	
Healthy control > DOC patients with ALFF studies						
1	R medial dorsal nucleus of the thalamus	—	8	−16	8	1,800
	L medial dorsal nucleus of the thalamus	—	−6	−14	8	
2	L cingulate gyrus	23	2	−22	34	960
3	L posterior cingulate cortex	31	−4	−56	26	576
	L precuneus	7	−2	−56	38	
4	L middle temporal gyrus	39	−50	−66	24	304
5	L cingulate gyrus	31	0	−40	34	288
6	L precuneus	39	−44	−70	42	248
7	L middle frontal gyrus	9	−54	20	28	216
Healthy control > DOC patients without ALFF studies						
1	R medial dorsal nucleus of the thalamus	—	8	−16	8	1,824
	L medial dorsal nucleus of the thalamus	—	−6	−14	8	
2	L cingulate gyrus	23	2	−22	34	968
3	L medial temporal gyrus	39	−50	−66	24	304
4	L cingulate gyrus	31	0	−40	34	296
5	L precuneus	39	−44	−70	42	248
6	L posterior cingulate cortex	31	−4	−56	26	224
7	L middle frontal gyrus	9	−54	20	28	216
Healthy control > VS patients						
1	L cingulate gyrus	31	0	−40	34	744
2	R medial dorsal nucleus of the thalamus	—	10	−16	8	536
3	L medial dorsal nucleus of the thalamus	—	−6	−14	8	416
Healthy control > MCS patients						
1	R medical dorsal nucleus of the thalamus	—	8	−16	6	320
2	R cingulate gyrus	24	6	18	30	208
Healthy control > DOC patients related to anoxia						
1	L precuneus	7	−2	−56	38	568
2	R medial dorsal nucleus of the thalamus	—	10	−16	8	552
3	L medial dorsal nucleus of the thalamus	—	−6	−14	8	504
4	R middle frontal gyrus	6	48	4	54	288
Areas that correlated with CRS-R score						
1	L middle frontal gyrus	6	−32	6	54	320
2	L superior frontal gyrus	8	−4	48	40	264
3	L cingulate gyrus	31	2	−34	34	256
Conjunction analysis of MCS and VS						
1	R medial dorsal nucleus of the thalamus	—	8	−16	8	104

Abbreviations: ALFF = amplitude of low-frequency fluctuations; CRS-R = Coma Recovery Scale-Revised; DOC = disorders of consciousness; MCS = minimally conscious state; MNI = Montreal Neurological Institute; VS = vegetative state.

Coordinates of local maxima of impaired activity, cluster volume, and the associated anatomical areas in each of the following categories: healthy controls vs DOC patients with and without ALFF studies, healthy controls vs VS patients, healthy controls vs MCS patients, areas that correlated with CRS-R score, and conjunction analysis of MCS and VS; reported in MNI space.

components of the DMN, a distributed neuronal system whose properties and function are actively investigated.^{53,54} The DMN is activated during the resting

condition and deactivated during engagement in a task; its activity is predictably anticorrelated with other task-activated networks.⁵⁵ Modifications in

Figure 2 Results of activation likelihood estimate coordinate-based meta-analysis

Results of the coordinate-based meta-analysis visualized on Montreal Neurological Institute template in (A) areas that showed decreased activity in patients with disorders of consciousness compared with healthy controls, and (B) areas that correlated with Coma Recovery Scale-Revised score.

DMN structure and function have been reported in a range of neurologic and psychiatric disorders,⁶ and converging evidence points to significant DMN alterations in patients with DOC including dimensional reductions and decreased intrinsic functional and anatomical connectivity.^{16,18,19,23,25,30,34,40,56} In our systematic review and meta-analysis, the thalamus and PCC/precuneus complex appear to be most frequently affected in DOC, and activity or connectivity of the precuneus may correlate with the magnitude of impairment in consciousness.^{29,33,40} The precuneus is the posterior region of the medial parietal cortex (Brodmann area 7) and represents one of the most highly connected and metabolically active regions of the brain^{57,58}; it is believed to be involved (with other nodes of the DMN) in self-referential tasks.⁵⁷

A small number of studies reported increased activity or increased functional connectivity in patients with DOC when compared with HCs. Patients in VS had higher activity in the brainstem,³⁹ cerebellum, supramarginal cortex,²⁶ and externally oriented networks, such as the insula and premotor area,¹⁶ in addition to increased connectivity of the DMN to structures within the limbic system.²³ The significance of such increases in connectivity or activity is unknown, but they might represent compensatory/adaptive or maladaptive mechanisms. The number of studies reporting hyperactivation or hyperconnectivity was not sufficient to perform a meta-analysis.

A potential limitation of this meta-analysis is the small number of studies. To limit heterogeneity, we used strict study inclusion criteria. To minimize bias in coordinate-based meta-analysis, we excluded studies that used seed-based correlation methods. Thirteen studies were ultimately selected for meta-analysis, which is similar to the number of studies in other published coordinate-based meta-analyses.^{14,59} Another limitation is the inherent differences between ALFF and ICA in analyzing BOLD response. To address this, we performed 2 different analyses, with and without the ALFF studies, an approach that did not significantly change the results. The consistent findings of impaired resting-state activity in our meta-analysis suggest greater functional impairment in the identified structures in DOC, despite unavoidable fluctuations in resting-state functional activity that are known to present in HCs. Finally, ALE does not integrate the degree of impairment in functional activation. We therefore performed separate analyses of differences in peak activity in MCS and VS subjects, and of the relationship between peak activity and CRS-R score. Despite concerns about the validity of inferences made from BOLD signal differences across brain regions, fMRI remains the most extensively validated method to map brain functional activity in humans.⁶⁰ Our coordinate-based meta-analysis of advanced neuroimaging studies demonstrated regional changes in activity that were highly consistent across a range of DOC etiologies and imaging modalities (additional detailed discussion of these points is available in appendix e-3).

Studies supporting the use of functional neuroimaging for determination of prognosis are limited in number.² Two of our included studies that evaluated fMRI in relation to patients' outcome showed correlation of impaired functional connectivity of the DMN and PCC and poor outcome.^{19,30} Research is needed to accurately and reliably map patterns of functional activation in brain-injured patients, to determine how early functional activation patterns can be used to model coma emergence and long-term functional and cognitive recovery.⁴ Predictive models based on functional neuroimaging will need to integrate the etiology of injury (traumatic vs non-traumatic), the time elapsed between injury and imaging, and potential alterations in neurovascular coupling due to age, cerebrovascular disease, sedation, and systemic physiologic perturbations.

AUTHOR CONTRIBUTIONS

Yousef Hannawi: study design, data extraction, analysis and interpretation of the data, drafting the manuscript, and critically revising it for intellectual content. Martin A. Lindquist: analysis and interpretation of the data, critically revising the manuscript for its intellectual content. Brian S. Caffo: critically revising the manuscript for its intellectual

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