



Exploring the prognostic value of resting state brain activity in Disorders of Consciousness: A coordinate-based meta-analysis

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ABSTRACT

The prognostic value of spontaneous brain activity in patients with Disorders of Consciousness (DoC) remains questionable due to methodological heterogeneity, small sample sizes, and the difficulty in conducting longitudinal studies on this clinical population. We performed a coordinate-based meta-analysis of the studies adopting resting state brain imaging techniques to identify whether the spontaneous activity of specific brain areas has a prognostic value for DoC patients. We included studies published until 2025 providing the peak coordinates deriving from contrasting brain activations of patients showing full consciousness recovery (Good Outcome; GO) and patients showing either no consciousness recovery or death (Bad Outcome; BO) with voxel-wise whole-brain analyses. Twelve studies were included in the meta-analysis containing data from 332 DoC patients (n = 192 BO) in the post-acute phase, assessed through resting state functional Magnetic Resonance Imaging. Compared to BO, GO patients showed increased spontaneous activity in sensory and associative areas, including visual areas, precuneus, temporo-parietal, and, marginally, premotor regions. Taken together, the results suggest preservation of posterior brain areas is pivotal in assisting prognosis, with a marginal role played by the premotor areas. However, both low-level sensory and high-level associative areas contribute to outcome prediction of DoC patients, possibly due to the need to integrate low-level sensory information to enable functional interaction with the environment.

1. Introduction

Severe Acquired Brain Injuries (sABI) may lead to Disorders of Consciousness (DoC) lasting from a few months to many years (Kowalski et al., 2021). This clinical condition ranges from Unresponsive Wakefulness Syndrome (UWS) to Minimal Conscious State (MCS; Laureys et al., 2010). Whilst the former is clinically characterized by the presence of sleep/wake cycle and only reflexive responses to external stimulation, MCS is characterized by the presence of cognitively-mediated behaviors, further dividing this category into MCS+ (i.e., patients showing language-related behaviors such as commands following, intelligible verbalization, and/or intentional communication) and MCS- (Thibaut et al., 2020). These conditions can persist

over time or evolve. Indeed, the literature highlighted the possibility of either a diagnostic change (e.g., from UWS to MCS or from MCS- to MCS+) or consciousness recovery even after long periods (Baricich et al., 2017; Estraneo et al., 2010; Nakase-Richardson et al., 2012). For this reason, identifying reliable prognostic markers is of uttermost importance to properly inform families, clinicians, and more in general, the national health systems that should be prepared for DoC patients management.

Some demographic (e.g., younger age at the acute event) and clinical (e.g., traumatic etiology, MCS diagnosis, DoC duration) features are clear indicators of a higher chance of full recovery of consciousness (Bruno et al., 2012; Estraneo et al., 2013; Luauté et al., 2010); however, the adoption of instrumental tools can refine the prognostic evaluation

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and increase its predictive power (Song et al., 2018), although a definite clinical consensus is still internationally lacking (Magnani et al., 2022). Indeed, the European Academy of Neurology does not provide any recommendation about the adoption of instrumental tools for DoC prognosis (Kondziella et al., 2020), whilst the American Academy of Neurology recommends the adoption of event-related potentials, electroencephalography, structural Magnetic Resonance Imaging (MRI), Single-Photon Emission Computed Tomography (SPECT), and BOLD functional MRI (fMRI) for assisting the prognosis of post-traumatic UWS patients, although at a weak to moderate grade (Giacino et al., 2018). On the contrary, the UK Royal College of Physicians states that “*more sophisticated electrophysiology and brain imaging techniques*” do not have a clear “*prognostic utility over and above expert clinical [...] assessment*” (The Royal College of Physicians, 2020; p. 68, recommendation 2.7). This scenario is due to the limited availability of longitudinal studies adopting instrumental tools to predict DoC outcomes, and the heterogeneity characterizing studies’ methodology (Magnani et al., 2022).

In the last decades, much attention has been given to brain imaging techniques (e.g., fMRI, Positron Emission Tomography; PET), as they can inform about the neural underpinnings of consciousness, having both theoretical and clinical meaning (Koch et al., 2016). From a theoretical point of view, shedding light on brain structures mainly involved in the generation and maintenance of consciousness allows testing the existing theories of consciousness and suggesting new hypotheses of functioning which, in turn, can orient the clinical practice towards, for instance, the adoption of treatments targeting specific brain areas (Cacciatore et al., 2025; Edlow et al., 2020; Mencarelli et al., 2020). From a clinical point of view, knowing if there exist neural signatures informing about patients’ outcomes could orient the clinical practice and ameliorate communication with patients’ families (Boegle et al., 2022). To these purposes, a large body of studies adopted resting state fMRI (rs-fMRI) or PET since they have the advantage of not requiring the active involvement of patients during images acquisition while exploring the brain functioning after sABI (Snider and Edlow, 2020; Stender et al., 2014). The results seem to go in a similar direction by highlighting the pivotal role of brain areas belonging to the Default Mode Network (DMN) in predicting DoC outcomes (Di Perri et al., 2016; Vanhaudenhuyse et al., 2010; Wu et al., 2015). For instance, DMN integrity in the acute phase was associated with both full recovery of consciousness and consciousness level improvement in terms of diagnostic change (Koenig et al., 2014; Kondziella et al., 2017); moreover, within-DMN correlation and DMN anticorrelation with other networks (e.g., salience and executive control networks) have been shown to be associated with full recovery of consciousness at 6 months (Threlkeld et al., 2018) and 1 year (Sair et al., 2018) post injury. Importantly, Song and colleagues (2018) showed that a multidomain prognostic model encompassing both clinical and rs-fMRI variables can predict a 1-year outcome with a higher accuracy than considering clinical variables alone. Notably, the functional connectivity between the anterior medial prefrontal cortex of the DMN and the dorsal medial prefrontal cortex of the executive control network was the most important predictor in the model (Song et al., 2018).

Although the DMN-established centrality for consciousness is well-explained by the role of this network for self-awareness and self-referential thinking (Fransson and Marrelec, 2008), other networks are likely to contribute to full recovery of consciousness, especially when adopting a neurofunctional perspective. To recover consciousness, a system must be in principle able to select, process, and integrate information (Tononi, 2008), suggesting the need for the sparing of associative and sensory-motor areas, besides the most anterior ones. Moreover, it has been suggested that specialized structures in the thalamocortical system must effectively interact to sustain consciousness (Cacciatore et al., 2025; White and Alkire, 2003). For these reasons, it is conceivable that other networks than the DMN can contribute to predicting DoC outcomes as well. For instance, a recent study employing a multidomain prognostic model encompassing hormonal variables,

behavioral features, and rs-fMRI measures reached 91% of accuracy in predicting DoC outcomes, with sensory-motor and fronto-parietal networks contributing most (Wu et al., 2025).

One of the main issues in establishing which brain structures have a clear prognostic value is represented by the heterogeneity of the existing studies employing resting state neuroimaging techniques. Indeed, most of these studies was conducted on small samples with heterogeneous clinical features (e.g., time since injury, etiology), and considered diverse metrics in data analyses (e.g., Regional Homogeneity, ReHo; Functional Connectivity, FC; Amplitude of Low Frequency Fluctuations, ALFF). Hence, replicating studies’ results while overcoming the heterogeneity of studies’ features might help. However, to our knowledge, no meta-analyses of resting state neuroimaging studies have been conducted to identify the brain regions’ spontaneous activation most informative for DoC prognosis yet, despite the existence of similar works on DoC diagnosis (Hannawi et al., 2015; Mencarelli et al., 2020). A valuable exception is represented by the meta-analysis conducted by Kotchoubey and Pavlov (2018), who, however, considered studies adopting “*any functional brain data*” to predict DoC outcomes. This implies that, in their work, both neuroimaging and neurophysiological data deriving from paradigms either at rest or employing stimulations (either passive or active paradigms) have been considered (Kotchoubey and Pavlov, 2018), thus precluding a straightforward identification of the brain structures’ spontaneous activity most informative of DoC prognosis.

To overcome the above-mentioned issues, with the present work, we aim at meta-analyzing the existing studies relating resting state brain activity to DoC patients’ outcome to explore whether the functioning of specific brain areas is informative for full recovery of consciousness (Good Outcome, GO). Additionally, we aim to explore whether the identified brain areas mainly belong to specific functional networks.

2. Methods

The present meta-analysis was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Page et al., 2021) to search and extract eligible studies.

2.1. Search strategy

Relevant studies were identified by searching the following databases: PubMed, Scopus, and Web of Science. A customized search strategy was developed for each database based on its specific thesaurus (see [Supplementary Materials](#) for combinations of terms). The publication dates were initially set from January 1990 to December 2024 and then updated until June 26th, 2025. All searches were restricted to studies published in English. Moreover, the reference lists of both topic-relevant reviews and included studies were reviewed to identify further eligible studies. Importantly, the publication date was initially set from 1990 to include as many articles as possible, although the formal distinction between UWS and MCS is dated to 2002 (Giacino et al., 2002). Indeed, since the primary aim of the meta-analysis was to explore the prognostic value of the spontaneous brain activity for recovering consciousness, we could have included data concerning a full recovery of consciousness even in the absence of a formal distinction between UWS and MCS, eventually controlling for this variable in a further step.

The duplicates deletion was carried out using Mendeley, a web-based bibliographic management software (accessed on 14 December 2024 and 26 June 2025). The records were then imported into a customized Excel spreadsheet, which included the title, abstract, and record information for each study.

2.2. Selection criteria

Studies were eligible if they met all the following criteria: (i) peer-reviewed studies involving adult DoC patients (i.e., age ≥ 18 years old), (ii) including rs-fMRI, PET, or SPECT data, (iii) adopting voxel-wise whole-brain analysis, including the whole-brain ALFF, ReHo, Cerebral Blood Flow (CBF), seed-based FC,² Independent Component Analysis (ICA), or Degree Centrality (DC), as already done in previous meta-analyses (Jiang et al., 2020; Peng et al., 2022), and (iv) reporting standard three-dimensional spatial coordinates either in Talairach or Montreal Neurological Institute (MNI) spaces. Finally, we included only longitudinal studies reporting patients' outcomes, such as clinical status or level of consciousness assessed at a different time point from the acquisition of neuroimaging data. In other words, studies were eligible if they reported resting state neuroimaging data of DoC patients for whom the outcome was known and assessed at a time point following the imaging acquisition. To include as many studies as possible, we did not set any a-priori restriction on the time passed between images acquisition and outcome assessment. The same reasoning applies to the time passed from the acute event to the time of images acquisition.

Initially, we considered both single-subject experimental designs and group-level contrast studies (including comparisons among groups of patients, and comparisons between patients and healthy controls). This approach would allow us to conduct separate meta-analyses, if an adequate number of studies was available for each contrast.

2.3. Study selection and data extraction

The studies' eligibility was checked through a three-step procedure by three independent raters.

In the first step, a preliminary screening based on the title, abstract, and keywords was performed independently by raters #1 and #2 by adopting the following assessment rating scale: 0 = exclusion, 1 = inclusion, 2 = doubt. In the second step, the same assessment rating scale was adopted to assess the eligibility of the full-text studies selected after the first step. In both steps, rater #3 reviewed the records in case of doubt or discrepancy between raters #1 and #2. Raters' agreement was computed through Cohen's K (Landis and Koch, 1977). In the third step, raters independently extracted data from the included studies using a custom-built data extraction Excel sheet, which was pilot tested on five randomly selected included studies.

The following variables have been extracted from each included study:

- (i) Metric considered in the analysis (e.g., ALFF, ReHo, CBF, seed-based FC)
- (ii) Contrast analysis (i.e., which groups were considered in the contrast analysis and its direction)
- (iii) Sample size of groups included in the contrast analysis
- (iv) Stereotactic coordinates of the peaks
- (v) Stereotactic space adopted (e.g., Talairach, Montreal Neurological Institute; MNI)
- (vi) Peak t-value; if results were presented as z-values or p-values, they were converted into t-values using the online converter within the Seed-based d Mapping (SDM) software available at <https://www.sdmproject.com/utilities/?show=Statistics>,
- (vii) Software used for the analyses (e.g., SPM, DPARSFA)
- (viii) Clinical data of DoC patients' group, including diagnosis (if available) at the time of image acquisition (UWS; MCS), Time Since Injury (TSI) at the time of image acquisition, and the outcome time point (i.e., the time passed from the image acquisition to outcome assessment)

² Functional Connectivity data were considered only if derived from seed-to-whole-brain analysis without including seed-related peak of activation.

- (ix) Outcome, including the standardized clinical scale adopted to assess patients' outcome. Importantly, we considered patients' outcome as GOOD (GO) if there was evidence of full recovery of consciousness. On the contrary, if patients were still in a DoC condition, or death occurred, the outcome was considered BAD (BO).

Considering the contrast analysis adopted by each selected study, we checked for the possibility of conducting separate meta-analyses. Specifically, we computed the number of studies reporting peaks for GO and BO depending on the contrast adopted (e.g., contrast between GO and BO patients, contrast between patients and healthy controls).

2.4. Quality assessment

An 11-point checklist, adapted from (Strakowski et al., 2000), was adopted to assess the quality of the studies included in the meta-analysis, according to previous neuroimaging meta-analysis (Du et al., 2014; Mao et al., 2023; Shepherd et al., 2012; Wu et al., 2025). Specifically, the checklist focuses on the rigor in (i) selecting and reporting demographic/clinical information about the sample, (ii) the methods for image acquisition and analysis, and (iii) reporting the conclusions with results (Supplementary Table S1). Each study was assessed and rated by two independent raters. In the case of disagreement, the study was discussed among the raters to reach a consensus.

2.5. Meta-analysis

A coordinate-based meta-analysis was performed using Anisotropic Effect-Size Seed-based d Mapping (AES-SDM, version 5.142), a software based on peak-probability methods (e.g., Activation Likelihood Estimation; ALE; Turkeltaub et al., 2002). AES-SDM 5.142 was chosen based on the following characteristics: firstly, unlike previous methods, it enables assessing the direction (positive or negative) of the effect at the peak coordinates. In other words, AES-SDM considers both positive and negative differences, such as hyperactivations and hypoactivations on the same map, improving the accuracy of identifying significant differences between groups (Radua et al., 2012). Secondly, it was demonstrated to have higher voxel-based sensitivity with respect to the later version (SDM-Permutation of Subject Images version 6.23; Albajes-Eizaguirre et al., 2019), mainly in reference to meta-analyses conducted with peak information in the absence of statistical parametric maps (Albajes-Eizaguirre et al., 2019).

For each study included, SDM table and text files were created and imported into the software, including the sample size of each group in contrast analysis, peak coordinates, and their corresponding t-value.

According to the SDM pipeline, peak coordinates for each contrast were preprocessed to recreate the individual effect-size and variance maps of the studies in a voxel-wise manner, by using the gray matter correlation template with a fully anisotropic (= 1.0) Gaussian kernel, with full-width at half-maximum (FWHM) set to 20 mm within the gray matter mask, and a voxel size of 2 mm (Radua et al., 2014). The selected settings have been previously shown to optimally balance sensitivity and specificity (Radua et al., 2012).

To compute the voxel-wise mean of all contrast maps (i.e., the meta-analytic map), random-effects models were implemented, whose statistical significance was assessed through Monte Carlo permutation testing (Radua et al., 2014). The meta-analytic map was thresholded using a voxel-wise significance level of uncorrected $p < .005$, with a cluster size extended threshold of at least 10 voxels and an additional z-based threshold > 1 to minimize the risk of false positives (Radua et al., 2012).

The heterogeneity among the studies was assessed by adopting the standard metrics Cochran's Q, and the heterogeneity measure I^2 statistics (Cochran, 1954; Higgins et al., 2003; Higgins and Thompson, 2002). Specifically, the Q test was computed according to Cochran (Cochran,

1954), and the I^2 index was derived as a function of Q (Higgins et al., 2003; Higgins and Thompson, 2002) to quantify the proportion of true heterogeneity, expressed as the percentage of variability in effect size between-studies (Huedo-Medina et al., 2006). Specifically, I^2 is derived as follows: $I^2 = (Q - df/Q) 100$, with df being the degrees of freedom (the number of studies included in the analyses minus one). Moreover, publication bias was evaluated in RStudio (version 2022.12.0 +353) with Egger's test (Egger et al., 1997) and through visual inspection of funnel plots graphically representing the effect size (expressed as the standardized mean difference) on the x-axis and the standard error on

the y-axis, to facilitate the identification of asymmetry (Borenstein et al., 2021). For Egger's regression test, study-specific effect size estimates and variances were imported into R, and the standard error for each study was computed as the square root of its variance. A random-effects meta-analysis was then performed using the *metagen* function of the *meta* package with the effect size and estimating between-study heterogeneity via the restricted maximum-likelihood method (REML; Veroniki et al., 2016). Egger's test was subsequently conducted with the *metabias* function using linear regression (i.e., Egger) method.

Finally, the reproducibility of SDM meta-analysis results was

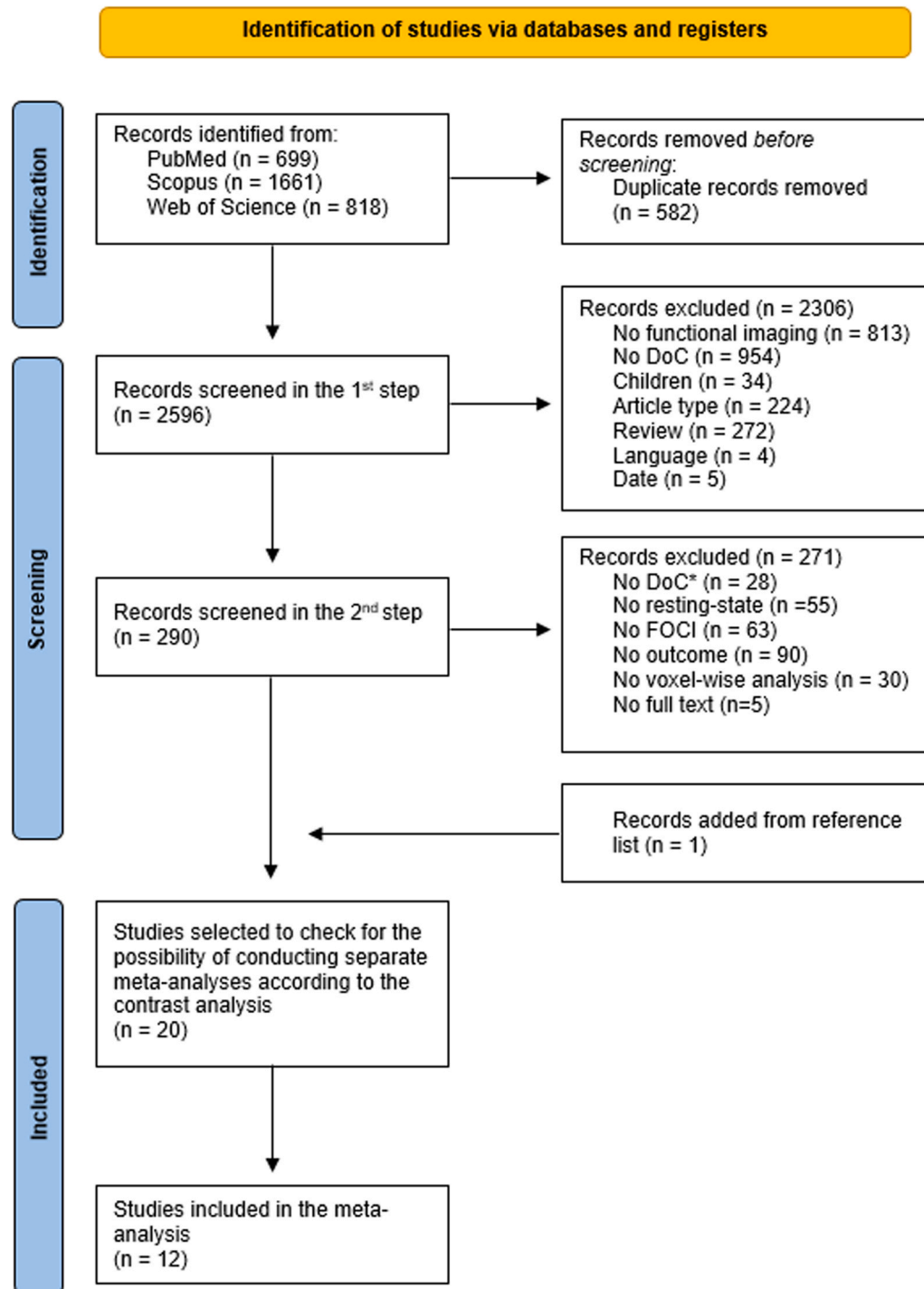


Fig. 1. PRISMA flow diagram. The diagram shows the number of studies screened and selected for the meta-analysis along with reasons for exclusion according to (Page et al., 2021). *The “No DoC” exclusion criterion was considered also in the second step for studies which included patients who were not DoC at the time of images acquisition, and studies considering mixed samples of patients with and without DoC, without providing separate analyses.

assessed via the jackknife sensitivity analysis, consisting of repeating the main analysis, discarding one study at a time, and evaluating the stability of the results across them (Radua et al., 2012). The same threshold as above (i.e., $p < .005$, cluster size ≥ 10 voxels, and $z > 1$) was applied to correct jackknife meta-analytic maps. We considered the results to be reliable and sensitive if they were consistent across more than 50% of the studies according to previous meta-analyses adopting the same methods (Radua and Mataix-Cols, 2009; Yan et al., 2025).

2.6. Networks' correspondence

To explore whether the brain areas identified in the meta-analysis belong to specific functional networks, spatial correspondence between the meta-analytic map and functional networks was assessed using the Network Correspondence Toolbox (NCT; https://github.com/rubykong/cbig_network_correspondence) (Kong et al., 2025). According to the recommendations of the Workgroup for Harmonized Taxonomy of Networks (WHATNET; Uddin et al., 2023), several widely used functional network atlases were used as references (see Supplementary Table S6). For each atlas, spatial correspondence between the meta-analytic map and functional networks was quantified using the Dice coefficient, which ranges from 0 (no spatial overlap) to 1 (complete spatial overlap) (Kong et al., 2025). To test the significance of the Dice overlap, a spin test implemented in Python 3.14 was performed with 1000 permutations for each functional network atlas (Vos de Wael et al., 2020).

3. Results

3.1. Study selection and data extraction

A total of 3178 studies were retrieved, and the automatic removal of duplicates resulted in 2596 studies.

In the first step, raters #1 and #2 agreed upon including 255 studies, whereas 35 were included by rater #3, who screened 65 records for which there was no agreement between raters #1 and #2 (Cohen's $K = 0.91$; 'Almost perfect' concordance; Landis and Koch, 1977). In the second step, raters #1 and #2 agreed upon the inclusion of 18 studies, whereas 1 study was included by rater #3 (Cohen's $K = 0.67$; 'Substantial' concordance; Landis and Koch, 1977). Moreover, an additional study has been identified by checking the reference list of topic-relevant reviews. Consequently, a total of 20 studies were included for data extraction (Fig. 1).

Supplementary Table S2 provides a summary of the methodological characteristics of the 20 studies selected to check for the possibility of conducting separate meta-analyses according to the contrast analysis adopted. Overall, 14 studies (Aubinet et al., 2019; Guo et al., 2019; Koenig et al., 2014; Laureys et al., 2000, 1999; Li et al., 2023, 2024; Shao et al., 2024; Wang et al., 2024; Wu et al., 2022; Zhang et al., 2023, 2022b, 2022a, 2020) reported peaks for GO patients, 4 studies reported peaks for BO patients (Boly et al., 2009; Bruno et al., 2010; Norton et al., 2012; Zhang et al., 2025), and 2 studies (Chen et al., 2024; Zhang et al., 2018) reported peaks for both GO and BO patients. Among the studies reporting GO-related peaks, 12 studies relied on contrasts between GO and BO patients (Chen et al., 2024; Guo et al., 2019; Koenig et al., 2014; Li et al., 2023, 2024; Shao et al., 2024; Wang et al., 2024; Wu et al., 2022; Zhang et al., 2022a, 2018, 2023, 2022b), while 4 studies relied on contrasts between GO patients and healthy controls (Aubinet et al., 2019; Laureys et al., 2000, 1999; Zhang et al., 2020). When considering the studies reporting BO-related peaks, 2 studies (Chen et al., 2024; Zhang et al., 2025) relied on contrast between BO and GO patients, whilst the remaining 4 studies made a comparison between patients and healthy controls (Boly et al., 2009; Bruno et al., 2010; Norton et al., 2012; Zhang et al., 2018).

In summary, only the contrast between GO and BO patients had a sufficient number of studies to perform a formal meta-analysis (Eickhoff

et al., 2016; Radua et al., 2012; Radua and Mataix-Cols, 2009). Consequently, a total of 12 studies comparing brain activation between GO and BO patients were included in the meta-analysis (Chen et al., 2024; Guo et al., 2019; Koenig et al., 2014; Li et al., 2023, 2024; Shao et al., 2024; Wang et al., 2024; Wu et al., 2022; Zhang et al., 2022a, 2018, 2023, 2022b). None of the included studies used overlapping samples, to our knowledge.

All the studies included in the meta-analysis employed rs-fMRI relying on different metrics (Table 1). Most of them considered the FC from a seed region to whole brain, which was located over the following regions: anterior insula (Zhang et al., 2018), posterior cingulate cortex (Guo et al., 2019), medial prefrontal cortex (Zhang et al., 2022a), thalamus (Zhang et al., 2022b), prefrontal cortex, precentral/postcentral gyrus, cingulate gyrus, and posterior medial cortex (Zhang et al., 2023). Importantly, pooling network-level and local activity metrics allows to detect the convergent spatial distribution of increases and decreases in resting state activity, rather than biologically specific effects.

The studies included in the meta-analysis reported either increased or decreased activity, meaning that both $GO > BO$ and $GO < BO$ contrasts have been considered. Specifically, 6 studies reported increased resting state activity in GO compared to BO patients (i.e., $GO > BO$ contrast; Chen et al., 2024; Guo et al., 2019; Koenig et al., 2014; B. Li et al., 2023; Wang et al., 2024; H. Wu et al., 2022), 4 studies reported decreased activity in GO than BO patients (i.e., $GO < BO$ contrast; C. Li et al., 2024; Zhang et al., 2023, Zhanget al., 2022a, 2022b), one study (Shao et al., 2024) reported both increased and decreased resting state activity in GO compared to BO patients (i.e., $GO > BO$ and $GO < BO$ contrasts), and one study (Zhang et al., 2018) showed no significant results when considering $GO > BO$ contrast. It was included as well in the meta-analysis, according to AES-SDM indications. It is worth noticing

Table 1
Methodological characteristics of the studies included in the meta-analysis.

Study	Metric	Contrast	Software	Space	MRI scanner	QS score
Wang et al. (2024)	ALFF	$GO > BO$	SPM	MNI	3 T	10/11
Chen et al. (2024)	ReHo	$GO > BO$	REST	MNI	3 T	9.5/11
Shao et al. (2024)	ReHo	$GO > BO$ $GO < BO$	DPARF	MNI	3 T	10.5/11
Li et al. (2024)	mALFF	$GO < BO$	DPABI	MNI	3 T	9.5/11
Zhang et al. (2023)	FC	$GO < BO$	DPABI	MNI	3 T	9.5/11
Li et al. (2023)	fALFF	$GO > BO$	SPM	MNI	3 T	9.5/11
Wu et al. (2022)	DC	$GO > BO$	AFNI	MNI	3 T	8.5/11
Zhang et al. (2022b)	FC	$GO < BO$	SPM	MNI	3 T	9.5/11
Zhang et al. (2022a)	FC	$GO < BO$	SPM	MNI	3 T	9.5/11
Guo et al. (2019)	FC	$GO > BO$	DPARF	MNI	3 T	8.5/11
Zhang et al. (2018)	FC	$GO > BO$	BRANT	MNI	1.5 T	8.5/11
Koenig et al. (2014)	CS	$GO > BO$	SPM	Tal	3 T	8/11

Note: ALFF, Amplitude of Low-Frequency Fluctuations; BO, Bad Outcome; BRANT, Brain Analysis Toolkit; CS, Connectivity Strength; DC, Degree Centrality; DPARF, Data Processing Assistant for Resting-State fMRI – Advanced; fALFF, fractional Amplitude of Low-Frequency Fluctuations; FC, Functional Connectivity; GO, Good Outcome; mALFF, mean Amplitude of Low-Frequency Fluctuations; MNI, Montreal Neurological Institute; ReHo, Regional Homogeneity; QS: Quality assessment; REST, Resting-State fMRI Data Analysis Toolkit; SPM, Statistical Parametric Mapping; TAL, Talairach Atlas; 3/1.5 T, 3/1.5 Tesla

that one study (Wu et al., 2022) did not report the t-value for peak coordinates; thus, the corresponding p-values were converted into t-values using the SDM online converter (<https://www.sdmproject.com/utilities/?show=Statistics>).

Overall, $n = 332$ post-acute DoC patients were included ($n = 192$ BO), with a prevalence of traumatic etiology ($n = 238$). Unfortunately, the diagnosis was not available for each study included in the meta-analysis. Indeed, only 3 studies (Chen et al., 2024; Wu et al., 2022; Zhang et al., 2018) relied on the reference standard (i.e., Coma Recovery Scale-revised; CRS-r; Giacino et al., 2004) to clinically diagnose DoC and distinguish between UWS and MCS; 8 studies (Guo et al., 2019; Li et al., 2023, 2024; Wang et al., 2024; Zhang et al., 2023, 2022a, 2022b) adopted the Glasgow Coma Scale (Jennett and Teasdale, 1977) that, while allowing to detect a DoC, does not allow for differentiating between UWS and MCS. Moreover, a study (Shao et al., 2024) relied on the presence/absence of a specific behaviour (i.e., command following), thus making it impossible to distinguish between UWS and MCS as well. A similar heterogeneity characterized the clinical scales adopted to measure patients' outcome. Indeed, only 3 studies (Chen et al., 2024; Wang et al., 2024; Zhang et al., 2018) adopted the CRS-r as outcome measure, 2 studies administered the Cerebral Performance Category (CPC) scale (Koenig et al., 2014; Shao et al., 2024), and the remaining 7 studies relied on the Glasgow Outcome Scale (GOS) or the GOS-Extended (GOS-E) to determine patients' outcome (Guo et al., 2019; Li et al., 2023, 2024; Wu et al., 2022; Zhang et al., 2023, 2022b, 2022a). A side note is due here as all the above-mentioned scales allow to detect full recovery of consciousness vs DoC persistence or death. Indeed, across the included studies, patients classified as GO consistently showed full recovery of consciousness, regardless of the scale adopted for outcome assessment. Specifically, in the studies adopting CRS-r, the GO category corresponded to patients in eMCS at the outcome assessment time point; in the studies adopting GOS, GOS-E, or CPC, the GO category corresponded to conscious patients, independently of the grade of disability associated with the specific scales' total score. However, the reporting of death across studies was not rigorous. Indeed, one study

(Koenig et al., 2014) explicitly reported 3 deaths due to withdrawal of care, while 6 studies did not provide sufficient information to distinguish between deaths due to the natural course of the disease and deaths potentially influenced by withdrawal of care. Specifically, in these cases, deaths were either reported without clarification of their causes (Chen et al., 2024; Shao et al., 2024) or not reported at all by providing aggregated outcome measures (Guo et al., 2019; Li et al., 2023; Zhang et al., 2023, 2022a). The remaining five studies did not mention any deaths at the time of outcome assessment (Wang et al., 2024; Wu et al., 2022; Zhang et al., 2018; Li et al., 2024; Zhang et al., 2022b). Table 2 shows the socio-demographic and clinical data of the included patients.

3.2. Meta-analysis results

Starting from the 12 included studies, 13 contrasts comparing the resting state activity between GO and BO patients were considered. A total of 38 foci were included in the meta-analysis: 23 foci reflecting hyperactivity and 15 reflecting hypoactivity in GO patients. Table 1 summarizes the main characteristics of the studies included in the meta-analysis and their quality assessment score (QS; see also Supplementary Table S3).

The activations characterizing GO described across the included studies were located in three clusters (Fig. 2; Table 3). Specifically, the biggest cluster spanned the occipital cortex bilaterally and the right precuneus ($p < .0001$). The second cluster encompassed right temporoparietal regions, including the right superior and middle temporal gyri and right supramarginal gyrus ($p < .001$). Finally, significant activations were found in the right middle frontal gyrus ($p = .002$). No significant decrease in resting state activity was found in GO.

Heterogeneity analysis revealed non-significant between-study heterogeneity for the cluster #1 ($Q = 11$, $p = .442$; $I^2 = 0.05\%$) and #2 ($Q = 11.13$, $p = .431$; $I^2 = 1.22\%$). In contrast, both the Q and I^2 statistics indicated moderate heterogeneity (Cochran, 1954; Higgins et al., 2003; Higgins and Thompson, 2002) for cluster #3 ($Q = 27.30$, $p = .004$; $I^2 = 59.71\%$).

Table 2
Socio-demographic and clinical data of the included patients.

Study	Sample size GO/BO (n)	Gender GO/BO (n, M)	Age GO/BO ($\bar{X}$; years)	Etiology GO/BO	Diagnosis GO/BO	TSI GO/BO ($\bar{X}$; days)	Outcome's time point GO/BO ($\bar{X}$; days)	Outcome measure
Wang et al. (2024)	13/24	8/13	57.7/62.5	7/11 TBI, 6/13 HBI	Na *	15.4/16.9	74.6/73.1	CRS-r
Chen et al. (2024)	20/10	19/8	48/56.7	3/9 TBI, 16/1 HBI, 0/1 AIE	1/7 UWS, 4/4 MCS, 6/0 eMCS, 8/0 LIS	71/79	294/286	CRS-r; GOS
Shao et al. (2024)	12/19	8/12	55/59	12/19 AIE	Na ♦	1	90/90	CPC
Li et al. (2024)	13/8	8/7	52.2/59.3	13/8 TBI	Na *	17.5/17.7	180/180	GOS-E
Zhang et al. (2023)	8/20	5/14	64.3/54.9	8/20 TBI	Na *	15/15	180/180	GOS-E
Li et al. (2023)	18/45	11/28	50.2/52.8	18/45 TBI	Na *	14.5/15.8	165.4/164.1	GOS-E
Wu et al. (2022)	13/14	9/11	40/47.8	12/7 TBI, 1/1 AIE, 0/6 HBI	13/14 UWS	108.1/102	90/90	GOS
Zhang et al. (2022b)	13/8	7/8	52.2/59.3	13/8 TBI	Na *	15/15	180/180	GOS-E
Zhang et al. (2022a)	8/20	5/14	64.3/54.9	8/20 TBI	Na *	15/15	180/180	GOS-E
Guo et al. (2019)	12/9	18	38.3	12/9 TBI	Na *	4.3	175.6	GOS
Zhang et al. (2018)	4/5	3/2	22.8/48	4/3 TBI, 0/1 AIE	2/0 MCS, 2/5 UWS	62.3/51.2	249.7/64.2	CRS-r
Koenig et al. (2014)	8/9	6/8	55	8/9 AIE	Na *	5/5	10/55.5	CPC

Note: AIE, Anoxic-Ischemic Encephalopathy; BO, Bad Outcome; CPC, Cerebral Performance Category scale; CRS-r, Coma Recovery Scale – revised; GCS, Glasgow Coma Scale; GOS-E, Glasgow Outcome Scale – Extended; GO, Good Outcome; HBI, Hemorrhagic Brain Injury; MCS, Minimally Conscious State; TBI, Traumatic Brain Injury; UWS, Unresponsive Wakefulness Syndrome; * Studies adopting the Glasgow Coma Scale to diagnose DoC, preventing the differentiation between UWS and MCS patients; ♦ Study relying on the absence of command-following behaviour to diagnose DoC, thus not allowing the differentiation between UWS and MCS patients; $\bar{X}$, mean

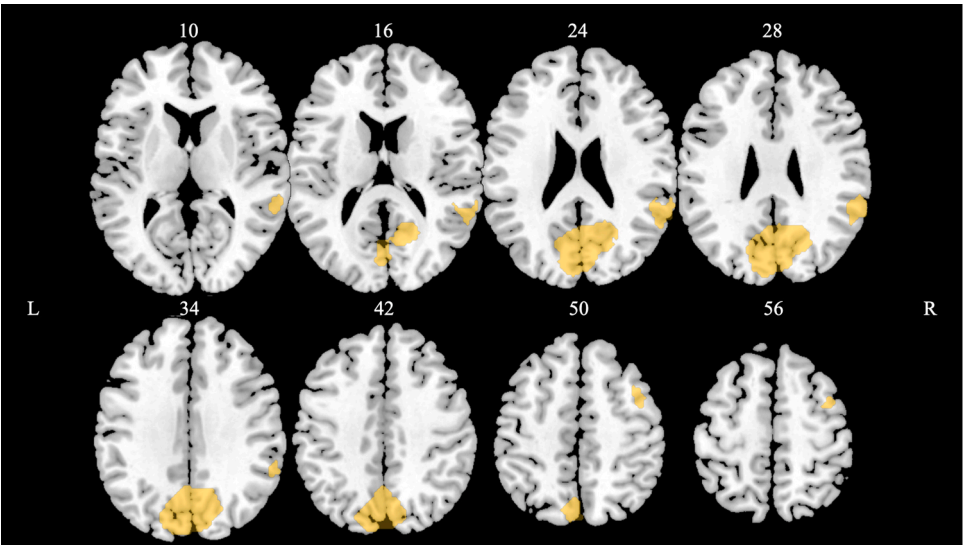


Fig. 2. Meta-analytic map. Meta-analytic map (i.e., GO > BO; in yellow) rendered on eight axial representative sections of MNI template (Rorden and Brett, 2000). The z-coordinate is indicated on top of each slice. L= Left; R= Right.

Table 3
Difference in resting state activity between GOOD outcome (GO) and BAD outcome (BO) patients. Clusters' peak MNI coordinates (in bold) and their local peaks are reported (voxels 2x2x2 mm³ ≥ 96; SDM-Z ≥ 1.361; p < .005).

Cluster	Voxel	SDM-Z	Side	Brain region	x	y	z	Q (p)	I ² (%)	Egger (p)	Jackknife
GO > BO											
1	3705	2.613	R	Median network, cingulum	10	-60	24	.442	0.05	.378	11 out of 12
		2.577	R	Cuneus cortex, BA 23	12	-64	20				
		2.551	R	Precuneus	16	-64	30				
		2.548	R	Median network, cingulum	12	-60	28				
		2.542	R	Cuneus cortex, BA 18	16	-72	32				
		2.516	R	Precuneus, BA 23	10	-66	24				
		2.511	R	Cuneus cortex	14	-72	28				
		2.500	R	Cuneus cortex; BA 18	6	-82	28				
		2.498	L	Cuneus cortex, BA 23	-8	-68	24				
		2.489	L	Cuneus cortex, BA 18	0	-84	26				
		2.464	L	Cuneus cortex	-8	-76	24				
		2.455	L	Cuneus cortex	-8	-84	26				
		2.438	R	Cuneus cortex, BA 19	8	-82	34				
		1.955	R	Precuneus	22	-54	22				
		1.950	R	Precuneus	2	-78	48				
2	509	1.625	R	Superior Occipital Gyrus	26	-66	28	.431	1.22	.180	11 out of 12
		1.756	R	Superior temporal gyrus, BA 22	60	-48	16				
		1.753	R	Supramarginal gyrus, BA 48	54	-44	26				
		1.742	R	Supramarginal gyrus, BA 48	64	-42	24				
		1.742	R	Supramarginal gyrus, BA 48	56	-44	30				
		1.737	R	Superior temporal gyrus; BA42	52	-46	20				
		1.737	R	Supramarginal gyrus, BA 22	56	-48	16				
		1.704	R	Supramarginal gyrus, BA 48	62	-42	30				
		1.634	R	Middle temporal gyrus, BA 42	60	-42	10				
		1.614	R	Superior temporal gyrus, BA 41	50	-42	20				
3	96	1.613	R	Superior temporal gyrus, BA 42	62	-38	10	.004	59.71	.216	10 out of 12
		1.482	R	Superior temporal gyrus, BA 42	64	-36	14				
		1.480	R	Middle frontal gyrus, BA 6	40	6	52				

Note: BA, Broadman area; BO, Bad Outcome; GO, Good Outcome; L, left; MNI, Montreal neurological institute; N., cluster's number; (p), p value; R, right

No significant evidence of publication bias was detected, as assessed by Egger's test at each peak voxel level (all $p > .05$; Table 3). Funnel plots for all brain clusters, along with the corresponding Egger's test results, are provided in the [Supplementary Materials \(Figures S1–S3\)](#).

The jackknife sensitivity analysis resulted in a total of 12 separate meta-analyses. All identified clusters showed high stability across the analyses (Table 3).

See [Supplementary Materials](#) for exploratory meta-regression on TSI (Table S4 and Figure S4–8) and the outcome time point (Table S5 and Figure S9–13).

3.3. Network correspondence

The meta-analytic map showed significant spatial overlap with several networks across multiple atlases, including visual, DMN, and fronto-parietal (i.e., “ControlC”; Yeo et al., 2011) networks (Fig. 3). Among these, the precuneus network from the Shirer's atlas (Shirer et al., 2012) showed the highest Dice spatial overlap coefficient (Dice coefficient=.3749, $p = .002$). The network correspondence results for each atlas are reported in [Supplementary Materials \(Table S6 and Figure S14\)](#).

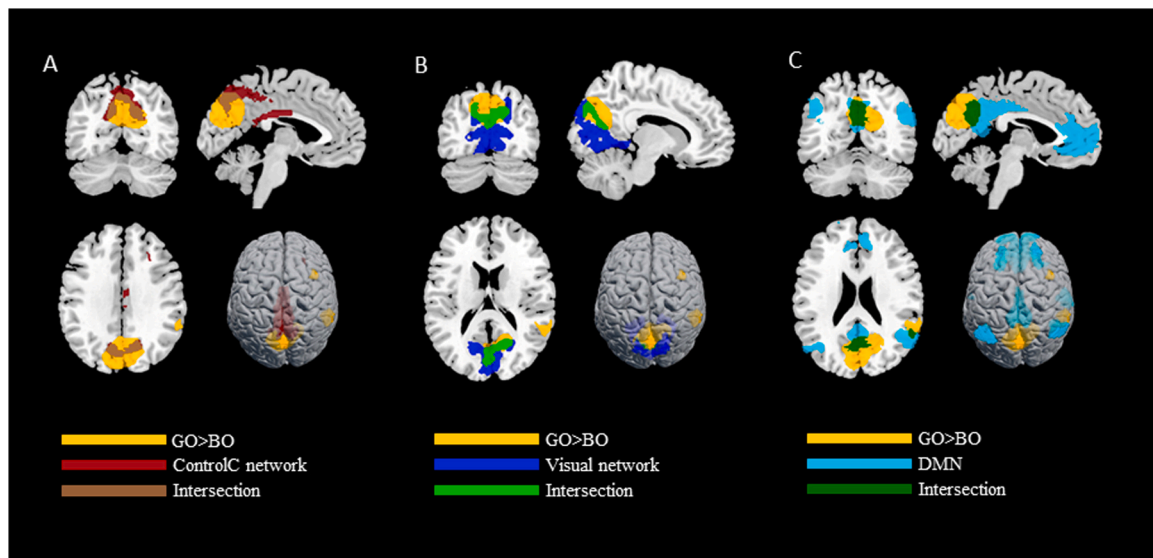


Fig. 3. Network correspondence. Spatial overlap (i.e., intersection) between the meta-analytic map and the fronto-parietal (i.e., “Control C”; Panel A), visual (Panel B), and the DMN (Panel C) networks rendered on eight representative sagittal section of MNI template. Each network has been graphically represented adopting the 17-network atlas of Yeo et al. (Yeo et al., 2011). The x-coordinate is indicated on top of each slice. BO, Bad Outcome; DMN, Default Mode Network; GO, Good Outcome.

4. Discussion

Assisting the prognosis of DoC patients is as important as it is challenging (Fischer and Edlow, 2024), especially when considering the prognostic utility of resting state brain imaging. Indeed, no clear prognostic recommendations have been internationally provided yet, due to the heterogeneity characterizing the existing studies, the small sample sizes considered, and the limited availability of rigorous longitudinal studies on DoC patients employing resting state brain imaging techniques. For these reasons, we conducted a meta-analysis aimed at exploring whether the spontaneous activity of specific brain regions is informative for full recovery of consciousness in DoC patients. Our results on 12 studies suggested that the activation of sensory and associative areas is pivotal in predicting DoC patients’ outcome, with the greatest significance for the posterior cluster encompassing bilateral occipital areas and precuneus.

The role of posterior brain areas has received much attention over the years (see, for instance, the theories on the posterior hot zone for consciousness; (Koch et al., 2016)), and exploring their activity has been shown to be informative of both the diagnosis (Clementi et al., 2025; Deruti et al., 2026; Medina Carrion et al., 2025) and prognosis (Wijnen et al., 2014) in DoC patients, especially when referring to the precuneus and visual network (Deruti et al., 2026). Interestingly, Voss and colleagues (Voss et al., 2006) described a patient who recovered consciousness 19 years after the traumatic brain injury, possibly due to the reorganization of white matter within occipital cortices, and this interpretation was supported by preserved metabolism in occipital areas as compared across the other brain areas. In the same direction, studies on large cohorts of patients suffering from anoxic brain injury after cardiac arrest, found that apparent diffusion coefficient signal in occipital area was more strongly associated with DoC than whole-brain apparent diffusion coefficient signal (Snider et al., 2022) and it is significantly different between patients with good and poor outcome, principally involving putamen, parietal, and occipital areas (Wu et al., 2009). Similarly, Tan et al. (Tan et al., 2017) reported a significant increase in the fibres’ distribution in several posterior brain regions encompassing the right cuneus in a patient who improved from UWS to MCS. Furthermore, it is important considering both the anatomical proximity and the functional interconnection between cuneus and precuneus (Cavanna and Trimble, 2006). Indeed, the precuneus is one of the main

hubs of the DMN, contributing to self-awareness, visuo-spatial processing, memory, and multisensory integration (Fransson and Marrelec, 2008; Lyu et al., 2023), also mediating between internal activity (e.g., self-referential thinking) and high-level functioning (e.g., episodic memory) (Fransson and Marrelec, 2008). To fulfil these functions, the precuneus needs to receive information from several brain structures, which are then elaborated and integrated. Among the information directed to the precuneus, the visual ones deserve particular attention from a neurocognitive perspective as they could be the ground to build mental visuo-spatial representations allowing the interaction with the external environment (Cocchini et al., 2007). In other words, the precuneus likely depends on having the information to be integrated and employed for high-level functioning. Thus, without the functioning of low-level areas providing such information, the precuneus possibly cannot carry out its role for consciousness. Not by chance, when exploring the correspondence between our meta-analytic map and functional networks across several atlases, we found significant overlap with both the visual network and DMN, with precuneus reaching the highest spatial overlap coefficient. Moreover, the precuneus has strong interconnections with several other brain structures, including temporo-parietal, motor, and premotor areas (Cauda et al., 2010), which were found being part of the other two clusters in the present meta-analysis.

As for the right temporo-parietal cluster, it is important to consider its role for sensory input processing, spatial representation, and language functions (Price, 2012). Indeed, the superior temporal gyrus is involved in both perceptual and conceptual acoustic processing (Baker et al., 2018), and several evidence indicate the involvement of the anterior part of the temporal lobes in the semantic representations of words, objects, and social cognition (Damasio et al., 2004; Lambon Ralph et al., 2010; Trumpp and Kiefer, 2025; Zhang et al., 2024). Although a clear functional lateralization of the above-mentioned functions within the temporal lobe is still a matter of debate (Ramos Nuñez et al., 2020; Rice et al., 2015), a lot of neuropsychological studies have traditionally associated language-related functions with the left side of this area (Boatman et al., 1995; Kreisler et al., 2000; Wise et al., 2001). Indeed, lesions to BA 42 and BA 22 in the left hemisphere cause impairments in verbal comprehension and speech processing (Boatman et al., 1995; Wise et al., 2001), whilst when the same areas are lesioned in the right hemisphere, patients manifest impairments in visuo-spatial

awareness (Karnath, 2001). Similarly, the right BA 48 being part of the same cluster in our meta-analysis plays a pivotal role for visuo-spatial orientation (Baltaretu et al., 2023, 2020). This evidence supports the hypothesis that intact sensory and associative brain structures are necessary to sustain consciousness, which, quoting H.O. Karnath, “*might work together to create networked representations about the world, allowing us to interact successfully with our environment*” (Karnath, 2001; p.568). When considering previous evidence on DoC patients, an increased activity in temporal areas (i.e., right STG, right Heschl’s gyrus, and right Wernicke’s area) following training involving unimodal auditory (Pape et al., 2015) or multimodal (Cheng et al., 2018) sensory stimulations was associated with an improvement in the level of consciousness. Additionally, a study adopting diffusion-weighted MRI to explore any differences among DoC patients after cardiac arrest depending on their outcome found significant diffusion coefficient reduction in temporal areas, along with occipital areas and putamen, characterizing poor outcome patients (Mlynash et al., 2010). In summary, similarly to what was observed for the most posterior cluster, temporo-parietal areas might play a role in predicting DoC patients’ outcome, given their role in receiving and elaborating information useful for high-level functioning and allowing the mental representations driving environmental interaction.

A similar reasoning, concerning the need of spared brain structures supporting environmental interaction, might explain the role of the third cluster, located in the right middle frontal gyrus (BA 6). Indeed, it encompasses the supplementary motor area (SMA) and the premotor (PM) cortex, which are pivotal for planning internally and externally (i.e., based on visual or auditory information) driven movements, respectively (Thut et al., 2000). Moreover, these regions are strongly interconnected to the precuneus as well (Cauda et al., 2010; Mailo and Tang-Wai, 2015), suggesting they contribute to precuneus functioning by providing visuo-spatial guidance for movements in the external environment (Cavanna and Trimble, 2006). Indeed, SMA activation in patients with DoC has been found during the picture naming task used as a proxy of command-following, also in patients not showing any motor response when assessed behaviourally (Rodríguez Moreno et al., 2010), meaning that preservation of typically related motor areas is importantly related to the consciousness level behind the overt responses. Furthermore, Schiff and colleagues described a patient who lately improved the level of consciousness due to Deep Brain Stimulation targeting the central lateral thalamic nucleus, which mainly innervates PM and SMA, thus providing indirect evidence for the role of these areas in recovering consciousness (Schiff et al., 2007). The cluster encompassing SMA and PM found in the present meta-analysis, despite being the smallest and characterized by a significant heterogeneity across the included studies, might represent the ground to promote voluntary interaction with the environment. However, whilst the role of this cluster appears reasonable from a theoretical point of view, the result did not appear stable enough when controlling for confounding factors such as the outcome time point, which was highly heterogeneous across studies. Indeed, different from the other individuated clusters, it was no longer found in the meta-regression when controlling for the outcome time point (see [Supplementary Materials](#)), which, however, should be interpreted with caution, given the small number of included studies. Indeed, these results might be influenced by study-specific noise rather than reflecting a robust overall effect. Further data is needed to better explore the potential role of premotor areas in predicting DoC patients’ outcomes.

In summary, the results of the present meta-analyses, taken together, support the role of posterior brain areas for recovering consciousness after SABI, in line with both Integrated Information Theory (Tononi, 2004) and the Recurrent Processing framework (Lamme and Roelfsema, 2000), which postulate that posterior cortical areas are important for consciousness. This finding is somewhat in contrast with theories of consciousness relying also on the contribution of high-level anterior brain areas, despite not exclusively (see, for instance, the

Global Neuronal Workspace Theory and Higher Order Theory; Dehaene and Changeux, 2011; Lau and Rosenthal, 2011). The centrality of the anterior areas for consciousness is supported by the functional role of these regions, that contribute to attentional processing, inhibition, motor planning, and, more generally, executive functioning. Supporting this view, a review on the prognostic value of functional activations studies conducted on UWS patients during passive/active paradigms highlighted that patients recovering consciousness showed brain activations not limited to primary sensory areas and involving high-level associative cortical areas encompassing the most anterior ones (Di et al., 2008). Similarly, another review of studies exploring brain areas’ implication in recovery of consciousness adopting different techniques (e.g., fMRI; PET; diffusion tensor tractography; EEG) concluded for a pivotal role of supratentorial areas, including parietal cortex, anterior cingulate cortex, basal forebrain, and prefrontal cortex (Jang and Kwon, 2019). Coherently, when looking at the overlap between our meta-analytic map and networks from different atlases, we also found consistency across atlases for the overlap with frontoparietal networks in addition to the visual network and DMN, meaning that diverse networks contribute to consciousness recovery, although none of the clusters found in the meta-analysis encompassed the prefrontal areas, being instead limited to the involvement of premotor areas. The hypothesis of the involvement of diverse networks for consciousness recovery is in line with a recent adversarial collaboration aimed at explaining the brain activity underlying the conscious experience (Ferrante et al., 2025). Specifically, the authors argued for the contribution of both low-level posterior and high-level anterior brain areas, which are deputed to different aspects of the conscious experience (Ferrante et al., 2025). Indeed, low-level posterior and high-level anterior areas are functionally interconnected, and both can contribute to consciousness’ recovery. Specifically, a study adopting High-Definition transcranial Direct Current Stimulation over the dorso-lateral prefrontal cortex to improve the level of consciousness of DoC patients showed a significant increase in Power Spectra Density of different frequency bands (i.e., theta, alpha, and beta) in parieto-occipital regions (Han et al., 2022). Importantly, these changes were recorded before the patients’ behavioral improvement emerged, indicating that the connection between anterior and posterior brain areas is important for consciousness recovery. Moreover, a recent study highlighted that both anterior and posterior brain areas contribute to consciousness recovery since repetitive Transcranial Magnetic Stimulation on either dorso-lateral prefrontal cortex or occipital areas significantly increases the level of consciousness in DoC patients, independently of the stimulation site (Wang et al., 2024). Nevertheless, our results may suggest the importance of preserved activity in the posterior brain areas to promote the above-mentioned exchange of information with most anterior areas, leading to consciousness recovery over time. In other words, the present meta-analysis suggests that, without the functional integrity of posterior brain areas in the post-acute phase, there is a lower chance of recovering consciousness over time for patients with DoC; notwithstanding, we cannot rule out the contribution of anterior brain areas, such as the prefrontal ones, to ensuing processes of consciousness recovery. Future studies could explore resting state brain activity of DoC patients at different time points to dynamically follow the brain functional changes leading to the recovery. Overall, the results of the present meta-analysis suggest that diverse networks should be functioning to allow consciousness recovery, which can be possible if stimuli deriving from the external environment are (i) processed, (ii) integrated, and (iii) elaborated to eventually (iv) act upon them. All these steps can be guaranteed by the functioning of the areas we found to be part of the three clusters in the present meta-analysis. Low-level sensory areas are needed to detect and further process information deriving from the outside world, while high-level associative areas are needed to integrate the information and allow interaction with the outside world. Importantly, the precuneus could be a pivotal structure receiving and integrating information useful to create visuo-spatial representations of the outside world to further act

upon them and promote environmental interaction.

4.1. Limitations

However, it is important to address some limitations. First, we included a small number of studies due to methodological heterogeneity. Therefore, we could not control several factors already known to affect DoC patients' outcomes, such as the etiology, age at the acute event, and diagnosis. Importantly, the diagnosis was not determined by adopting the reference standard to diagnose DoC, namely the CRS-r, in most of the studies. Instead, in most of them, GCS was used, thus preventing the distinction between UWS and MCS, despite detecting DoC (see Table 1). Moreover, even when adopting CRS-r to diagnose DoC in two studies (Chen et al., 2024; Zhang et al., 2018), the contrasted groups were heterogeneous and lacked stratification by diagnosis, thus preventing to determine the role played by diagnosis in patients' outcome. A similar scenario characterized the variable etiology with studies contrasting heterogeneous groups (Chen et al., 2024; Wang et al., 2024; Wu et al., 2022; Zhang et al., 2018) and limiting the possibility to control the effect of this variable on patients' outcome. Moreover, a relevant limitation of this work lies in the incomplete reporting of causes of death (i.e., natural history vs withdrawal of care). This might represent a source of bias since we cannot identify how many patients have been withdrawn from care. Indeed, practices related to withdrawal of care vary across countries and healthcare systems, thus influencing mortality rates independently of patients' neurological condition. Future studies should report information on withdrawal of care to allow consideration of this factor when interpreting mortality data. Furthermore, we cannot rule out that some of the results of the present meta-analysis were triggered by the methodology adopted for images acquisition. Indeed, the main significant cluster encompassed visual areas; concurrently, we did not know whether the patients had their eyes open or closed during image acquisition, except for a study that clearly reported this finding (Koenig et al., 2014). If patients had eyes open during images acquisition, it is possible that results were driven by this factor. Future studies adopting resting state imaging should clearly report all the methodological details that can affect results. Similarly, studies on DoC patients should try to compare homogenous groups of patients to avoid any confounder in the results. Finally, an additional methodological limitation concerns the lack of differentiation between distinct rs-fMRI metrics, which would ideally require separate quantitative syntheses. However, the limited number of available studies prevented reliable metric-specific subgroup analyses. Consequently, the results should be interpreted with caution, as they reflect convergent spatial distributions of increase and decrease in resting state activity across heterogeneous metrics, rather than metric-specific effects, which could not be systematically disentangled.

4.2. Conclusion

In summary, to date, the time has not come to clearly indicate which areas' spontaneous activity predicts DoC patients' outcome for clinical management. This difficulty is directly related to the quality of the existing studies adopting resting state imaging techniques in DoC patients. However, the present meta-analysis, despite including a limited number of studies, suggests both low-level and high-level associative areas contribute to DoC patients' outcome prediction, possibly due to the need of having low-level sensory information as the ground to build mental representations driving environmental interaction.

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No AI tool was used to generate any part of the paper

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2026.106837.

Data availability

Data are available on request to the authors

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