Received: 12 December 2022 | Revised: 30 August 2023 | Accepted: 11 September 2023

DOI: 10.1111/ejn.16149

SPECIAL ISSUE REVIEW

EJN European Journal of Neuroscience FENS WILEY

New Trends in the Empirical Study of Consciousness: Measures and Mechanisms

Multimodal approaches supporting the diagnosis, prognosis and investigation of neural correlates of disorders of consciousness: A systematic review

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Funding information
Italian Ministry of Health, Grant/Award Number: GR-2016-02361494; Italian Ministry of Health – RicercaCorrente 2022; Fondazione Regionale per la Ricerca Biomedica (Regione Lombardia), Grant/Award Number: GA 779282

Edited by: Simone Sarasso

Abstract

The limits of the standard, behaviour-based clinical assessment of patients with disorders of consciousness (DoC) prompted the employment of functional neuroimaging, neurometabolic, neurophysiological and neurostimulation techniques, to detect brain-based covert markers of awareness. However, uni-modal approaches, consisting in employing just one of those techniques, are usually not sufficient to provide an exhaustive exploration of the neural underpinnings of residual awareness. This systematic review aimed at collecting the evidence from studies employing a multimodal approach, that is, combining more instruments to complement DoC diagnosis, prognosis and better investigating their neural correlates. Following the PRISMA guidelines, records from PubMed, EMBASE and Scopus were screened to select peer-review original articles in which a multi-modal approach was used for the assessment of adult patients with a diagnosis of DoC. Ninety-two observational studies and 32 case reports or case series met the inclusion criteria. Results highlighted a diagnostic and prognostic advantage of multi-modal approaches that involve

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electroencephalography-based (EEG-based) measurements together with neuroimaging or neurometabolic data or with neurostimulation. Multimodal assessment deepened the knowledge on the neural networks underlying consciousness, by showing correlations between the integrity of the default mode network and the different clinical diagnosis of DoC. However, except for studies using transcranial magnetic stimulation combined with electroencephalography, the integration of more than one technique in most of the cases occurs without an a priori-designed multi-modal diagnostic approach. Our review supports the feasibility and underlines the advantages of a multimodal approach for the diagnosis, prognosis and for the investigation of neural correlates of DoCs.

KEYWORDS
diagnosis, disorders of consciousness, multimodal approach, systematic review

1 | INTRODUCTION

Brain injuries of traumatic or non-traumatic aetiology can lead to extended impairments affecting behaviour, cognition and awareness. Indeed, following acute brain damage, some patients fully recover, whereas others fall into a state of altered awareness, the so-called disorders of consciousness (DoC). DoC involves several conditions characterized by different levels of arousal and self and environmental consciousness: coma, vegetative state (VS) or successively called unresponsive wakefulness syndrome (VS/UWS; Laureys et al., 2010; The European Task Force on DoC, 2010) and minimally conscious state (MCS). Coma is a transient state characterized by a complete lack of wakefulness and awareness. In this condition, sleep–wake cycles are absent; patients lie down with closed eyes, unable to communicate or respond to any command. Coma usually lasts up to 1 month before moving towards brain death or recovery of wakefulness (Posner et al., 2007). The emergence of observable sleep–wake cycles defines the VS/UWS, a condition in which patients are awake but unaware (Laureys et al., 2010). In the presence of reproducible albeit fluctuating signs of consciousness, patients are diagnosed as MCS. Both VS/UWS and MCS conditions are termed chronic after 3 months in the case of non-traumatic brain injuries and after 12 months for traumatic aetiology (TBI, traumatic brain injury; Giacino, Katz, Schiff, Whyte, Ashman, Ashwal, Barbano, Hammond, Laureys, Ling, Nakasse-Richardson, et al., 2018; Giacino, Katz, Schiff, Whyte, Ashman, Ashwal, Barbano, Hammond, Laureys, Ling, Nakase-Richardson, et al., 2018). When patients recover communication and/or functional objects use, they emerge from MSC (EMSC; Giacino et al., 2002). MCS patients can be further divided into MCS + and MCS−, based on the presence or absence of behavioural evidence of verbal processing and command following (Bruno et al., 2012; Thibaut et al., 2020).

Nowadays, the prevailing approach (Kondziella et al., 2020) used to detect and evaluate the level of consciousness of brain-injured individuals relies upon the bedside clinical observation of the ability to communicate and interact with the surrounding environment (Giacino et al., 2009). Several standardized scales have been employed either in the context of intensive care units (ICUs) or in a subsequent rehabilitation stage, throughout the recovery. To date, the most sensitive and validated scale is the Coma Recovery Scale-Revised (CRS-R; Giacino et al., 2004). Due to the fluctuations, CRS-R should be performed at least five times, every other day, in a short time interval (e.g., 10 days or 2 weeks) and at different times of the day (Seel et al., 2010; Wannez et al., 2017).

However, behavioural assessment can also be affected by the complex clinical conditions of DoC patients, which might prevent them from showing reliable signs of consciousness, for instance, due to presence of life-saving devices (e.g., verbal responses could not be tracked in case of individuals with artificial respiratory help), neurological deficits (e.g., aphasia and agnosia), muscle paralysis, acute pain (Schnakers, 2012) or sedating medications (Whyte et al., 2013), which might impair their ability to communicate or interact, leading to fluctuating and ambiguous responses (Gill-Thwaites, 2006). Moreover, on one hand, the level of expertise of clinicians could influence the evaluation as only well-trained and experienced personnel could effectively manage the behavioural scales (Schnakers et al., 2009). On the other hand, the lack of behavioural evidence is not necessarily an index of the absence of awareness (Owen et al., 2006), since brain-damaged patients may be covertly conscious without the ability to prove it behaviourally, thus affecting the clinical diagnostic procedures (Giacino et al., 2009; Schnakers et al., 2009).

For these reasons, in the last two decades, new and promising instrumental approaches have been developed to directly examine brain activity to achieve a more

objective, brain-based measure of consciousness, thus complementing both the behavioural diagnosis and prognosis, as well as to enhance the differential diagnosis of DoC and to better understand the neural mechanisms underlying the loss of consciousness. These approaches are mainly based on the use of neuroimaging and neurometabolic techniques, such as computed axial tomography (CT), fluorodeoxyglucose positron emission tomography (FDG-PET) and magnetic resonance (MRI); neurophysiological techniques, such as electroencephalography (EEG) and magnetoencephalography (MEG); or non-invasive neurostimulation techniques, such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS). Recently, all these techniques expanded the possibility of detecting neural markers of residual consciousness otherwise not observable from overt behaviour due to the cognitive-motor dissociation (CMD) or the higher order motor dissociation (HMD; Edlow et al., 2017). Indeed, CMD is a condition in which a patient behaviourally diagnosed as VS/UWS or MCS shows signs of residual command-following abilities only during the instrumental evaluation of brain activity. HDM condition, instead, occurs when the patients, during passive stimulation based on language, show concordant responses in the associative cortices, despite the absence of overt responses during the behavioural assessment (Edlow et al., 2017). Early detection of covert consciousness is a crucial element for guiding clinicians in the selection of appropriate care programs and time-sensitive decisions about holding life-sustaining therapies. Several reviews have already described these novel diagnostic procedures (Giacino et al., 2014; Gosseries et al., 2014; Harrison & Connolly, 2013), reporting their crucial impact in understanding the neural underpinnings of awareness and how their extensive employment may improve the diagnosis, the prognosis and treatment paths of DoC patients.

Despite these encouraging results, these reviews also highlight the limits of one-dimensional assessment, pointing to the convenience for large-scale, multicentre validation studies and suggesting the advantages of integrating more than one technical instrument in multimodal approaches. Each instrument alone, indeed, presents limits, due to the spatial or temporal resolution, the specific accuracy of the outcome measures as a probe of consciousness or the presence of counter-indications. The possibility of combining and integrating different paraclinical tools in a multimodal approach, instead, allows to sum up the respective advantages and overcome the specific limits of each technique.

This systematic review aims to complement the existing literature, by reporting the results of studies that applied multimodal approaches, beyond the standard clinical bedside evaluation, for the diagnosis and prognosis of DoC patients. Crucially, we considered 'multimodal' the approaches that combined or employed at least two different neurophysiological, neuroimaging, neurometabolic or non-invasive brain stimulation tools, to collect evidence of brain functioning and responsiveness. More in detail, for the purpose of this systematic review, we excluded from our analysis studies considering only indexes or measures derived from the same type of functional assessment (e.g., for our scope, we did not consider as 'multimodal', previous studies that combined spontaneous EEG-based markers with somatosensory evoked potentials (SSEPs) and/or brainstem auditory evoked potentials (BAEPs). Moreover, CRS-R and all the other traditional clinical evaluations were not considered as additional diagnostic tools for defining a study as 'multimodal' but were just used as references for confirming DoC diagnosis.

2 | METHODS

2.1 | Literature search

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009) to conduct this systematic review (see Appendix S4 for the PRISMA checklist). We used PubMed, Scopus and EMBASE (Ovid) as database search to combine the following keywords: 'consciousness disorders', 'persistent vegetative state', 'minimally conscious state', 'unresponsive wakefulness syndrome' and 'coma' on one hand and 'electroencephalography', 'magnetic resonance imaging', 'positron emission tomography', 'evoked potentials', 'transcranial magnetic stimulation', 'transcranial direct current stimulation', 'magnetoencephalography', 'diffusion tensor imaging', 'functional near-infrared spectroscopy', 'polysomnography', 'transcranial alternating current stimulation', 'non invasive brain stimulation' and 'ultrasound stimulation' on the other hand (see Appendix S1 for the details regarding search strategies and combinations).

2.2 | Selection process and criteria

We used Rayyan, a web-based systematic review manager (Ouzzani et al., 2016) to remove duplicates and screen the retrieved articles, first based on title/abstract and then on full-text papers. In the title/abstract screening phase, six blinded authors (A. G., E. V., L. D. M., G. H., M. R. and L. J. R. L.), in pairs, assessed papers as

TABLE 1 Detailed information about the EEG-based studies included in the review.

EEG-based studies (64)						
Author	**Sample**	**CG**	**Age sample**	**Age CG**	**Gender sample**	**Gender CG**
EEG-neuroimaging studies (36)						
Bekinschtein et al. (2011)	5	3	Range = 20–40 y (average = 30 y)	Range = 23–28 y (average = 25.5 y)	3 M, 2 F	3 M
Beuchat et al. (2020)	78[a]	/	NFC mean = 54.9 y, sd = 16.3 y; FC mean = 52.8 y, sd = 9.9 y	/	NFC: 41 M, 26 F; FC: 8 M, 3 F	/
Bosco et al. (2014)	81	/	Mean = 26 y; sd = 14 y; range = 12–64 y	/	59 M, 22 F	/
Braiman et al. (2018)	21	13	Range = 7–47 y (average = 27 y)	Range = 20–52 y (average = 36 y)	14 M, 7 F	6 M, 7 F
Chatelle et al. (2020)	17	16	Mean = 27 y; sd = 7 y	Mean 28.5 y; sd = 7.8 y	13 M, 4 F	12 M, 4 F
Chennu et al. (2013)	2	8	Range = 19–60 y (average = 39.5 y)	Mean = 27.9 y; sd = 4.1 y	16 M, 6 F	3 M, 5 F
Cho et al. (2020)	20	/	nr	/	nr	/
Curley et al. (2018)	28	15	Mean age at time of injury = 26.1 y; range = 12–53 y; mean age at time of assessment = 31.6 y	Mean = 40.0 y; range = 23–55 y	21 M, 7 F	7 M, 8 F
Edlow et al. (2017)	16	16	Mean = 28.9 y; sd = 9.2 y	Mean = 28.5 y; sd = 7.8 y	12 M, 4 F	12 M
Gibson et al. (2016)	14	15	Mean = 41 y; range = 19–58 y	Mean = 18 y; range = 17–23 y	nr	nr
Gobert et al. (2018)	7	/	Mean = 56 y; range = 29–75 y	/	2 M, 5 F	/
Gofton et al. (2009)	19	10	Mean = 62.5 y; sd = 16.5 y; range = 17–85 y	Mean = 27.4 y; range = 25–34 y	12 M, 7 F	6 M, 4 F
Isono et al. (2002)	12	/	Mean = 39.7 y; range = 10–69 y	/	8 M, 4 F	/
Kassab et al. (2021)	7	/	Mean = 44.1 y; range = 31–57 y	/	5 M, 2 F	/
Keijzer et al. (2022)	50	/	Group 'good outcome': Mean = 55 y; range = 49–57 y; Group 'poor outcome': Mean = 70 y; range = 64–74 y	/	39 M, 11 F	/
Kim et al. (2021)	38[b]	106[b]	nr	ISO range = 20–40 y; PSY + KET range = 20–40 y	nr	nr
Lee, Sreepada, et al. (2022)	50	25	Mean = 60.9 y; sd = 12.7 y	Mean 57.9 y; sd = 7.0 y; range = 45–70 y	31 M, 19 F	25 M
Li et al. (2015)	22	7	Range = 17–70 y (average = 43.5 y)	Range = 19–40 y (average = 29.5 y)	17 M, 5 F	2 M, 5 F

TABLE 1 (Continued)

EEG-based studies (64)						
Author	**Sample**	**CG**	**Age sample**	**Age CG**	**Gender sample**	**Gender CG**
Lutkenhoff, Nigri, et al. (2020)	61	/	Mean = 53 y; range = 20–82 y	/	36 M, 25 F	/
Mikell et al. (2015)	9	16	Mean = 66 y; sd = 12 y; range = 50–85 y	Mean = 54 y; sd = 15 y; range = 27–82 y	4 M, 5 F	8 M, 8 F
Othman et al. (2021)	9	14	Mean = 65 y, range = 55–79 y	nr	6 M, 3 F	nr
Petzinka et al. (2018)	89	/	Mean = 63 y; range = 52–73 y	/	60 M, 29 F	/
Portnova et al. (2020)	10	15	Mean = 37.8 y; sd = 29.8 y	Mean = 29.6 y; sd = 3.5 y	8 M, 2 F	9 M, 6 F
Rae-Grant et al. (1996)	69	/	Mean = 36 y; sd = 17 y; range = 15–82 y	/	48 M, 21 F	/
Sangare et al. (2022)	20	/	Mean 51 y; range = 37–57 y	/	9 M, 11 F	/
Scarpino, Lolli, Lanzo, Carrai, Spalletti, Valzania, Lombardi, Audenino, Celani, Marelli, et al. (2019)	346	/	Mean = 68 y; range = 48–71 y	/	216 M, 130 F	/
Scarpino, Lolli, Lanzo, Carrai, Spalletti, Valzania, Lombardi, Audenino, Celani, Marrelli, et al. (2019)	346	/	Mean = 68 y; range = 48–70 y	/	216 M, 130 F	/
Scarpino et al. (2020)	210[c]	/	Mean = 64 y; range = 18–85 y	/	140 M, 70 F	/
Snider et al. (2022)	204	48	Mean = 55 y	Mean = 51 y	131 M, 73 F	13 M, 35 F
Soldner et al. (2001)	30	/	Mean = 26.9 y	/	23 M, 7 F	/
Valente et al. (2002)	24	/	Mean = 41 y; sd = 17.1 y; range = 16–74 y	/	19 M; 5 F	/
Velly et al. (2018)	150	50 P (as validation cohort); a minimum of 5 HC for each centre (14)	Mean = 56 y	50 P: mean = 50 y; sd = 16 y HC: nr	97 M, 53 F	50 P: 40 M, 10 F HC: nr
Wedekind et al. (1999)	57	/	Range = 13–68 y (average = 40.5 y)	/	44 M, 13 F	/
Wedekind, Hesselmann, and Klug (2002)	35	/	Mean = 36.6 y; range = 17–65 y	/	22 M, 13 F	/
Wedekind, Hesselmann, Lippert-Grüner, and Ebel (2002)	20	20	Mean = 31.9 y; range 17–56 y	Mean = 32.9 y; range = 19–50 y	15 M, 5 F	15 M, 5 F

TABLE 1 (Continued)

EEG-based studies (64)						
Author	**Sample**	**CG**	**Age sample**	**Age CG**	**Gender sample**	**Gender CG**
Zhang et al. (2011)	88	25	Mean = 62 y; sd = 14 y; range = 23–85 y	nr	47 M, 41 F	nr
EEG-metabolic studies (7)						
Candia-Rivera et al. (2021)	68	/	Mean = 38 y; range 18–73 y	/	38 M, 30 F	/
Chennu et al. (2017)	104	26	Mean = 34.99 y	/	/	/
Coleman et al. (2005)	6	4	Mean = 51 y; range 20–67 y	Mean = 54 y; range 40–70 y	3 M, 3 F	2 M, 2 F
Hermann et al. (2021)	57	32	Mean = 45.6 y; range 28.9–56.2 y	nr	34 M, 23 F (M/F ratio 1.6)	nr
Hildebrandt et al. (2007)	13	8	Mean = 48.3 y; sd = 15.1 y	Mean = 46.0; sd = 12.3 y	/	/
Laureys et al. (2000)	5	rCMRGlu = 53; rCBF = 18	P1: 42 y P2: 37 y P3: 52 y P4: 28 y P5: 63 y	rCMRGlu: mean = 42 y; range = 18–78 y; rCBF: mean = 33 y; range = 19–45 y	2 M, 3 F	rCMRGlu: 35 M, 18 F; rCBF: 8 M, 10 F
Rudolf et al. (1999)	24	18	Mean = 48 y; range 17–72 y	Mean = 46.1 y; range 28–73 y	15 M, 9 F	14 M, 4 F
EEG-neuroimaging-metabolic studies (7)						
Carriére et al. (2020)	186	nr	Mean = 39 y; sd = 16 y	nr	120 M, 66 F	nr
Ferraro et al. (2020)	11	38	Mean = 50.63 y; range 19–69 y	Range 23–67 y	4 M, 7 F	15 M, 23 F
Forgacs et al. (2014)	44	/	Range = 16 y 9 m–57 y 6 m (average 32 y)	/	31 M, 13 F	/
Hermann et al. (2020)	96	/	Mean = 42.2 y; sd = 16.4 y	/	62 M, 34 F (M/F ratio 1.8)	/
Laureys et al. (2002)	15	15	Mean = 48 y; sd = 17 y	Mean = 40 y; sd = 9 y	12 M, 3 F	8 M, 7 F
Sattin et al. (2020)	54	/	Group 'blink': Mean = 49.36 y, sd = 18.18 y; Group 'visual pursuit': Mean = 54.24 y, sd = 26.28 y	/	32 M, 22 F	/
Sattin et al. (2021)	58[d]	/	Group 'fixation' mean = 66.72 y, sd = 25.07 y; Group 'blink': Mean = 49.36 y, sd = 18.18 y; Group 'visual pursuit': Mean = 54.24 y, sd = 26.28 y	/	33 M, 25 F	/

(Continues)

TABLE 1 (Continued)

EEG-based studies (64)						
Author	**Sample**	**CG**	**Age sample**	**Age CG**	**Gender sample**	**Gender CG**
EEG-neurostimulation studies (14)						
Fekete et al. (2021)	116	/	Mean = 70 y; sd = 11 y	/	M/F ratio (%) = 65.5/34.4	/
Lapitskaya et al. (2013)	47	14	VS/UWS: mean = 45 y; sd = 22 y; MCS: mean = 41 y; sd = 17 y	Mean = 33 y; sd = 11 y	35 M, 12 F	8 M, 6 F
Naro, Leo, Filoni, et al. (2015)	14	7	MCS: mean = 53 y; sd = 17 y; VS/UWS: mean = 59 y; sd = 16 y	Mean = 55.3 y; sd = 5.8 y	6 M, 8 F	3 M, 4 F
Naro, Calabrò, Russo, et al. (2015)	22	23	MCS: mean = 57 y; sd = 7 y; MCS TBI: mean = 54 y; sd = 8 y; VS/UWS: mean = 56 y; sd = 4 y; VS/UWS TBI: mean = 52 y; sd = 6 y	HC: mean = 56.5 y; sd = 6.3 y; LIS: 51 y, EMCS: 45 y and 65 y	10 M, 12 F	EMCS: 2 M; LIS: 1 M; HC: nr
Naro, Leo, Cannavò, et al. (2015)	20	10	MCS: mean = 47 y; sd = 18 y; VS/UWS: Mean = 56 y; sd = 14 y	Mean = 45.3 y; sd = 6.2 y	8 M, 12 F	4 M, 6 F
Naro, Leo, Bramanti, and Calabrò (2015)	20	10	MCS: mean = 52 y; sd = 5 y; VS/UWS: mean = 54 y; sd = 3 y	Mean = 55.8 y; sd = 5.7 y	11 M, 9 F	nr
Naro, Leo, et al. (2016)	26	15	MCS: mean = 55 y; sd = 19 y; VS/UWS: mean = 51 y; sd = 13 y	Mean = 54 y; sd = 9 y	10 M, 16 F	8 F, 6 M
Naro, Bramanti, et al. (2016)	14	10	MCS: mean = 53 y; sd = 17 y; VS/UWS: mean = 59 y; sd = 14 y	Mean = 54.2 y; sd = 4.9 y	6 M, 8 F	4 M, 6 F
Naro et al. (2017)	20	10	MCS: mean = 57; sd = 5 y; VS/UWS: mean = 54 y; sd = 2 y	Mean = 54 y; sd = 1 y	11 M, 9 F	4 M, 6 F
Naro et al. (2018)	40	25	MCS: mean = 55 y; sd = 12 y; VS/UWS: mean = 52 y; sd = 11 y	Mean = 52 y; sd = 5 y	20 M, 20 F	11 M, 14 F
Odinak et al. (2014)	25	/	Range = 28–54 y	/	nr	/
Pisani et al. (2015)	10	/	VS/UWS: mean = 48 y; sd = 12 y; MCS: mean = 54 y; sd = 18 y	/	4 M, 6 F	/
Zhang et al. (2020)	13[e]	6	Mean = 53.8 y; sd = 13.5 y	nr	8 M, 5 F	nr

TABLE 1 (Continued)

EEG-based studies (64)						
Author	**Sample**	**CG**	**Age sample**	**Age CG**	**Gender sample**	**Gender CG**
Zhang et al. (2022)	31	/	Mean 56.2 y; sd = 16 y	/	20 M, 11 F	/

Note: The studies are grouped in four categories related to the different techniques combined: EEG-neuroimaging; EEG-metabolic; EEG-neuroimaging-metabolic; EEG-neurostimulation.
Abbreviations: ABR, auditory brainstem response; BAEP, brain stem auditory evoked potential; CRS, Coma Recovery Scale; CRS-R, Coma Recovery Scale – Revised; CT, computed tomography; CAP, Confusion Assessment Protocol; CS, conscious state; cEEG, continuous EEG; CG, control group; d, days; DTI, diffusion tensor imaging; DRS, Disability Rating Scale; ECG, electrocardiogram; EEG, electroencephalography; EMG, electromyography; EOG, electrooculography; EMCS, emerging from minimally conscious state; ERPs, event-related potentials; EPS, evoked-potentials; ECMO, extracorporeal membrane oxygenation; F, females; fVEPs, flash visual evoked potentials; FDG-PET, fluorodeoxyglucose-positron emission tomography; FC, follow command; FOUR, Full Outline of UnResponsiveness; fMRI, functional magnetic resonance; fNIRS, functional near-infrared spectroscopy; GBS, Gullain-Barré syndrome; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; GOSE, Glasgow Outcome Scale-Extended; CPC, Glasgow-Pittsburgh Cerebral Performance Categories; HC, healthy controls; hd-EEG, high density-EEG; h, hours; HE, hypoglycaemic encephalopathy; ICU, intensive care unit; ISO, isoflurane anaesthesia; KET, ketamine anaesthesia; PSY, ketamine psychedelic state; LIS, locked-in syndrome; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; M, males; MSEP, median nerve evoked somatosensory potential; MLAEP, middle-latency auditory evoked potential; mlSEP, middle-latency somatosensory evoked potential; MCS, minimally conscious state; min, minutes; MMN, mismatch negativity; mRS, modified ranking scale; m, months; MEP, motor evoked potential; NIRS, near-infrared spectroscopy; NSE, neuron-specific enolase; NFC, not follow command; nr, not reported; OPG, ocular plethysmography; P, patient; PMB, pons and/or midbrain; PET, positron emission tomography; PTCS, post-traumatic confusional state; rCBF, regional cerebral blood flow; rCMRGlu, regional cerebral metabolic rate for glucose; rTMS, repetitive transcranial magnetic stimulation; slSEP, short-latency somatosensory evoked potential; SPECT, single photon emission computed tomography; SEP, somatosensory evoked potential; SEPs, somatosensory evoked potentials; sd, standard deviation; SE, status epilepticus; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; TCD, transcranial Doppler; TMS, transcranial magnetic stimulation; tRNS, transcranial random noise stimulation; TBI, traumatic brain injury; VS/UWS, Vegetative State/Unresponsive Wakefulness Syndrome; VEPs, visual evoked potentials; WFNS, World Federation of Neurological Surgeons; y, years; /, not present in the study.
[a]Dataset already published in Dhakar et al. (2018), Szumita et al. (2010) and Oddo et al. (2014).
[b]Dataset already published with different analyses and hypotheses in Lee et al. (2019) and Huang et al. (2020).
[c]Part of the dataset already published in Scarpino, Lolli, Lanzo, Carrai, Spalletti, Valzania, Lombardi, Audenino, Celani, Marelli, et al. (2019); Scarpino, Lolli, Lanzo, Carrai, Spalletti, Valzania, Lombardi, Audenino, Celani, Marrelli, et al. (2019).
[d]Part of the dataset already published in Sattin et al. (2020).
[e]Part of the dataset already published in Zhang et al. (2017).

TABLE 1 (Continued)

EEG-based studies (64)							
Author	**Diagnosis sample**	**Diagnosis CG**	**Time from onset**	**Score evaluation test**	**Aetiology**	**Techniques**	**Aims**
EEG-neuroimaging studies (36)							
Bekinschtein et al. (2011)	VS/UWS	HC	Range post-injury = 5–20 m (average = 12.5 m)	CRS-R (range = 4–8; average = 6)	TBI (4); multiple aetiology (1)	MRI, ERPs, SSEP, BAEP, ECG	Differential diagnosis/ neural correlates
Beuchat et al. (2020)	NFC (67); FC (11)	/	Primary outcome through coma recovery to command following; secondary outcome at 3 m with CPC	CPC at discharge: FC (11); Died (67); CPC 4 (3); CPC 3 (10); CPC 2 (3); CPC 1 (1)	CA	EEG, MRI	Improve diagnosis and prognosis

TABLE 1 (Continued)

EEG-based studies (64)

Author	Diagnosis sample	Diagnosis CG	Time from onset	Score evaluation test	Aetiology	Techniques	Aims
Bosco et al. (2014)	Coma	/	Within the first 6 d post-injury	GCS (range = 3–8)	TBI	CT, EEG	Improve diagnosis and prognosis
Braiman et al. (2018)	VS/UWS (3); MCS (12); EMCS (6)	HC	nr	CRS-R (range = 1–19; average = 10)	TBI (18); stroke (2); other (1)	MRI, EEG	Differential diagnosis
Chatelle et al. (2020)	PTCS (6); MCS+ (5); MCS− (3); VS/UWS (2); Coma (1)	HC	Mean d post injury = 97.5 d; sd = 282.4 d	CRS-R	TBI	EEG, fMRI	Improve diagnosis and prognosis
Chennu et al. (2013)	VS/UWS (9); MCS (12)	HC	Mean post-injury = 19.43 m; range = 4–86 m	CRS-R (VS/UWS range = 7–8; MCS range = 8–19)	TBI (17); anoxic (4)	MRI, EEG	Differential diagnosis/ neural correlates
Cho et al. (2020)	Coma	/	From 1 d of ECMO cannulation to discharge or death	GCS ≤ 8	CA (18), anoxic (2)	EEG, TCD, SSEP, CT, MRI	Improve diagnosis and prognosis
Curley et al. (2018)	VS/UWS (3); MCS (17); EMCS (8)	HC	nr	CRS-R (range = 5–23)	TBI (23); anoxic (5); stroke (3); multiple aetiology (3)	MRI, EEG	Differential diagnosis/ neural correlates
Edlow et al. (2017)	Coma (2); VS/UWS (3); MCS− (3); MCS+ (4); EMCS (4)	HC	FMRI post-injury = 9.2 d; sd = 5.0 d; EEG post-injury = 9.8 d; sd = 4.6 d	GCS (range = 3–8); CRS-R; CAP (for PTCS diagnosis in EMCS patients); GOSE	TBI	MRI, EEG	Differential diagnosis/ neural correlates
Gibson et al. (2016)	VS/UWS (7); MCS (4); EMCS (2); LIS (1)	HC	Range post-injury = 0.9–20.4 y (average = 7.8 y)	CRS-R	TBI (6); anoxic (6); stroke (2)	MRI, EEG (active paradigm)	Differential diagnosis/ neural correlates
Gobert et al. (2018)	Coma	/	Range post-injury = 3–29 d	GCS; WFNS 5 (6); WFNS 4 (1); GOS	Stroke	EEG, slSEP, mlSEP, BAEP, MLAEP, N100, MMN	Improve diagnosis and prognosis
Gofton et al. (2009)	Coma	HC	Mean post-injury = 3.1 d; sd = 1.2 d	GCS (mean = 5.3; sd = 2.4); GOS	Anoxic	MRI (tactile somatosensory stimulation), SSEP	Differential diagnosis
Isono et al. (2002)	VS/UWS	/	Range post-injury = 3–18 m (average = 7 m)	nr	Anoxic (3); stroke (5); other (4)	MRI, EEG, SEPs, ABR	Improve diagnosis and prognosis

TABLE 1 (Continued)

EEG-based studies (64)							
Author	**Diagnosis sample**	**Diagnosis CG**	**Time from onset**	**Score evaluation test**	**Aetiology**	**Techniques**	**Aims**
Kassab et al. (2021)	Comatose	/	Range post-injury = 1–26 d	nr	Acute encephalopathy; SE	cEEG-fNIRS	Improve diagnosis and prognosis
Keijzer et al. (2022)	Coma	/	Range post-injury = 1–3 d	GCS ≤ 8	CA	SEP, EEG, MRI	Improve diagnosis and prognosis
Kim et al. (2021)	VS/UWS (22); MCS (16)	HC: Conscious State (24); PSY (15); ISO (9); KET (15)	nr	CRS-R	Ischaemic stroke; intracerebral haemorrhage; subarachnoid haemorrhage; subdural haematoma; TBI; meningitis; hyperglycaemic brain injury	EEG, fMRI	Neural correlates
Lee, Sreepada, et al. (2022)	Coma	HC	MRI/MRS mean post-injury = 6.4 d, sd = 6.3 d; EEG within 24 h of MRI/MRS (47), EEG with a mean 5 d delay of MRI/MRS	GCS	CA	cEEG, MRI, MRS	Improve diagnosis and prognosis
Li et al. (2015)	VS/UWS (12); MCS (10)	HC	Range post-injury = 21–60 d	CRS-R	TBI (8); anoxia (9); stroke (2); other (3)	MRI, EEG (active paradigm with thermal stimulation)	Differential diagnosis
Lutkenhoff, Nigri, et al. (2020)	VS/UWS (37); MCS− (17); MCS+ (7)	/	Range post-injury = 5–198 m (average = 24 m)	CRS-R (VS/UWS mean = 6.24; sd = 1.01; MCS− mean = 9.24; sd = 1.25; MCS+ mean = 10.43; sd = 1.90)	TBI (20); anoxic (18); stroke (23)	MRI, EEG, EOG, EMG	Improve diagnosis and prognosis
Mikell et al. (2015)	Coma	Awake	MRI obtained within 2 weeks of ictus. EEG recorded on the same day as the MRI.	GCS (range = 4–8; range CG = 10–15)	Stroke	MRI, EEG	Neural correlates
Othman et al. (2021)	Coma (5); VS/UWS (1); Conscious (3)	Conscious patients	NIRS-EEG from 1 d after the ICU admission	FOUR	TBI (1); CA (7); GBS (1)	NIRS-EEG	Improve diagnosis and prognosis

TABLE 1 (Continued)

EEG-based studies (64)							
Author	**Diagnosis sample**	**Diagnosis CG**	**Time from onset**	**Score evaluation test**	**Aetiology**	**Techniques**	**Aims**
Petzinka et al. (2018)	Coma (6); VS/UWS (83)	/	Range NSE serum post-injury = 48–96 h; range SSEP post-injury = 24 h–4 d; range EEG post-injury = 1–10 d	CRS-R	Anoxic	CT, SSEP, EEG, NSE serum concentration	Improve diagnosis and prognosis
Portnova et al. (2020)	Coma	HC	Mean post-injury = 22.05 d, range = 57.58 d	GCS ≤ 8	TBI	EEG, MRI	Improve diagnosis and prognosis
Rae-Grant et al. (1996)	Coma	/	Range post-injury = 1–7 d; patients enrolled 48 h after TBI	GCS (day 2: Mean = 5.17; sd = 0.24; range = 3–10. Day 7: Mean = 7.12; sd = 0.42; range = 3–15. Months 6: 13.11; sd = 0.47; range = 3–15); GOS; DRS	TBI	CT, EEG, SSEPs, BAEPs, OPG, TCD	Improve diagnosis and prognosis
Sangare et al. (2022)	VS/UWS (9); MCS (10); Conscious (1)	/	Time between hypoglycaemia and multimodal assessment: Mean = 50 d, range = 22–92 d	GCS at assessment: mean = 7, range = 3–9; FOUR at assessment: mean = 10.5, range = 8–13; CRS-R at assessment: mean 7, range = 6–9.5	HE (hypoglycaemic encephalopathy)	EEG, hd-EEG, SSEP, ERP, MRI	Improve diagnosis and prognosis
Scarpino, Lolli, Lanzo, Carrai, Spalletti, Valzania, Lombardi, Audenino, Celani, Marelli, et al. (2019)	Coma	/	Three evaluation times post-injury = 12 h–24 h–72 h	GCS (mean = 3; range = 3–8)	Anoxic	CT, EEG, SEPs	Improve diagnosis and prognosis

TABLE 1 (Continued)

EEG-based studies (64)							
Author	**Diagnosis sample**	**Diagnosis CG**	**Time from onset**	**Score evaluation test**	**Aetiology**	**Techniques**	**Aims**
Scarpino, Lolli, Lanzo, Carrai, Spalletti, Valzania, Lombardi, Audenino, Celani, Marrelli, et al. (2019)	Coma	/	Three evaluation times post-injury = 12 h–24 h–72 h	GCS (mean = 3; range = 3–8)	Anoxic	CT, EEG, SEPs	Improve diagnosis and prognosis
Scarpino et al. (2020)	Coma	/	nr	GCS at ICU admission: Mean = 3, range = 3–8; GCS at 72 h: Mean = 3, range = 3–8; CPC at 6 m mean: CPC1 = 10 (21); CPC2 = 11.9 (25); CPC3 = 3.8 (8); CPC4 = 17.1 (36); CPC5 = 57.1 (120)	CA	EEG, SSEPs, CT	Improve diagnosis and prognosis
Snider et al. (2022)	DoC with CA	Brain pathology without CA	nr	nr	Anoxic	EEG, MRI	Neural correlates/improve diagnosis and prognosis
Soldner et al. (2001)	Mixed: Severe TBI (27); Moderate TBI (2); Light TBI (1)	/	nr	GCS (severe TBI range = 3–8; moderate TBI range = 9–12; light TBI range = 13–15)	TBI	CT, MRI, EEG	Improve diagnosis and prognosis
Valente et al. (2002)	Coma	/	Acute stage: Within less than 24 h after admission; subacute stage: At least 24 h after sedative drugs and neuroprotective drugs withdrawal	GCS ≤ 8	TBI	CT, EEG, 24 h	

TABLE 1 (Continued)

Author	Diagnosis sample	Diagnosis CG	Time from onset	Score evaluation test	Aetiology	Techniques	Aims
EEG-based studies (64)							
Velly et al. (2018)	Coma	HC and coma	At least 7 d post-injury	GCS (mean = 3); CPC	Anoxic	MRI, EEG	Improve diagnosis and prognosis
Wedekind et al. (1999)	Mixed: Severe TBI (43); Moderate TBI (14)	/	Range MRI post-injury = 1–39 d (average = 14 d); EEG post-injury = 24 h and repeated every 3 d or 5 d for 3 w	GCS (Severe TBI (43) < 8; Moderate TBI (14) ≥ 8	TBI	MRI, EEG, MSEP, BAEP, eps	Improve diagnosis and prognosis
Wedekind, Hesselmann, and Klug (2002)	Coma	/	EEG post-injury = 24 h; mean MRI post-injury = 12 d	GCS (range = 3–10); GOS	TBI	MRI, EEG, BAEP	Improve diagnosis and prognosis
Wedekind, Hesselmann, Lippert-Grüner, and Ebel (2002)	Coma with PMB lesion	Coma with non-PMB lesion	Range MRI post-injury = 1–39 d (average = 12 d); EEG post-injury = 24 h and repeated every 3 d or 5 d for 3 w	GCS (PMB range = 3–7; mean = 5. CG range = 3–7; mean = 6); GOS; DRS	TBI	MRI, EEG	Improve diagnosis and prognosis
Zhang et al. (2011)	Coma	HC	Range post-injury = 1–7 d	GCS ≤ 8; mRS	Stroke	slSEP, mlSEP	Improve diagnosis and prognosis
EEG-metabolic studies (7)							
Candia-Rivera et al. (2021)	VS/UWS; MCS	/	Mean since onset = 30 m (range = 1–168)	CRS-R	TBI (27); anoxic (26); multiple aetiology (3); other (12)	FDG-PET, EEG	Differential diagnosis
Chennu et al. (2017)	VS/UWS (23); MCS (66); EMCS (11); LIS (4)	HC	/	CRS-R: Mean = 10.5	TBI (51); NO-TBI (53)	FDG-PET, EEG	Improve diagnosis and prognosis
Coleman et al. (2005)	VS/UWS	MCS	nr	nr	Stroke (7); TBI (3)	PET, EEG	Differential diagnosis
Hermann et al. (2021)	VS/UWS (23); MCS (34)	HC	Prolonged DoC: Mean post-injury = 533.4 d; range 31–2488 d	CRS-R	Anoxic (21); TBI (18); vascular (8); other (10)	FDG-PET, EEG (oddball)	Differential diagnosis

TABLE 1 (Continued)

EEG-based studies (64)							
Author	**Diagnosis sample**	**Diagnosis CG**	**Time from onset**	**Score evaluation test**	**Aetiology**	**Techniques**	**Aims**
Hildebrandt et al. (2007)	VS/UWS	Recovering VS/UWS	VS/UWS = mean 98.8 d; sd 60.8 d; recovering VS/UWS = mean 93.0 d; sd 72.3 d	CRS: VS/UWS mean = 5.42; sd = 2.02; recovering VS/UWS mean = 9.17; sd = 4.83	Hypoxia	SPECT, VEPs, ERPs	Neural correlates
Laureys et al. (2000)	VS/UWS	HC	P1: 38 d; P2: 3 d; P3: 19 d; P4: 13 d; P5: 36 d	Criteria of ANA Committee on Ethical Affairs, 1993 and Multi-society Task Forceon PSV, 1994	Hypoxia	PET, MRI, EEG	Neural correlates
Rudolf et al. (1999)	VS/UWS	HC	15–45 min	GOS; coma outcome scores	Anoxia	SEPs, EEG, FDG-PET	Differential diagnosis
EEG-neuroimaging-metabolic studies (7)							
Carriére et al. (2020)	VS/UWS (64); MCS− (28); MCS+ (71); EMCS (23)	HC	Median interval = 9 m; (range = 1 m–29 y)	CRS-R	TBI (100); non-TBI (86)	FDG-PET, fMRI; EEG	Differential diagnosis
Ferraro et al. (2020)	VS/UWS (4); MCS+ (2); MCS− (5)	HC	Median post-injury: 27 m (range = 5–252)	CRS-R: Mean = 8.9	TBI (4); anoxic (2); haemorrhagic (5)	BAEP, MRI, DTI, FDG-PET	Improve diagnosis and prognosis
Forgacs et al. (2014)	VS/UWS; MCS−; MCS+; EMCS	/	Range post-injury = 6 m–26 y (average = 6 y, 6 m)	CRS and CRS-R (scores range = 4–23; average = 12.94)	TBI (28); anoxic (6); multiple aetiology (2); nr (8)	44 long term EEG, 26 fMRI with motor imaginary protocol, 26 FDG-PET	Improve diagnosis and prognosis
Hermann et al. (2020)	VS/UWS; MCS	/	Mean = 58 d; range = 31–236 d	CRS-R: Mean = 7; range = 5–10	TBI (27); anoxic (39); vascular (12); other (18)	EEG, FDG-PET, DTI MRI	Improve diagnosis and prognosis
Laureys et al. (2002)	VS/UWS	HC	Mean = 36 y; sd = 9 d	GCS: Mean = 4.9; sd = 2.5	Anoxic (8); TBI (3); other (4)	EEG (SEPs), PET, MRI	Neural correlates

TABLE 1 (Continued)

EEG-based studies (64)							
Author	**Diagnosis sample**	**Diagnosis CG**	**Time from onset**	**Score evaluation test**	**Aetiology**	**Techniques**	**Aims**
Sattin et al. (2020)	VS/UWS; MCS	/	Mean from acute event group 'blink' = 29.33 m; mean from acute event group 'visual pursuit' = 29.06 m	CRS-R: Group 'blink' mean = 7; group 'visual pursuit' mean = 9.5	TBI (17); other (18)	EEG, fVEPs, MRI, FDG-PET	Neural correlates
Sattin et al. (2021)	VS/UWS	/	From acute event group 'fixation' mean = 71.85 m, sd = 90.25 m; Group 'blink' mean = 29.33 m, sd = 28.71 m; Group 'visual pursuit' mean = 29.06 m, sd = 51.58 m	CRS-R: Group 'fixation' mean = 9; Group 'blink' mean = 7; group 'visual pursuit' mean = 9.5	TBI (17); Other (41)	EEG, fVEPs, MRI, FDG-PET	Differential diagnosis/ neural correlates
EEG-neurostimulation studies (14)							
Fekete et al. (2021)	Coma (13%); Moderate disturbance (34.5%); Minor disturbance (52.5%)	/	Mean = 14 d; sd = 2 d	GCS mean = 12, sd = 3	Stroke	EEG, TMS	Improve diagnosis and prognosis
Lapitskaya et al. (2013)	VS/UWS (23); MCS (24)	HC	MCS: 36 ± 65 m post injury; VS/UWS: 16 ± 55 m	CRS-R mean = MCS 13 ± 5; VS/UWS 4 ± 1	TBI (22); anoxic (16); stroke (4); other (6)	EMG, SEPs, RMT, TMS, MEP, SAI	Differential diagnosis
Naro, Leo, Filoni, et al. (2015)	VS/UWS (7); MCS (7)	HC	MCS: 13 ± 6 m post injury; VS/UWS: 9 ± 3 m post injury	CRS-R mean = MCS 14 ± 0.9; VS/UWS 9 ± 3	MCS: anoxic (3); TBI (4); VS/UWS: anoxic (3); TBI (4)	TDCS/TACS, TMS, EEG	Neuromodulation/ differential diagnosis
Naro, Calabrò, Russo, et al. (2015)	MCS (10); VS/UWS (12)	HC (20); LIS (1); EMCS (2)	Post anoxic MCS: 9 ± 2 m post injury; post traumatic MCS: 19 ± 5 m; post anoxic VS/UWS: 10 ± 2 m; post traumatic VS/UWS: 40 ± 11 m	CRS-R mean = MCS post anoxic 17 ± 1; MCS post traumatic 15 ± 1; VS/UWS post anoxic 6 ± 1; VS/UWS post traumatic 6 ± 1	Stroke or TBI	TMS, TDCS	Neuromodulation/ differential diagnosis

TABLE 1 (Continued)

EEG-based studies (64)

Author	Diagnosis sample	Diagnosis CG	Time from onset	Score evaluation test	Aetiology	Techniques	Aims
Naro, Leo, Cannavò, et al. (2015)	VS/UWS (10); MCS (10)	HC	MCS: 14 ± 5 m post injury; VS/UWS: 10 ± 4 m	CRS-R mean = MCS 24 ± .8; VS/UWS 5.9 ± 1.1	MCS: anoxic (5); TBI (5); VS/UWS: anoxic (4); TBI (6)	RTMS, rES	Differential diagnosis
Naro, Leo, Bramanti, and Calabrò (2015)	VS/UWS (10); MCS (10)	HC	MCS: 14 ± 4 m from the brain injury; VS/UWS: 15 ± 2 m from the brain injury.	CRS-R mean = MCS 16 ± 1; VS/UWS 5 ± 0.5	Anoxic (10); TBI (10)	RTMS, EEG	Neuromodulation/ differential diagnosis
Naro, Leo, et al. (2016)	MCS (12); VS/UWS (14)	HC	MCS: 11 ± 4 m post injury; VS/UWS: 8 ± 4 m	GCS mean <= 8; CRS-R = MCS 13 ± 3; VS/UWS: 6 ± 1	Anoxic (11); TBI (15)	EEG, tACS, tRNS	Neuromodulation/ differential diagnosis
Naro, Bramanti, et al. (2016)	MCS (7); VS/UWS (7)	HC	At least 3 m after the brain injury	CRS-R mean = MCS 14 ± 3; VS/UWS 5 ± 2	Anoxic (6); TBI (8)	TACS, TMS, EEG	Neuromodulation/ differential diagnosis
Naro et al. (2017)	VS/UWS (11); MCS (9)	HC	MCS: 13 ± 10 m post injury; VS/UWS: 13 ± 3 m	CRS-R MCS mean = 12 ± 4; VS/UWS 5 ± 2	Anoxic (7); TBI (13)	EEG, rTMS	Neuromodulation/ differential diagnosis
Naro et al. (2018)	MSC (19); VS/UWS (21)	HC	MCS: 18 ± 11 m post-injury; VS/UWS:17 ± 8 m post injury	CRS-R mean = MCS 15 ± 1; VS/UWS 6 ± 1	Stroke or TBI	TDCS, TMS	Differential diagnosis
Odinak et al. (2014)	VS/UWS	/	nr	GCS: Mean = 6.5	TBI	EEG, TMS, CT/MRI	Differential diagnosis
Pisani et al. (2015)	VS/UWS (6); MCS (4)	/	VS/UWS mean m post-injury = 12 ± 7 m; MCS mean m post injury = 12 ± 9 m	CRS-R	MCS: anoxic (3); TBI (1); VS/UWS: anoxic (2); TBI (4)	EEG 24 h	
Zhang et al. (2020)	VS/UWS (8); MCS (5)	HC	Mean m post-injury = 6,1 m; sd = 4.2 m	CRS-R	Anoxic (4); TBI (4); haemorrhagic (5)	ERP, FDG-PET, tDCS	Differential diagnosis

TABLE 1 (Continued)

EEG-based studies (64)							
Author	**Diagnosis sample**	**Diagnosis CG**	**Time from onset**	**Score evaluation test**	**Aetiology**	**Techniques**	**Aims**
Zhang et al. (2022)	MCS	/	Range post-injury = 1–11 m	CRS-R	TBI (11); haemorrhagic stroke (13); ischaemic stroke (4)	ERP, tDCS	Differential diagnosis/ neural correlates

Note: The studies are grouped in four categories related to the different techniques combined: EEG-neuroimaging; EEG-metabolic; EEG-neuroimaging-metabolic; EEG-neurostimulation.

Abbreviations: ABR, auditory brainstem response; BAEP, brain stem auditory evoked potential; CRS, Coma Recovery Scale; CRS-R, Coma Recovery Scale – Revised; CT, computed tomography; CAP, Confusion Assessment Protocol; CS, conscious state; cEEG, continuous EEG; CG, control group; d, days; DTI, diffusion tensor imaging; DRS, Disability Rating Scale; ECG, electrocardiogram; EEG, electroencephalography; EMG, electromyography; EOG, electrooculography; EMCS, emerging from minimally conscious state; ERPs, event-related potentials; EPS, evoked-potentials; ECMO, extracorporeal membrane oxygenation; F, females; fVEPs, flash visual evoked potentials; FDG-PET, fluorodeoxyglucose-positron emission tomography; FC, follow command; FOUR, Full Outline of UnResponsiveness; fMRI, functional magnetic resonance; fNIRS, functional near-infrared spectroscopy; GBS, Gullain-Barré syndrome; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; GOSE, Glasgow Outcome Scale-Extended; CPC, Glasgow-Pittsburgh Cerebral Performance Categories; HC, healthy controls; hd-EEG, high density-EEG; h, hours; HE, hypoglycaemic encephalopathy; ICU, intensive care unit; ISO, isoflurane anaesthesia; KET, ketamine anaesthesia; PSY, ketamine psychedelic state; LIS, locked-in syndrome; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; M, males; MSEP, median nerve evoked somatosensory potential; MLAEP, middle-latency auditory evoked potential; mlSEP, middle-latency somatosensory evoked potential; MCS, minimally conscious state; min, minutes; MMN, mismatch negativity; mRS, modified ranking scale; m, months; MEP, motor evoked potential; NIRS, near-infrared spectroscopy; NSE, neuron-specific enolase; NFC, not follow command; nr, not reported; OPG, ocular plethysmography; P, patient; PMB, pons and/or midbrain; PET, positron emission tomography; PTCS, post-traumatic confusional state; rCBF, regional cerebral blood flow; rCMRGlu, regional cerebral metabolic rate for glucose; rTMS, repetitive transcranial magnetic stimulation; slSEP, short-latency somatosensory evoked potential; SPECT, single photon emission computed tomography; SEP, somatosensory evoked potential; SEPs, somatosensory evoked potentials; sd, standard deviation; SE, status epilepticus; tACS, transcranial alternating current stimulation; tDCS, transcranial direct current stimulation; TCD, transcranial Doppler; TMS, transcranial magnetic stimulation; tRNS, transcranial random noise stimulation; TBI, traumatic brain injury; VS/UWS, Vegetative State/Unresponsive Wakefulness Syndrome; VEPs, visual evoked potentials; WFNS, World Federation of Neurological Surgeons; y, years; /, not present in the study.

[a]Dataset already published in Dhakar et al. (2018), Szumita et al. (2010) and Oddo et al. (2014).

[b]Dataset already published with different analyses and hypotheses in Lee et al. (2019) and Huang et al. (2020).

[c]Part of the dataset already published in Scarpino, Lolli, Lanzo, Carrai, Spalletti, Valzania, Lombardi, Audenino, Celani, Marelli, et al. (2019); Scarpino, Lolli, Lanzo, Carrai, Spalletti, Valzania, Lombardi, Audenino, Celani, Marrelli, et al. (2019).

[d]Part of the dataset already published in Sattin et al. (2020).

[e]Part of the dataset already published in Zhang et al. (2017).

'included', 'excluded' or 'unsure'. Then, in the full-papers phase, the same pairs reviewed the records in the 'included' and 'unsure' categories. In both selection phases, conflicts about screening decisions were solved by consensus or, eventually, a third evaluator was consulted if needed.

We based the screening process on the following hierarchy of inclusion/exclusion criteria: (a) English language; (b) articles involving humans; (c) articles involving adults (aged >18); (d) peer-review original articles; (e) articles including patients with a diagnosis of DoC; (f) articles applying a multimodal approach as described in the introduction section; (g) articles with diagnostic purposes (e.g., improved diagnosis of DoC, discriminate between MCS and VS/UWS, etc.), while interventional studies with treatment purposes were excluded. We opted for avoiding selection criteria based on the sample size. Therefore, also those studies with $N < 10$ were included, although considered separately, as case reports and case series.

2.3 | Data extraction and synthesis

Tables 1–4 were used to extract data from the included studies. Their content was checked for accuracy and completeness by all authors; discrepancies were solved by consensus. We extracted the following variables: authors, sample size, sample age, sample gender, control group size, control group age, control group gender, diagnosis sample, diagnosis control group, time from the onset (i.e., the time occurring between the onset of the DoC and the time of evaluation), scales employed for the clinical assessment, aetiology of brain injury, technical instruments employed and study aim. For case reports and case series, we extracted the DoC's disease course rather than the time from the onset because these articles tend to report the initial consciousness state and its changes throughout time.

2.4 | Quality assessment

To evaluate the studies' quality, we slightly adapted the Quality Assessment of Diagnostic Accuracy Studies tool – second version (QUADAS-2; Whiting et al., 2011) according to the aim of the present review and in line with a previous meta-analysis focused on DoC patients (Schnakers, 2012). Our modified version of QUADAS-2 (see Appendix S2 for details) allowed to assess the 'risk of bias' in four domains: (i) patient selection; (ii) presence of a control group; (iii) conventional diagnostic procedures/instruments; (iv) timing of measurements. We also evaluated the 'applicability problems' based on three items: (i) study sample constituted only by DoC patients; (ii) study procedures properly investigating the consciousness status; (iii) use of a validated diagnostic scale for detecting DoC.

Four blinded authors (A. G., E. V., L. D. M., and G. H.), in pairs, used this adapted version of the QUADAS-2 to assess the quality of the observational diagnostic studies by evaluating items of each domain as 'high risk', 'low risk' or 'unclear risk'. Conflicts were solved by consensus of authors in each pair; a third author (L. J. R. L.) was involved in case of residual discrepancies.

For the quality assessment of case reports and case series, we used a modified version of the Joanna Briggs Institute (JBI; https://joannabriggs.org/) Critical Appraisal Checklist For Case Reports (Gagnier et al., 2013; Moola et al., 2017) and of the JBI Critical Appraisal Checklist For Case Series (Munn et al., 2020), as recommended by Ma et al. (2020) (see Appendix S3 for details). Adapting the JBI Critical Appraisal Checklist For Case Report scale allowed us to evaluate whether (i) articles reported patients' demographic characteristics and a clear description of the DoC evolution from admission to discharge; (ii) diagnostic tests used were best suited to identify the type of DoC; (iii) a multimodal approach was clearly described (i.e., any integration or comparison of different technical instruments relevant for the purposes of this review). The modified version of the JBI Critical Appraisal Checklist For Case Series scale additionally evaluated whether (i) clear inclusion criteria were applied; (ii) DoC was assessed in a standard and reliable way for all participants; (iii) patient enrolment occurred consecutively or continuously within the time frame of the study, where the latter indicates that all DoC patients hospitalized in a given time interval were included; (iv) sociodemographic information of the clinical population were reported. Two blinded authors (L. D. M. and M. R.) evaluated the quality of case reports and case series by assigning to each item the label 'Yes', 'No', 'Unclear' and 'Not applicable'. Conflicts were solved by consensus or by involving a third author (L. J. R. L.) if needed.

3 | RESULTS

3.1 | Records selection

The screening process is shown in Figure 1a–c. Our first research strategy till October 2020 (see Figure 1a) retrieved 4276 records. Among these, 1132 were removed as duplicates, and 3144 were screened based on title/

TABLE 2 Detailed information about the TMS-EEG studies included in the review.

TMS-EEG studies (14)							
Author	**Sample**	**CG**	**Age sample**	**Age CG**	**Gender sample**	**Gender CG**	**Diagnosis sample**
Bodart et al. (2017)	20[a]	4	VS/UWS: mean = 34.7 y; sd = 9.29 y; MCS: mean = 35 y; sd = 13.9 y	Mean = 33.8 y; sd = 13.25 y	VS/UWS: 5 M, 4 F; MCS: 6 M, 5 F	EMCS = 2 M; LIS = 2 F	VS/UWS (9); MCS (11)
Bodart et al. (2018)	23[b]	14	Mean = 37 y; sd = 15 y	Mean = 25 y; sd = 4 y	13 M, 10 F	5 M, 9 F	LIS (2); EMCS (3); MCS+ (7); MCS− (8); VS/UWS (3)
Casali et al. (2013)	20[c]	32	Range = 15–88 y	nr	13 M, 7 F	nr	VS/UWS (6); MCS (6); LIS (2); EMCS (6)
Casarotto et al. (2016)	81[d]	150	Mean = 49.5 y; sd = 17.7 y; range = 18–84 y	HC range = 18–80 y; brain injured patients = nr	56 M, 25 F	HC: 39 M, 63 F; brain injured patients: nr	MCS+ (17); MCS− (20); VS/UWS (42)
Formaggio et al. (2016)	5	5	Mean = 59.6 y; sd = 15.5 y	Mean = 25.7 y; sd = 4.2 y	2 M, 3 F	4 M, 1 F	VS/UWS (4); MCS (1)
Lee, Sanz, et al. (2022)	34[e]	22[e]	VS/UWS mean = 38.8 y; sd = 25.1 y; MCS mean = 38.5 y; sd = 17.5 y; MCS* mean = 36.3 y; sd = 10.5 y	HC for sleep data mean = 23.7 y; sd = 3.2 y; HC for anaesthesia data range = 18–28 y	VS/UWS: 8 M, 7 F; MCS: 11 M, 4 F; MCS*: 2 M, 2 F	HC for sleep data: 5 M, 1 F; HC for anaesthesia data: 8 M, 8 F	VS/UWS (15); MCS (15); MCS* (4)
Li et al. (2023)	15	/	Mean = 43.7 y	/	8 M, 7 F	/	VS/UWS
Lutkenhoff, Johnson, et al. (2020)	40	/	Mean = 51.2 y	/	29 M, 11 F	/	VS/UWS (24); MCS+ (6); MCS− (10)
Mensen et al. (2020)	7	/	Mean = 34.7 y, sd = 10.5 y	/	3 M, 4 F	/	VS/UWS (1); MCS* (2); MCS− (1); MCS+ (3)
Ragazzoni et al. (2013)	13	5	Mean = 59 y; range = 25–89 y	Range = 24–43 y	9 M, 4 F	4 M, 1 F	VS/UWS (8); MCS (5)
Rosanova et al. (2012)	12	5	Mean = 50.3 y; sd = 26.21 y	Mean = 51.2 y; sd = 23.05 y	7 M, 5 F	2 M, 3 F	VS/UWS (5); MCS (5); LIS (2)

TABLE 2 (Continued)

TMS-EEG studies (14)							
Author	**Sample**	**CG**	**Age sample**	**Age CG**	**Gender sample**	**Gender CG**	**Diagnosis sample**
Rosanova et al. (2018)	16	20	Mean = 56.5 y; sd = 19.4 y; range = 19–83 y	Mean = 38.9 y; sd = 17.6 y; range = 19–80 y	10 M, 6 F	12 M, 8 F	VS/UWS
Sinitsyn et al. (2020)	24	/	Range = 19–55 y	/	14 M, 10 F	/	VS/UWS (11); MCS− (4); MCS+ (8); EMCS (1)
Wang et al. (2022)	181	30	Range = 20–60 y	Range = 33–64 y	120 M, 61 F	15 M, 15 F	VS/UWS (105); MCS (76)

Abbreviations: CRS-R, Coma Recovery Scale – Revised; d, days; DRS, Disability Rating Scale; EEG, electroencephalography; EMCS, emerging from minimally conscious state; ERPs, event-related potentials; F, females; FDG-PET, fluorodeoxyglucose-positron emission tomography; HC, healthy controls; LIS, locked-in syndrome; M, males; m, months; MRI, magnetic resonance imaging; MCS, minimally conscious state; nr, not reported; SEPs, somatosensory evoked potentials; sd, standard deviation; TMS-EEG, transcranial magnetic stimulation with electroencephalography; TBI, traumatic brain injury; VS/UWS, Vegetative State/Unresponsive Wakefulness Syndrome; w, weeks; y, years; /, not present in the study.

[a]Part of the dataset already published in Casali et al. (2013), Casarotto et al. (2016) and Stender et al. (2014).

[b]Part of the dataset already published in Bodart et al. (2017), Casali et al. (2013) and Casarotto et al., 2016.

[c]Part of the dataset already published in Rosanova et al. (2012).

[d]Part of the dataset already published in Casali et al. (2013).

[e]Part of the dataset already published in Bodart et al. (2017), Nieminen et al. (2016), Rosanova et al. (2012) and Sarasso et al. (2015).

TABLE 2 (Continued)

TMS-EEG studies (14)						
Author	**Diagnosis CG**	**Time from onset**	**Score evaluation test**	**Aetiology**	**Techniques**	**Aims**
Bodart et al. (2017)	EMCS (2); LIS (2)	Non-acute DoC - Median time since onset (w range): VS/UWS 25 w (5–1116); MCS 188 w (23–1371); EMCS-LIS 111.5 w (21–200)	CRS-R	TBI (12); mixed (12)	FDG-PET, TMS-EEG	Techniques' comparison
Bodart et al. (2018)	HC	More than 4 w post-onset - median time since injury 33 w (5–1371)	CRS-R	nr	TMS-EEG, MRI	Techniques' comparison
Casali et al. (2013)	HC: Wakefulness condition (8); Wake/sleep Condition (6); anaesthesia condition (18)	12–1399 d after insult; mean = 324.35 d	CRS-R (range for DoC patients = 3–23)	TBI (9); stroke (10); other (1)	TMS-EEG	Differential diagnosis

TABLE 2 (Continued)

TMS-EEG studies (14)

Author	Diagnosis CG	Time from onset	Score evaluation test	Aetiology	Techniques	Aims
Casarotto et al. (2016)	Brain-injured conscious patients (48): LIS (5); conscious brain-injured patients (34); EMCS (9); HC (102)	At least 20 d after DoC onset and 3 d after withdrawal of sedation.	CRS-R	Anoxic (27); TBI (26); stroke (28)	TMS-EEG	Differential diagnosis
Formaggio et al. (2016)	HC	Range of m post injury: 8–72 m	DRS	Anoxic (2); haemorrhagic (2); stroke (1)	TMS-EEG	Differential diagnosis
Lee, Sanz, et al. (2022)	HC	VS/UWS: mean 8.4 m; range of m post injury 1–47 m; MCS: mean 64.3 m; range of m post injury 1–343 m; MCS*: mean 18.5 m; range of m post injury 3–32 m	CRS-R	Anoxic (15); TBI (19)	TMS-EEG; FDG-PET; rs-EEG	Neural correlates
Li et al. (2023)	/	Range of m post injury: 5–30 m	CRS-R	Anoxic	TMS-EEG, resting-state EEG	Improve diagnosis and prognosis/neural correlates
Lutkenhoff, Johnson, et al. (2020)	/	Range of m post injury: 1–128.40 m	CRS-R	Anoxic (18); TBI (10); Vascular (12)	TMS-EEG	Differential diagnosis
Mensen et al. (2020)	/	Mean of w post injury = 70.9 w; sd = 72 w; Range of w post injury: 13–200 w	CRS-R	TVI (4); stroke (2); anoxic (1)	TMS-EEG; tDCS; EEG; ERP	Improve diagnosis and prognosis/neural correlates
Ragazzoni et al. (2013)	HC	Chronic DoC: from 7 to 65 m post injury; mean 34.8 m	CRS-R	Anoxic (5); TBI (5); stroke (3)	TMS-EEG, ERPs, SEPs	Differential diagnosis
Rosanova et al. (2012)	3 VS/UWS that evolved to MCS and EMCS; 2 VS/UWS that remained with this diagnosis	Group 1: range of d after insult 12–1399; group 2: range of d after insult 12–62	CRS-R	Group 1: TBI (5); stroke (4); other (2); anoxic (1); Group 2: TBI (1); stroke (2); other (1); anoxic (1)	TMS-EEG, spontaneous EEG	Differential diagnosis
Rosanova et al. (2018)	HC	nr	CRS-R	Anoxic (8); TBI (5); stroke (3)	TMS-EEG	Differential diagnosis

TABLE 2 (Continued)

TMS-EEG studies (14)						
Author	**Diagnosis CG**	**Time from onset**	**Score evaluation test**	**Aetiology**	**Techniques**	**Aims**
Sinitsyn et al. (2020)	/	Range of m post injury: 2–58 m	CRS-R: EMCS = 23; MCS mean = 14.58, sd = 3.94; VS/UWS mean = 5.91, sd = 1.14	TBI (12); vascular (4); anoxic (6); other (2)	TMS-EEG	Differential diagnosis
Wang et al. (2022)	HC	VS/UWS: mean = 4.84 m, sd = 4.61 m; MCS: mean = 6.74 m, sd = 7.14 m	CRS-R VS/UWS: mean = 5.75, sd = 1.47; MCS: mean 9.44, sd = 2.36	Anoxic (61); haemorrhage (76), TBI (44)	TMS-EEG	Differential diagnosis

Abbreviations: CRS-R, Coma Recovery Scale – Revised; d, days; DRS, Disability Rating Scale; EEG, electroencephalography; EMCS, emerging from minimally conscious state; ERPs, event-related potentials; F, females; FDG-PET, fluorodeoxyglucose-positron emission tomography; HC, healthy controls; LIS, locked-in syndrome; M, males; m, months; MRI, magnetic resonance imaging; MCS, minimally conscious state; nr, not reported; SEPs, somatosensory evoked potentials; sd, standard deviation; TMS-EEG, transcranial magnetic stimulation with electroencephalography; TBI, traumatic brain injury; VS/UWS, Vegetative State/Unresponsive Wakefulness Syndrome; w, weeks; y, years; /, not present in the study.

[a]Part of the dataset already published in Casali et al. (2013), Casarotto et al. (2016) and Stender et al. (2014).

[b]Part of the dataset already published in Bodart et al. (2017), Casali et al. (2013) and Casarotto et al., 2016.

[c]Part of the dataset already published in Rosanova et al. (2012).

[d]Part of the dataset already published in Casali et al. (2013).

[e]Part of the dataset already published in Bodart et al. (2017), Nieminen et al. (2016), Rosanova et al. (2012) and Sarasso et al. (2015).

TABLE 3 Detailed information about the non-EEG-based studies included in the review.

Non-EEG-based studies (14)						
Metabolic and neuroimaging studies						
Author	**Sample**	**CG**	**Age sample**	**Age CG**	**Gender sample**	**Gender CG**
Annen et al. (2016)	25	25	Mean = 36.3 y	Mean = 40.9 y	13 M, 12 F	11 M, 14 F
Annen et al. (2018)	79	75	MCS: Mean = 36.7 y; sd = 13.0 y; VS/UWS: Mean = 48.1 y; sd = 16.5 y	LIS + EMCS, mean = 39.3 y; sd = 15.1 y; HC mean = 39.9 y; sd = 16.1 y	VS/UWS: 20 M, 10 F MCS: 33 M, 16 F	LIS + EMCS: 16 M, 7 F, HC: 25 M, 21 F, 6 nr
Aubinet et al. (2020)	87	70	For PET: MCS− mean = 41.57 y; sd = 17.57 y; MCS+ mean = 39.48 y; sd = 15.77 y. for VBM: MCS− mean = 37.9 y; sd = 13.65 y; MCS+ mean = 42.66 y; sd = 16.81 y	For PET: Range = 19–70 y, for VBM: Range = 20–75 y	52 M, 35 F	42 M, 28 F
Bedini et al. (2017)	44	/	Mean = 43 y; range = 17–81 y	/	26 M, 18 F	/
Di Perri et al. (2016)	58	35	Mean = 43 y; sd = 17 y	nr	20 M, 38 F	nr
Ferraro et al. (2019)	40[a]	30	VS/UWS: Mean = 54 y; sd = 13.6 y; MCS: Mean = 49 y; sd = 19.6 y	Mean = 39 y; sd = 10.9 y	20 M, 20 F	15 M, 15 F
Hattori et al. (2003)	23	11	Mean = 44 y; sd = 18 y; range = 17–81 y	Mean = 36 y; sd = 8 y	18 M, 5 F	7 M, 4 F
Juengling et al. (2005)	5	15	Mean = 49 y, range = 26–64 y	Mean = 48 y	3 M, 2 F	8 M, 7 F
Kassubek et al. (2003)	7	14	Mean = 50.5 y	nr	5 M, 2 F	nr
Qin et al. (2015)	12	9	Mean = 45.6 y; sd = 3.3 y	Mean = 35.6 y; sd = 4.06 y	8 M, 4 F	5 M, 4 F
Rosazza et al. (2016)	119	33	Mean = 52 y; range = 19–83 y	Mean = 39 y; range = 17 y-66 y	71 M, 48 F	nr

TABLE 3 (Continued)

Non-EEG-based studies (14)						
Metabolic and neuroimaging studies						
Author	**Sample**	**CG**	**Age sample**	**Age CG**	**Gender sample**	**Gender CG**
Sawamura et al. (2023)	86	/	Mean = 39.1 y; sd = 19.1	/	65 M, 21 F	/
Soddu et al. (2016)	15	16	VS/UWS: Mean = 50 y; sd = 14 y; LIS: Mean = 35 y; sd = 13 y	Mean = 45 y; sd = 16 y	VS/UWS: 5 M, 6 F LIS: 1 M, 3 F	10 M, 6 F
Stender et al. (2014)	126	39 (PET), 16 (fMRI)	Mean = 41 y; sd = 18 y	Mean = 46 y; sd = 18 y (PET); mean = 24 y; sd = 12 y (fMRI)	75 M, 51 F	17 M, 22 F (PET); 9 M, 7 F (fMRI)

[a]Dataset already published in Nigri et al. (2016, 2017) and Rosazza et al. (2016).

Abbreviations: CRS, Coma Recovery Scale; CRS-R, Coma Recovery Scale Revised; CT, computed tomography; d, days; DTI, diffusion tensor imaging; EMCS, emerging from minimally conscious state; F, females; FDG-PET and F-FDG PET, fluorodeoxyglucose positron emission tomography; GCS, Glasgow Coma Scale; HC, healthy controls; HBI, haemorrhagic brain injury; h, hours; LIS, locked-in syndrome; MRI, magnetic resonance imaging; MRI-DWI, magnetic resonance imaging diffusion-weighted imaging; M, males; MCS, minimally conscious state; m, months; NO-TBI, nontraumatic brain injury; nr, not reported; $^{15}O–H_2O$ PET, O-labelled water PET; PET, positron emission tomography; PVS, persistent vegetative state; rs-fMRI, resting-state functional magnetic resonance; SD, severe disability; sd, standard deviation; sMRI, structural magnetic resonance imaging; TBI, traumatic brain injury; VS/UWS, Vegetative State/Unresponsive Wakefulness Syndrome; VBM, voxel-based morphometry; y, years; /, not present in the study.

TABLE 3 (Continued)

Non-EEG-based studies (14)							
Metabolic and neuroimaging studies							
Author	**Diagnosis sample**	**Diagnosis CG**	**Time from onset**	**Score evaluation test**	**Aetiology**	**Techniques**	**Aims**
Annen et al. (2016)	VS/UWS (7); MCS (12); EMCS (6)	HC	Subacute patients: Range = 30 d–3 m, chronic patients: > 5 m, mean = 1.8 y, sd = 1.9 y	CRS-R mean = 10.6	TBI (12); anoxia (11); multiple aetiology (1); other (1)	FDG-PET, MRI-DWI	Neural correlates
Annen et al. (2018)	VS/UWS (30); MCS (49)	LIS (4); EMCS (19); HC (52)	VS/UWS mean = 1.9 y, sd = 4.1 y; MCS mean = 2.8 y, sd = 3.1; LIS + EMCS mean = 3.4 y, sd = 5.3 y	CRS-R	TBI; NO-TBI	MRI, F-FDG PET	Improve diagnosis and prognosis
Aubinet et al. (2020)	MCS− (26); MCS + (61)	HC	For PET: MCS− mean = 542.5 d, sd = 570.64 d, MCS+	CRS-R for PET: MCS−mean = 10.25; sd = 2.21; MCS+	TBI (47); NO-TBI (40)	FDG-PET, MRI with VBM	Neural correlates

TABLE 3 (Continued)

Non-EEG-based studies (14)							
Metabolic and neuroimaging studies							
Author	**Diagnosis sample**	**Diagnosis CG**	**Time from onset**	**Score evaluation test**	**Aetiology**	**Techniques**	**Aims**
			mean = 825.27 d, sd = 901.39 d. for VBM: MCS− mean = 540.76 d, sd = 508.76 d, MCS+ mean = 859.61 d, sd = 1024.91 d	mean = 13.05; sd = 3.55. For VBM: MCS− mean = 9.41; sd = 2.72; MCS+ mean = 12.22; sd = 3.69			
Bedini et al. (2017)	VS/UWS (23); MCS (21)	/	Mean = 5 y, range = 2–22 y	CRS-R Per3 $^{5/5}$ 10 range = 7–16; Per3 $^{4/4}$ 7 range = 5–9	TBI (19); stroke (25)	MRI, FDG-PET	Differential diagnosis
Di Perri et al. (2016)	VS/UWS (21); MCS (24); EMCS (13)	HC	Mean = 27 m, sd = 44 m	CRS-R mean = 10.6	Anoxia (14); TBI (29); multiple aetiology (7); stroke (6); other (2)	FDG-PET, rs-fMRI, sMRI	Neural correlates
Ferraro et al. (2019)	VS/UWS (20); MCS (20)	HC	Range = 5 m–252 m	CRS-R VS/UWS mean = 6.65; MCS mean = 9.5	VS/UWS: stroke (11); TBI (9); MCS: stroke (10); TBI (10)	SMRI, FDG-PET, DTI	Neural correlates
Hattori et al. (2003)	Coma (13); Non comatose patients (10)	HC	Mean = 62 h, sd = 30 h, range = 17 h–123 h	GCS median score = 8; range = 3–15	TBI	F-FDG PET, CT, MRI	Differential diagnosis
Juengling et al. (2005)	PVS	HC	Range 1–4 y, median = 2 y	Coma remission scale range = 6–8; median = 7	Anoxic	MRI in combination with VBM, FDG-PET	Neural correlates
Kassubek et al. (2003)	PVS	HC	Mean = 1.6 y	CRS P1:7–8; P2:6–7; P3:8; P4:8–9; P5:5–6; P6:7–8; P7:7–8	Anoxic	MRI, FDG-PET, ^{15}O–H_2O PET	Neural correlates
Qin et al. (2015)	VS/UWS (7); MCS (5)	HC	Range = 36–233 d	CRS-R mean = 6.5	TBI (10); stroke (2)	Rs-fMRI, [^{11}C] flumazenil-PET	Improve diagnosis and prognosis

TABLE 3 (Continued)

Non-EEG-based studies (14)							
Metabolic and neuroimaging studies							
Author	**Diagnosis sample**	**Diagnosis CG**	**Time from onset**	**Score evaluation test**	**Aetiology**	**Techniques**	**Aims**
Rosazza et al. (2016)	VS/UWS (72); MCS (36); SD (11)	HC	Mean = 26 m, range 2 m–252 m	CRS-R mean = 7; range = 3–22	Anoxic (42); vascular (41); TBI (36)	SMRI, rs-fMRI, FDG-PET	Differential diagnosis
Sawamura et al. (2023)	VS/UWS (40); MCS+ (14); MCS− (32)	/	/	CRS-R	TBI	MRI, FDG-PET	Improve diagnosis and prognosis
Soddu et al. (2016)	VS/UWS (11); LIS (4)	HC	nr	CRS-R range = 1–7	Stroke (5); anoxia (6); TBI (3); other (1)	FDG-PET, resting fMRI	Improve diagnosis and prognosis
Stender et al. (2014)	MCS (81); VS/UWS (41); LIS (4)	HC	MCS mean = 39 m, VS/UWS mean = 27 m, LIS mean = 48 m	CRS-R	TBI (48); NO-TBI (78)	F-FDG-PET, mental imagery fMRI	Differential diagnosis

[a]Dataset already published in Nigri et al. (2016, 2017) and Rosazza et al. (2016).

Abbreviations: CRS, Coma Recovery Scale; CRS-R, Coma Recovery Scale Revised; CT, computed tomography; d, days; DTI, diffusion tensor imaging; EMCS, emerging from minimally conscious state; F, females; FDG-PET and F-FDG PET, fluorodeoxyglucose positron emission tomography; GCS, Glasgow Coma Scale; HC, healthy controls; HBI, haemorrhagic brain injury; h, hours; LIS, locked-in syndrome; MRI, magnetic resonance imaging; MRI-DWI, magnetic resonance imaging diffusion-weighted imaging; M, males; MCS, minimally conscious state; m, months; NO-TBI, nontraumatic brain injury; nr, not reported; $^{15}O–H_2O$ PET, O-labelled water PET; PET, positron emission tomography; PVS, persistent vegetative state; rs-fMRI, resting-state functional magnetic resonance; SD, severe disability; sd, standard deviation; sMRI, structural magnetic resonance imaging; TBI, traumatic brain injury; VS/UWS, Vegetative State/Unresponsive Wakefulness Syndrome; VBM, voxel-based morphometry; y, years; /, not present in the study.

TABLE 4 Detailed information about the case reports and case series included in the review.

Case reports and case series (32)						
Author	**Sample**	**CG**	**Age sample**	**Age CG**	**Gender sample**	**Gender CG**
EEG-neuroimaging studies (17)						
Aboukasm and Barkley (1995)	1	/	86 y	/	nr	/
Carrai et al. (2009)	1	/	56 y	/	M	/
Delamarre et al. (2020)	1	/	51 y	/	M	/
Edlow and Fins (2018)	2	/	P1 = 51 y P2 = 19 y	/	1 M, 1 F	/
Edlow et al. (2013)	1	/	19 y	/	M	/
Fischer et al. (2020)	1	/	47 y	/	M	/
Legouy et al. (2020)	1	/	65 y	/	F	/
Moritz et al. (2001)	1	/	38 y	/	F	/
Nawfal et al. (2022)	1	/	24 y	/	F	/
Pfeiffer et al. (2014)	1	/	25 y	/	F	/
Pistoia et al. (2008)	1	/	52 y	/	M	/
Rommel et al. (2001)	1	/	35 y	/	M	/
Sangare et al. (2020)	1	/	56 y	/	M	/
Scarpino et al. (2021)	1	/	23 y	/	M	/
Tan et al. (2018)	1	/	23 y	/	M	/
Wijdicks et al. (2001)	10	/	P1 = 66 y P2 = 32 y P3 = 43 y P4 = 60 y P5 = 76 y P6 = 49 y P7 = 75 y P8 = 61 y P9 = 46 y P10 = 66 y Range = 32–76 y	/	5 M, 5 F	/
Zanatta et al. (2012)	3	/	P1 = 69 y P2 = 71 y P3 = 74 y	/	2 M, 1 F	/
EEG-neuroimaging-metabolic studies (13)						
Achard et al. (2011)	1	20	36 y	Same range of age as patient	M	/
Agardh et al. (1983)	1	/	30 y	/	M	/
Aubinet et al. (2018)	5	58 (34 for PET and 36 for MRI)	Range = 20–66 y	/	4 M, 1 F	/

TABLE 4 (Continued)

Case reports and case series (32)						
Author	**Sample**	**CG**	**Age sample**	**Age CG**	**Gender sample**	**Gender CG**
Bagnato et al. (2014)	1	/	46 y	/	M	/
Kanarsky et al. (2021)	3	/	P1 = 75 y P2 = 45 y P3 = 35 y	/	P1 = M P2 = M P3 = M	/
Laureys et al. (2004)	1	/	42 y	/	M	/
Migdady et al. (2021)	1	/	75 y	/	M	/
Owen et al. (2005)	1	/	30 y	/	M	/
Rousseau et al. (2008)	4	5 at inclusion	P1 = 36 y P2 = 18 y P3 = 40 y P4 = 38 y	Matched to patients	2 M, 2 F	Matched to patients
Schiff et al. (1999)	1	/	49 y	/	F	/
Schiff et al. (2002)	5	nr (only for MEG)	P1 = 52 y P2 = 42 y P3 = 49 y P4 = 21 y P5 = 26 y	/	4 M, 1 F	/
Vanhaudenhuyse et al. (2018)	1	/	41 y	/	M	/
Voss et al. (2011)	1	/	19 y	/	F	/
Neuroimaging-metabolic studies (2)						
Aubinet et al. (2019)	3	34 for PET	P1 = 26 y P2 = 21 y P3 = 36 y	Range = 19–70 y	/	19 M, 15 F
Plum et al. (1998)	3	/	P1 = 49 y P2 = 52 y P3 = 38 y	/	2 M, 1F	/

Note: The studies are grouped in three categories related to the different techniques combined: EEG-neuroimaging; EEG-neuroimaging-metabolic; neuroimaging-metabolic.

Abbreviations: BAEPs, brainstem auditory evoked potentials; BAER, brainstem auditory evoked response; CBF, cerebral blood flow; CRS, Coma Recovery Scale; CRS-R, Coma Recovery Scale – Revised; CT, computed tomography; d, days; DTI, diffusion tensor imaging; EEG, electroencephalography; EMCS, emerging from Minimally Conscious State; ERPs, event-related potentials; EPs, evoked potentials; F, females; FDG-PET, fluorodeoxyglucose-positron emission tomography; fMRI, functional magnetic resonance; GCS, Glasgow Coma Scale; HC, healthy controls; I-LIS, Incomplete Locked in Syndrome; LIS, Locked in Syndrome; LLC, long lasting coma; MRI, magnetic resonance imaging; MRSI, magnetic resonance spectroscopy; MEG, magnetoencephalography; DWI, diffusion-weighted imaging; M, males; MCS, Minimally Conscious State; MMN, mismatch negativity; m, months; MEPs, motor evoked potentials; nr, not reported; P, patient; PET, positron emission tomography; rCBF, regional cerebral blood flow; rCMRGlu, regional cerebral metabolic rate for glucose; SPECT, single photon emission computed tomography; SEPs, somatosensory evoked potentials; sd, standard deviation; TBI, traumatic brain injury; VEPs, visual evoked potentials; VS/UWS, Vegetative State/Unresponsive Wakefulness Syndrome; w, week; y, years; /, not present in the study; ^{133}Xe-CBF, 133 xenon cerebral blood-flow.

TABLE 4 (Continued)

Case reports and case series (32)						
Author	**Evolution of DoC condition**	**Diagnosis CG**	**Score evaluation test**	**Aetiology**	**Techniques**	**Aims**
EEG-neuroimaging studies (17)						
Aboukasm and Barkley (1995)	Coma (3 d); death	/	/	Stroke	EEG, MRI	Improve diagnosis and prognosis
Carrai et al. (2009)	Coma (1 w); LIS (17 d); recovery of consciousness	/	GCS = 4 – d 1 to 6	TBI	CT, EEG, SEPs, MRI, ERPs	Differential diagnosis
Delamarre et al. (2020)	Coma (from d 21 to d 25); verbal stereotypes and perseverations at d 26; complete motor recovery and comprehension of motor commands at d 29	/	GCS at d 21 = 6 (E1, V1, M4); GCS at d 22 = 3	Other	EEG, DWI-MRI	Improve diagnosis and prognosis
Edlow and Fins (2018)	P1: coma (8 d); covert consciousness (3 d); death P2: coma (5 d); VS/UWS (21); MCS+ (unclear); recovery of consciousness	/	P1: GCS = 3 (E1 V1 M1) – on admission P2: GCS = 5 – on admission	TBI	P1: CT, continuous EEG, clinical and investigational fMRI P2: CT, clinical and investigational fMRI, investigational EEG	Improve diagnosis and prognosis
Edlow et al. (2013)	Coma (17 d); VS/UWS (18 d); MCS (unclear); post-traumatic confusional state	/	GCS = 5 (E1 V1 M3) – day 8	TBI	CT, MRI, EEG, continuous EEG,	Improve diagnosis and prognosis
Fischer et al. (2020)	Fluctuation between coma and MCS from 20 d to 66 d	/	CRS-R	Other	EEG, rs-fMRI	Improve diagnosis and prognosis
Legouy et al. (2020)	Coma (8 d); MCS (4 m); death	/	GCS = 6 – day 1	Other	MRI, EEG; continuous EEG	Improve diagnosis and prognosis
Moritz et al. (2001)	Coma (unclear, less than 3 m); recovery of consciousness	/	GCS = 11 – on admission	Stroke	BAERs, SEPs, VEPs, MRI, fMRI	Improve diagnosis and prognosis
Nawfal et al. (2022)	Coma (32 d); VS/UWS (4 w); recovery of consciousness	/	GCS = 7 – day 3	Anoxic	MRI, EEG, SEPs	Improve prognosis
Pfeiffer et al. (2014)	Coma (7 m); MCS (unclear); recovery of consciousness	/	GCS = 4 (E1 V1 M2) – day 2	Anoxic	EEG, MRI, SEPs	Improve diagnosis and prognosis
Pistoia et al. (2008)	Coma (1 m); VS/UWS (1 m); MCS	/	GCS = 3 – on admission; GCS = 7 – 1 w; CRS-R = 13 – 4 w	Anoxic	EEG, SEPs, CT	Improve diagnosis and prognosis
Rommel et al. (2001)	Coma (3 m)	/	/	Anoxic	CT, BAEP, EEG, 24 h polysomnography, MRI	Improve diagnosis and prognosis
Sangare et al. (2020)		/	GCS at 36 d = 4 (E2, V1, M1);	Other	CT, MRI, SEP, BAEP, EEG, hd-EEG, ERP, MMN	Improve diagnosis and prognosis

TABLE 4 (Continued)

Case reports and case series (32)						
Author	**Evolution of DoC condition**	**Diagnosis CG**	**Score evaluation test**	**Aetiology**	**Techniques**	**Aims**
	VS/UWS from d 36 to d 68; functional communication at 71 d; completely recover at 5.5 m		GCS at 55 d = 4 (E2, V1, M1), FOUR at 55 d = 6 (E1, M0, B4, R1), CRS-R at 55 d = 2 (0–1–0–0–0–1); GCS at 65 d = 4 (E2, V1, M1), FOUR at 65 d = 7 (E2, M0, B4, R1), CRS-R at 65 d = 3 (1–1–0-0-0-1); GOSE at 5.5 m = 6			
Scarpino et al. (2021)	Coma (9 d); BD	/	GCS ≤ 3	Anoxic	CT, EEG, MRI, SSEPs	Improve diagnosis and prognosis
Tan et al. (2018)	VS/UWS (5 m); MCS	/	CRS-R = 4 – 6 w; CRS-R = 16 – m 5	TBI	CT, 24 hours EEG, ultra-high field MRI	Neural correlates
Wijdicks et al. (2001)	P1: coma; VS/UWS; P2: coma; death; P3: coma; death; P4: coma; VS/UWS; P5: coma; death; P6: coma; death; P7: coma; death; P8: coma; death; P9: coma; recovery of consciousness; P10: coma; recovery of consciousness	/	GCS = 3 – after cardiac arrest (P 4: GCS = 5; P10 GCS = 4)	Anoxic	CT, MRI, EEG SSEPs	Improve diagnosis and prognosis
Zanatta et al. (2012)	Coma (3 m); P1 recovery of consciousness; P2 MCS; P3 VS/UWS	/	GCS – after 2 d; 1 and 3 m P1: 3–5–15 P2: 3–6–8 P3: 3–5–7	Anoxic	SEPs, EEG, fMRI	Improve diagnosis and prognosis
EEG-neuroimaging-metabolic studies (13)						
Achard et al. (2011)	Coma (3 m); VS/UWS (4 m); death	HC	GCS = 3 on admission	Anoxic	EEG, FDG-PET, MRI, visual, auditory, SEPs	Improve diagnosis
Agardh et al. (1983)	Coma (1 w); VS/UWS (at least 34 m)	/	/	Other	CT, EEG, VEPs; SEPs, ^{133}Xe-CBF	Describe neural underpinnings
Aubinet et al. (2018)	P1: EMCS P2: EMCS P3: MCS+ P4: MCS− P5: MCS−	HC	CRS-R (at the time of the study) P1: 19/23 P2: 19/23 P3: 15/23 P4: 14/23 P5: 12/23	P1: TBI P2: Stroke P3: TBI P4: Stroke P5: Stroke	MRI, EEG, FDG-PET, CT	Improve diagnosis; describe neural underpinnings

TABLE 4 (Continued)

Case reports and case series (32)

Author	Evolution of DoC condition	Diagnosis CG	Score evaluation test	Aetiology	Techniques	Aims
Bagnato et al. (2014)	LLC (14 m)	/	GCS = 3 – on admission to 3 m; GCS = 4 (E1 V1 M2) – 4 m to 14 m; CRS-R = 0 – on admission to 3 m; CRS-R = 1 – 4 m to 14 m	Mixed aetiology	CT, MRI, EEG, ERPs, SEPs, BAEPs, FDG-PET	Differential diagnosis
Kanarsky et al. (2021)	P1: Coma (10 d), VS/UWS (6 m); P2: Coma (10 d); VS/UWS (7.6 m); P3: Coma (8 d), VS/UWS (6.6 m)	/	P1: CRS-R on admission = 4, CRS-R on follow up at 6 m = 5; P2: CRS-R on admission = 5, CRS-R on follow up at 7.6 m = 6; P3: CRS-R on admission = 4, CRS-R on follow up at 6.6 m = 4	CA	CT, CTP, polysomnography, SPECT, PER-CT, FDG-PET, MRI, EEG, SSEP, ASEP, VEP	Improve diagnosis
Laureys et al. (2004)	MCS (30 w); death	/	/	Stroke	CT, MRI, EEG, BAEPs, SEPs, FDG-PET, $H_2{}^{15}O$-PET, cognitive ERPs	Improve diagnosis; describe neural underpinnings
Migdady et al. (2021)	Comatose (3 w); recovery of consciousness	/	GOS at discharge = 3	Vascular	CT, EEG, MRI, PET	Improve diagnosis; describe neural underpinnings
Owen et al. (2005)	VS/UWS (4 years)	/	/	Stroke	MRI, BAER; MMN, $H_2{}^{15}O$-PET, fMRI	Improve diagnosis; describe neural underpinnings
Rousseau et al. (2008)	VS/UWS (5 years)	HC	GCS – Initial and at inclusion P1: 4 – 6 P2: 4 – 6 P3: 6 – 6 P4: 3 – 6	P1: TBI P2: Multiple aetiology P3: Stroke P4: Anoxic	CT (except for P3), MRI, MRSI, fMRI, EEG, ERPs	Describe neural underpinnings; improve prognosis
Schiff et al. (1999)	Coma (several w); VS/UWS (20 y)	/	/	Stroke	MRI, FDG-PET, MEG	Improve diagnosis and prognosis
Schiff et al. (2002)	P1: VS/UWS (6 m) P2: VS/UWS (7 y) P3: VS/UWS (25 y) P4: VS/UWS (7 m) P5: VS/UWS (6 y)	HC	/	P1: Anoxic P2: TBI P3: TBI P4: TBI P5: TBI	EEG (only P3 and P5), FDG-PET, MRI, MEG	Describe neural underpinnings
Vanhaudenhuyse et al. (2018)	VS/UWS (20 y); I-LIS	/	GCS = 4/15 on admission; CRS-R = 12 to 17 – 7 assessments over 1 week	TBI	CT, EEG, structural MRI + DTI, FDG-PET	Differential diagnosis
Voss et al. (2011)	Coma (5 m); MCS (5 m); recovery of consciousness	/	GCS = 3 – on admission; CRS-R = 14 – 6 m; CRS-R = 20 – 10 m	TBI	FMRI, structural MRI, FDG-PET	Improve diagnosis; describe neural underpinnings

TABLE 4 (Continued)

Case reports and case series (32)						
Author	Evolution of DoC condition	Diagnosis CG	Score evaluation test	Aetiology	Techniques	Aims
Neuroimaging-metabolic studies (2)						
Aubinet et al. (2019)	MCS– (1st w of assessment); MCS+ (2nd w of assessment)	HC	CRS-R < 6 (inclusion criteria)	P1: TBI P2: TBI P3: Stroke	FDG-PET, MRI	Describe neural underpinnings
Plum et al. (1998)	P1: VS/UWS (20 y) P2: VS/UWS (10 m) P3: VS/UWS (7 y)	/	/	P1: Stroke P2: Anoxic P3: TBI	MRI, PET, MEG	Describe neural underpinnings

Note: The studies are grouped in three categories related to the different techniques combined: EEG-neuroimaging; EEG-neuroimaging-metabolic; neuroimaging-metabolic.
Abbreviations: BAEPs, brainstem auditory evoked potentials; BAER, brainstem auditory evoked response; CBF, cerebral blood flow; CRS, Coma Recovery Scale; CRS-R, Coma Recovery Scale – Revised; CT, computed tomography; d, days; DTI, diffusion tensor imaging; EEG, electroencephalography; EMCS, emerging from Minimally Conscious State; ERPs, event-related potentials; EPs, evoked potentials; F, females; FDG-PET, fluorodeoxyglucose-positron emission tomography; fMRI, functional magnetic resonance; GCS, Glasgow Coma Scale; HC, healthy controls; I-LIS, Incomplete Locked in Syndrome; LIS, Locked in Syndrome; LLC, long lasting coma; MRI, magnetic resonance imaging; MRSI, magnetic resonance spectroscopy; MEG, magnetoencephalography; DWI, diffusion-weighted imaging; M, males; MCS, Minimally Conscious State; MMN, mismatch negativity; m, months; MEPs, motor evoked potentials; nr, not reported; P, patient; PET, positron emission tomography; rCBF, regional cerebral blood flow; rCMRGlu, regional cerebral metabolic rate for glucose; SPECT, single photon emission computed tomography; SEPs, somatosensory evoked potentials; sd, standard deviation; TBI, traumatic brain injury; VEPs, visual evoked potentials; VS/UWS, Vegetative State/Unresponsive Wakefulness Syndrome; w, week; y, years; /, not present in the study; ^{133}Xe-CBF, 133 xenon cerebral blood-flow.

abstract. Following our inclusion/exclusion criteria, we reviewed the full text of 292 articles, and 62 studies were finally considered for the qualitative analysis. An additional group of 23 records with a sample size <10 was included, although considered separately, as case reports and case series. We updated our first search from November 2020 to April 2023 (see Figure 1b). This updated search retrieved 1092 articles, while 182 were removed as duplicates. We screened the title/abstract of 910 records and the full text of 64 records. At the end of the screening process, we included 28 articles and 7 case reports/case series. Finally, we performed a new search (see Figure 1c), in which we added the following keywords: 'functional near-infrared spectroscopy', 'polysomnography', 'transcranial alternating current stimulation', 'non invasive brain stimulation' and 'ultrasound stimulation', till April 2023. This new search retrieved 239 papers. After removing duplicates, 156 papers were screened based on title/abstract, while 16 passed to the full-text assessment. At the end of the screening, 4 articles and 2 case reports/case series were included.

3.2 | Quality assessment

Based on our QUADAS-2 adapted version, the average quality of the included observational diagnostic studies was intermediate to low (see Figures 2 and 3). The 'standard diagnostic procedures/instruments' and 'presence of a control group' domains received a significant percentage of high-risk judgments. Concerning the other two domains, 'patients' selection' criteria were not always clearly reported, even though the item was mostly evaluated at low risk, and most of the studies lacked sufficient information about 'timing' (i.e., the time interval between DoC assessment and application of multimodal protocol). Regarding the applicability problems, the average quality of the included observational diagnostic studies was intermediate to high. Indeed, while in most studies validated diagnostic scales and appropriate experimental paradigms to assess DoC were used, it was not infrequent that experimental samples also included other clinical groups different from DoC.

Based on the JBI Critical Appraisal Checklist For Case Reports and on the JBI Critical Appraisal Checklist For Case Series' rating, the quality of the included case reports and case series was good to high (see Tables 5 and 6). Despite the diagnosis of DoC at admission was not always clear, both case reports and case series articles tended to provide adequate information on patients' demographic characteristics and on the evolution of their clinical condition. Most papers clearly reported

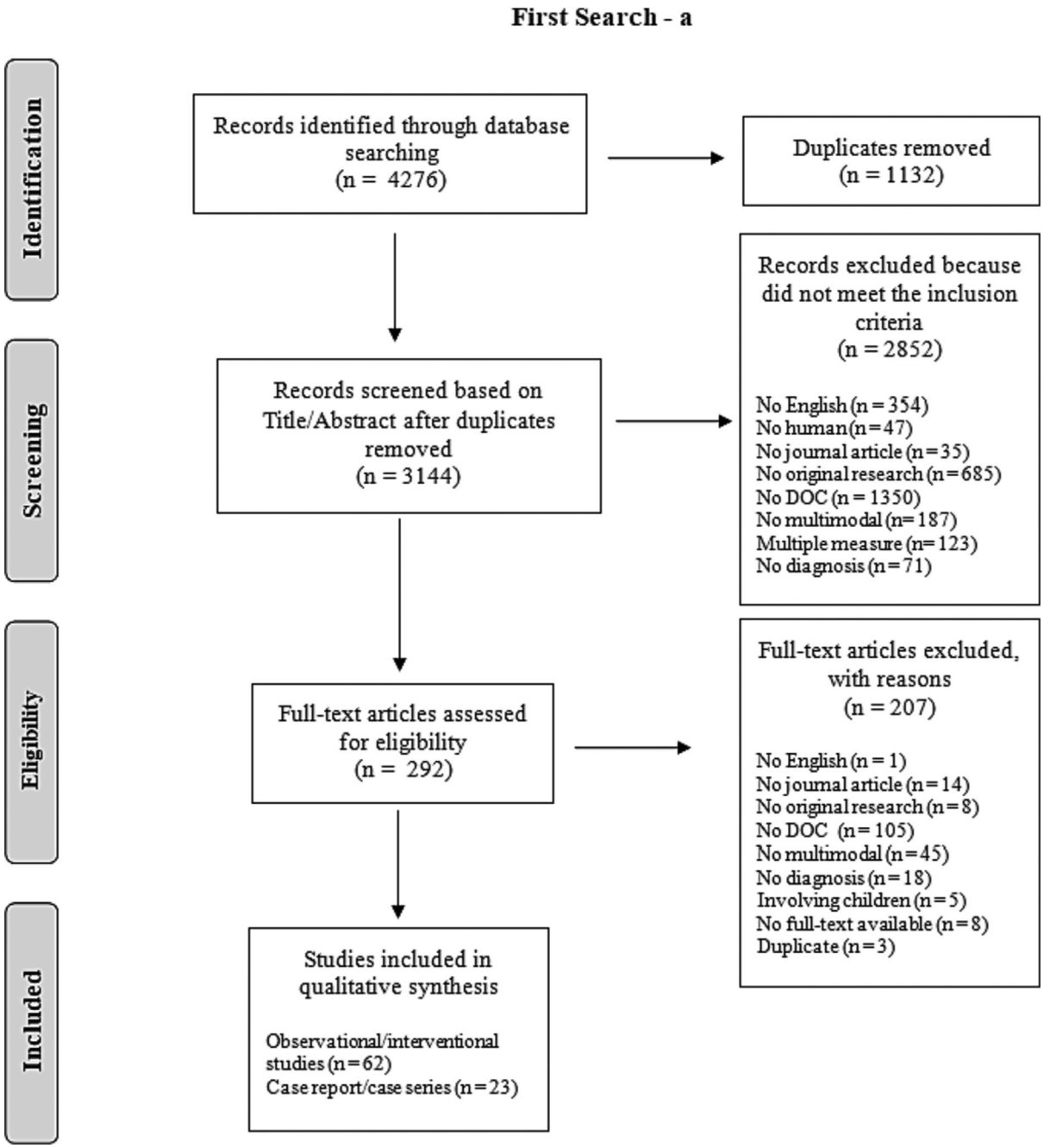

FIGURE 1 (a–c) PRISMA flowcharts of the screening process. Three rounds of research were performed. Panel (a) shows our first search, until October 2020. Panel (b) shows the flow chart of an Update of our first search screening literature from November 2020 to April 2023. Panel (c) shows a new search until April 2023 including the following new keywords: 'functional near-infrared spectroscopy', 'polysomnography', 'transcranial alternating current stimulation', 'non invasive brain stimulation' and 'ultrasound stimulation'. In all search, the screening phases were two, one (in the figure called 'Screening') based on Title/Abstract followed by another phase (in the figure called 'Eligibility') in which the screening was based on full-text.

participants' outcomes. The item concerning the use of adequate methods to assess patients' DoC was associated with the highest risk, because most of the articles employed the Glasgow Coma Scale (GCS; Teasdale et al., 1974) that allows only to diagnose coma, rather than the CRS-R. High risk of bias was also due to the fact that many studies did not provide a takeaway lesson that was relevant for the purpose of our work. Due to the different research designs, case reports were evaluated on some additional items. Case reports tended to provide clear inclusion criteria, even though it was often difficult to assess whether they were applied in a standard and

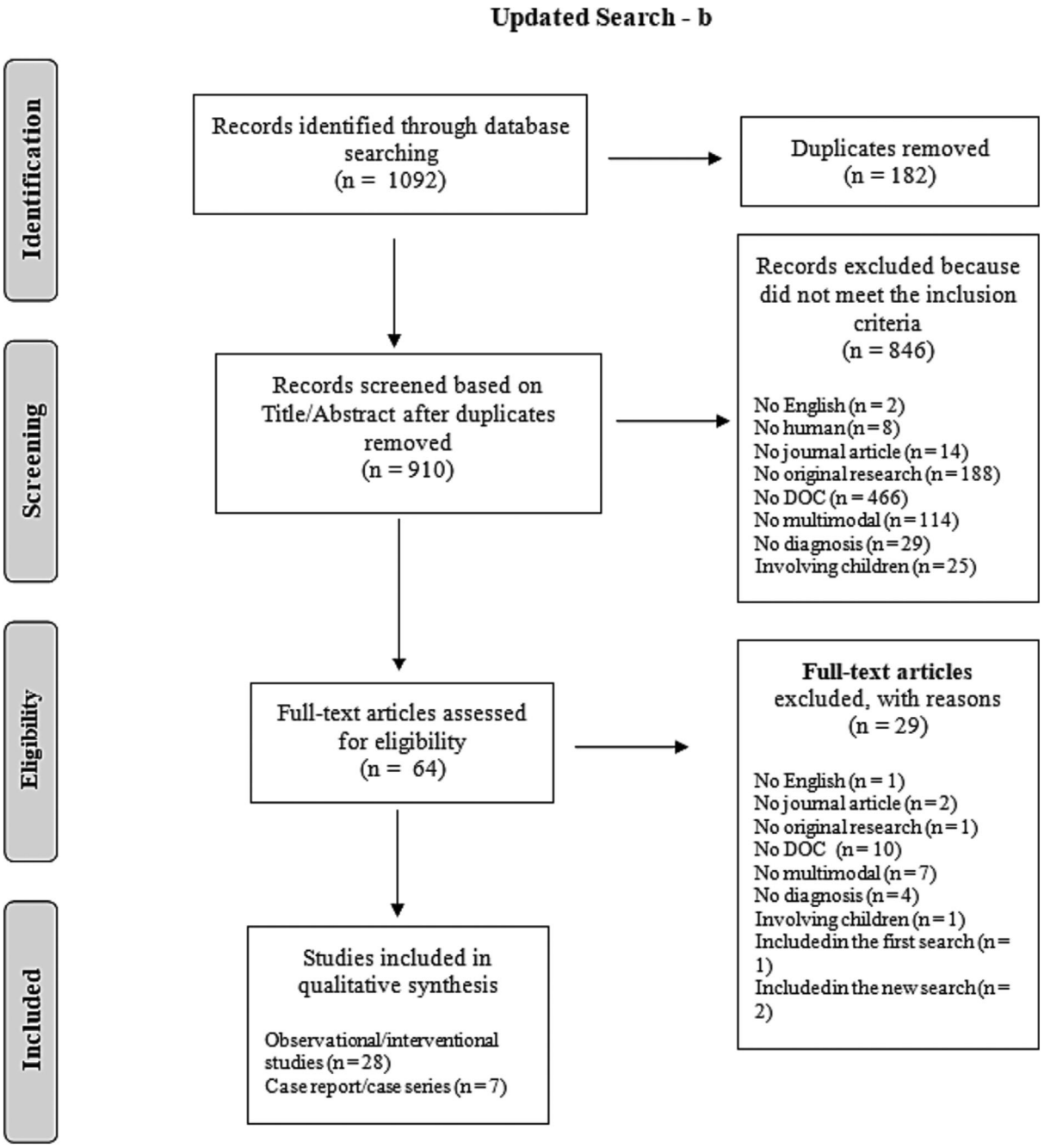

FIGURE 1 (Continued)

reliable way for all participants. Moreover, only two papers had consecutive inclusion of participants, while no paper had complete inclusion of participants and reported demographic information of the facility where the study was conducted.

3.3 | Records results

For the sake of clarity, we divided most of the included papers into two main subgroups, according to the employment ($N = 64$) or not ($N = 14$) of neurophysiological EEG-based measures in the multimodal approach. In each paragraph, we opted for presenting the data focusing on the advantages and achieved results in terms of (a) improving DoC diagnosis and prognosis, (b) enhancing the differential diagnosis between DoC subgroups and (c) providing evidence on the neural correlates of consciousness. In a further paragraph, we reported the TMS-EEG studies ($N = 14$) since, although they applied an EEG-based multimodal approach, we consider them somehow different from the other EEG-

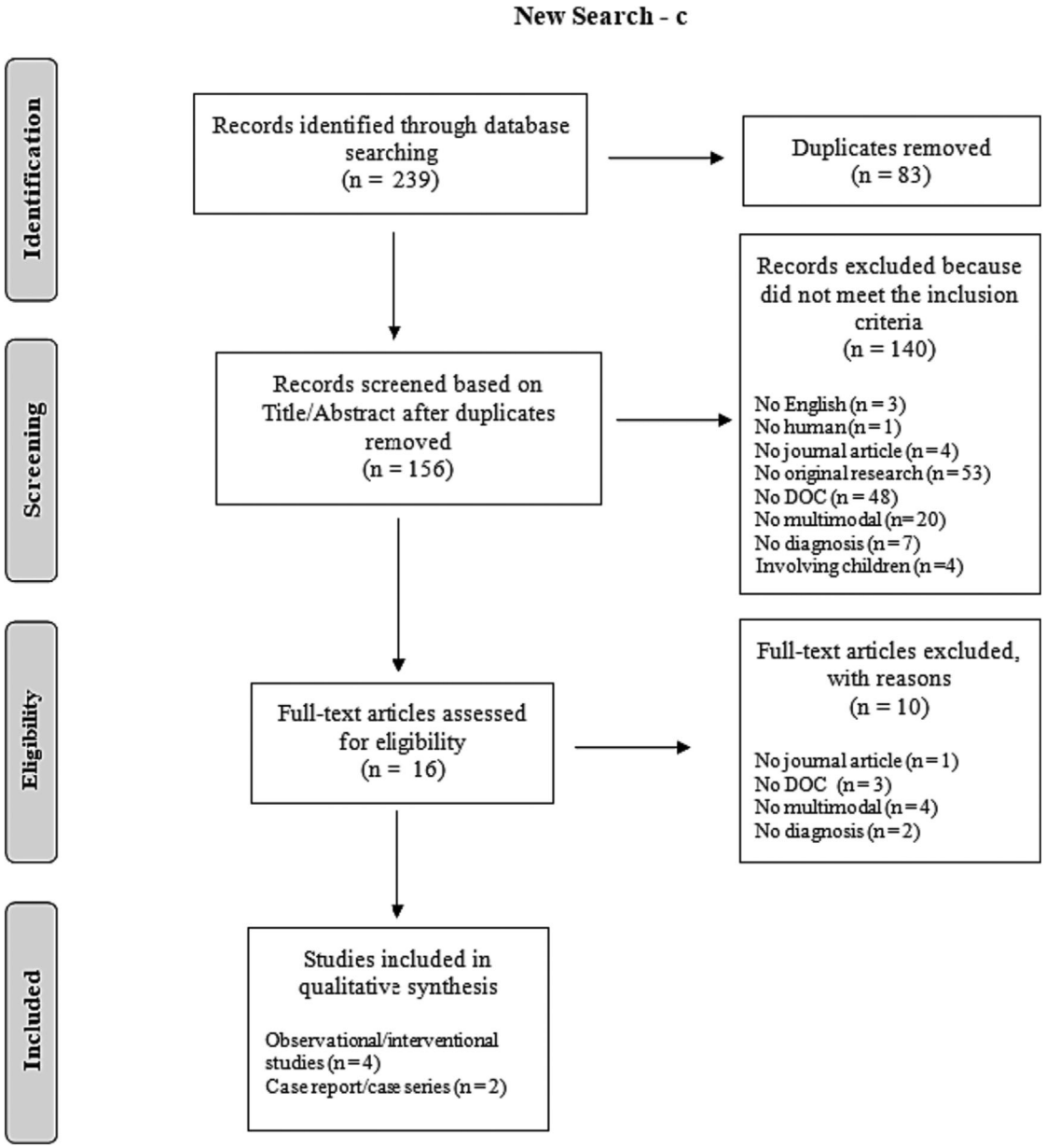

FIGURE 1 (Continued)

based papers, both for technical and theoretical reasons (see the paragraph below). The 32 case series and case reports were reported as well in a separate paragraph, grouping the studies according to the previously mentioned aims and type of multimodal instruments used.

3.4 | EEG-based multimodal studies

The 64 EEG-based studies were published between 1996 and 2023 and included a total of 2792 patients (Table 1). Thirty-six studies combined EEG with neuroimaging techniques, such as MRI and CT (e.g., Bosco et al., 2014; Gobert et al., 2018; Isono et al., 2002; Keijzer et al., 2022; Rae-Grant et al., 1996; Sangare et al., 2022; Scarpino et al., 2020; Scarpino, Lolli, Lanzo, Carrai, Spalletti, Valzania, Lombardi, Audenino, Celani, Marelli, et al., 2019; Scarpino, Lolli, Lanzo, Carrai, Spalletti, Valzania, Lombardi, Audenino, Celani, Marrelli, et al., 2019; Velly et al., 2018; Wedekind et al., 1999; Wedekind, Hesselmann, & Klug, 2002; Wedekind, Hesselmann, Lippert-Grüner, & Ebel, 2002; Zhang et al., 2011). Most of these works focused on resting-state paradigms, comparing and correlating baseline EEG recordings with the extent and type of cortical lesions, and/or with the integrity of the default mode network

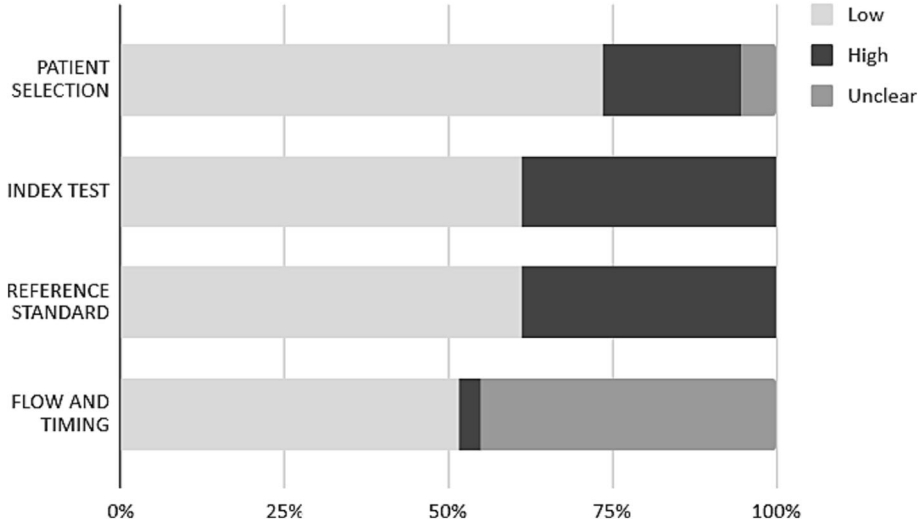

FIGURE 2 The risk of bias evaluations through the modified version of the QUADAS-2.

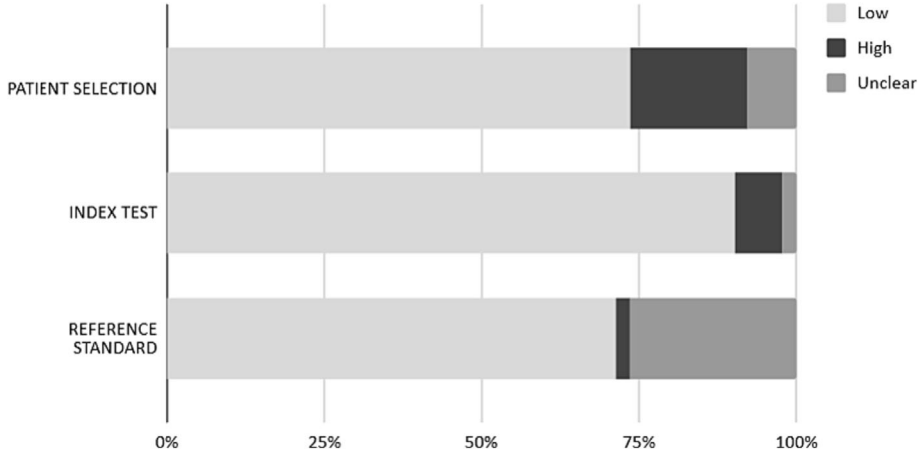

FIGURE 3 The risk of bias evaluations, applicability level, through the modified version of the QUADAS-2.

(DMN). Six studies used different EEG and/or MRI passive paradigms, such as auditory speech stimulation (Chatelle et al., 2020; Ferraro et al., 2020; Gobert et al., 2018; Hermann et al., 2021) and tactile or painful stimulation (Portnova et al., 2020; Zhang et al., 2011) to observe changes in brain activity and the eventual preservation of cognitive and language functions. In this group of papers, most of the patients had a diagnosis of Coma (19/36), or VS/UWS (10/36), while other papers considered mixed diagnosis (Coma, VS/UWS, MCS−, MCS+, EMCS, LIS) (e.g., Chatelle et al., 2020; Chennu et al., 2017; Edlow et al., 2017; Kim et al., 2021; Lutkenhoff, Johnson, et al., 2020; Othman et al., 2021; Sangare et al., 2022). The GCS and the CRS-R were equally applied for diagnosis and were mostly used to diagnose VS/UWS patients.

Seven papers considered EEG and metabolic data (FDG-PET; SPECT), while seven papers compared EEG data with both MRI and PET information (Carriére et al., 2020; Ferraro et al., 2020; Forgacs et al., 2014; Hermann et al., 2020; Laureys et al., 2002; Sattin et al., 2020, 2021). Only Laureys et al. (2002) included VS/UWS patients assessed by GCS; all the other six studies used the CRS-R to diagnose mixed DoC patients (VS/UWS, MCS−/+, EMCS). Fourteen out of 64 papers integrated EEG recordings and/or neuroimaging and metabolic data with neurostimulation techniques, considering VS/UWS or MCS patients diagnosed with the CRS-R. Only Fekete et al. (2021) work used GCS to evaluate post-stroke patients, of which only a small subgroup (13%) was diagnosed with Coma. Most of these studies applied TMS, while only a small group used tDCS or tACS.

3.5 | Studies improving the diagnosis and prognosis of DoC

Thirty studies focused on improving the diagnosis and prognosis of DoC patients by comparing EEG-based data with neuroimaging and/or metabolic data. In most cases,

TABLE 5 The risk of bias assessment for case reports.

Study	JBI case reports items			
	Patient's clinical evolution clearly described and presented as a timeline	Patient's demographic characteristics clearly described	Consciousness state on presentation clearly described	Diagnostic tests or assessment methods best suited to evaluate the DoC
Aboukasm and Barkley (1995)	Y	Y	Y	NA
Achard et al. (2011)	Y	Y	Y	N
Agardh et al. (1983)	Y	Y	Y	NA
Bagnato et al. (2014)	Y	Y	Y	Y
Carrai et al. (2009)	Y	Y	Y	N
Delamarre et al. (2020)	Y	Y	Y	Y
Edlow et al. (2013)	Y	Y	N	N
Fischer et al. (2020)	Y	Y	Y	N
Laureys et al. (2004)	Y	Y	U	Y
Legouy et al. (2020)	Y	Y	N	Y
Migdady et al. (2021)	Y	Y	N	N
Moritz et al. (2001)	Y	Y	N	N
Owen et al. (2005)	Y	Y	U	NA
Nawfal et al. (2022)	Y	Y	Y	N
Pfeiffer et al. (2014)	N	Y	Y	N
Pistoia et al. (2008)	Y	Y	Y	Y
Rommel et al. (2001)	Y	Y	Y	Y
Sangare et al. (2022)	Y	Y	Y	Y
Scarpino et al. (2020)	Y	Y	Y	Y
Schiff et al. (1999)	Y	Y	Y	NA
Tan et al. (2018)	Y	Y	Y	Y
Vanhaudenhuyse et al. (2018)	Y	Y	Y	Y
Voss et al. (2011)	Y	Y	Y	Y

Abbreviations: N, no; NA, not applicable; U, unclear; Y, yes.

[a]The percentages were calculated by dividing the number of high-risk items rated by the total number of the items rated, excluding the not applicable ones.

TABLE 5 (Continued)

Study	JBI case reports items					N. of high (%)[a]
	Diagnostic tests or assessment methods and the results clearly described	Multimodal approach clearly described	Multimodal techniques integrated or compared	Final consciousness state or outcome clearly described	Takeaway lessons	
Aboukasm and Barkley (1995)	NA	Y	Y	Y	Y	0%
Achard et al. (2011)	Y	Y	Y	Y	Y	11%
Agardh et al. (1983)	NA	Y	N	U	N	33%
Bagnato et al. (2014)	Y	Y	Y	N	U	11%
Carrai et al. (2009)	Y	Y	Y	Y	Y	11%
Delamarre et al. (2020)	Y	Y	N	N	Y	22%
Edlow et al. (2013)	Y	Y	N	Y	U	33%
Fischer et al. (2020)	N	Y	N	N	Y	44%
Laureys et al. (2004)	U	Y	Y	Y	N	11%
Legouy et al. (2020)	N	Y	N	N	Y	44%
Migdady et al. (2021)	Y	Y	N	Y	N	44%
Moritz et al. (2001)	Y	Y	Y	Y	Y	22%
Owen et al. (2005)	NA	Y	Y	N	Y	14%
Nawfal et al. (2022)	N	Y	Y	Y	Y	22%
Pfeiffer et al. (2014)	Y	Y	Y	Y	Y	22%
Pistoia et al. (2008)	Y	N	N	U	N	33%
Rommel et al. (2001)	Y	Y	N	Y	Y	11%
Sangare et al. (2022)	Y	Y	Y	Y	Y	0%
Scarpino et al. (2020)	Y	Y	N	Y	Y	11%
Schiff et al. (1999)	NA	Y	Y	U	Y	0%
Tan et al. (2018)	Y	Y	Y	Y	U	0%
Vanhaudenhuyse et al. (2018)	Y	Y	Y	Y	U	0%
Voss et al. (2011)	N	Y	Y	Y	N	22%

Abbreviations: N, no; NA, not applicable; U, unclear; Y, yes.

[a]The percentages were calculated by dividing the number of high-risk items rated by the total number of the items rated, excluding the not applicable ones.

EEG-based integrated measures combined with neuroimaging and/or neurometabolic data improved the diagnostic assessment compared to that performed with a single technique (Beuchat et al., 2020; Bosco et al., 2014; Cho et al., 2020; Fekete et al., 2021; Keijzer et al., 2022; Lee, Sreepada, et al., 2022; Lutkenhoff, Nigri, et al., 2020; Mikell et al., 2015; Petzinka et al., 2018; Sangare et al., 2022; Scarpino, Lolli, Lanzo, Carrai, Spalletti, Valzania, Lombardi, Audenino, Celani, Marelli, et al., 2019; Scarpino, Lolli, Lanzo, Carrai, Spalletti, Valzania, Lombardi, Audenino, Celani, Marrelli, et al., 2019; Scarpino et al., 2020; Snider et al., 2022; Soldner et al., 2001; Velly et al., 2018). For instance, the pattern of sleep organization determined by 24-h polysomnographic recording strongly correlates with both the severity of injury and the reliable prognosis in Coma patients (Valente et al., 2002). In addition, EEG increases in specific (alpha and beta) and decreases in non-specific (theta) oscillatory responses to tactile stimulation correlate with the severity of brain damage in comatose patients and appear to be a promising biomarker for their prognosis and rehabilitation (Portnova et al., 2020). These data also converge to suggest that polysomnographic recordings and EEG oscillatory analysis could be particularly useful in cases where DoC diagnosis remains uncertain in relation to the clinical examination. Moreover, EEG effectively detected residual frontoparietal brain activity in VS/UWS patients, predicting PET prognoses 1 year after the diagnosis (Chennu et al., 2017). In the same direction, the results of Othman et al. (2021) showed that neurovascular near-infrared spectroscopy (NIRS) signal coupling with EEG power band in frontal areas was sensitive and prognostic of changing consciousness level in acute DoC patients. Furthermore, Wedekind et al. (1999); Wedekind, Hesselmann, and Klug (2002); Wedekind, Hesselmann, Lippert-Grüner, and Ebel (2002) observed that EEG and MRI were equally effective in disclosing DoC aetiology (e.g., TBI). Only three studies did not observe any additional efficacy of EEG over the neuroimaging assessment (Isono et al., 2002; Rae-Grant et al., 1996).

Taken together, these results point towards the benefit of a multimodal approach, showing an improvement in the diagnosis/prognosis when EEG-based measurements come in pairs with neuroimaging or metabolic data and the clinical assessment (e.g., Bosco et al., 2014; Chatelle et al., 2020; Chennu et al., 2017; Forgacs et al., 2014; Portnova et al., 2020; Scarpino et al., 2020; Scarpino, Lolli, Lanzo, Carrai, Spalletti, Valzania, Lombardi, Audenino, Celani, Marelli, et al., 2019; Scarpino, Lolli, Lanzo, Carrai, Spalletti, Valzania, Lombardi, Audenino, Celani, Marrelli, et al., 2019; Soldner et al., 2001; Valente et al., 2002; Velly et al., 2018). Moreover, even though NIRS-EEG needs further exploration, it may be worthy of becoming an additional multimodal approach in the ICU setting due to its non-invasive and bedside applicability (Kassab et al., 2021; Othman et al., 2021).

3.6 | Studies focusing on the differential diagnosis among DoCs

Twenty-eight studies aimed to use a multimodal approach for better differentiating the DoC diagnoses (Bekinschtein et al., 2011; Braiman et al., 2018; Candia-Rivera et al., 2021; Carriére et al., 2020; Chennu et al., 2013; Coleman et al., 2005; Curley et al., 2018; Edlow et al., 2017; Forgacs et al., 2014; Gibson et al., 2016; Gofton et al., 2009; Hermann et al., 2021; Li et al., 2015; Lutkenhoff, Nigri, et al., 2020; Lapitskaya et al., 2013; Naro, Leo, Filoni, et al., 2015; Naro, Calabrò, Russo, et al., 2015; Naro, Leo, Cannavò, et al., 2015; Naro, Leo, Bramanti, & Calabrò, 2015; Naro, Leo, et al., 2016; Naro, Bramanti, et al., 2016; Naro et al., 2017, 2018; Odinak et al., 2014; Rudolf et al., 1999; Sattin et al., 2021; Zhang et al., 2020, 2022). For this purpose, patients have been either involved in active MRI tasks and/or EEG recording sessions (Bekinschtein et al., 2011; Braiman et al., 2018; Carriére et al., 2020; Chennu et al., 2013; Curley et al., 2018; Edlow et al., 2017; Forgacs et al., 2014; Gibson et al., 2016) or passively stimulated with auditory, visual or painful stimuli (Gofton et al., 2009; Hermann et al., 2021; Li et al., 2015; Sattin et al., 2021) or by means of TMS and tDCS (Lapitskaya et al., 2013; Naro, Leo, Filoni, et al., 2015; Naro, Calabrò, Russo, et al., 2015; Naro, Leo, Cannavò, et al., 2015; Naro, Leo, Bramanti, & Calabrò, 2015; Naro, Leo, et al., 2016; Naro, Bramanti, et al., 2016; Naro et al., 2017, 2018; Odinak et al., 2014; Pisani et al., 2015; Zhang et al., 2020, 2022).

Data demonstrated the effectiveness of a multimodal approach in improving DoC differential diagnosis, especially between VS/UWS and MCS patients. Candia-Rivera et al. (2021) observed that the brain response to an internal bodily signal, such as heartbeats, is a relevant indicator of consciousness even in the absence of behaviour. In particular, the heartbeat-evoked response could discriminate VS/UWS from MCS patients with high accuracy (87%) when the DoC diagnosis was based on the glucose metabolism in the DMN and in the right ventral occipitotemporal cortex (Candia-Rivera et al., 2021). In addition, the presence of an auditory localization behaviour should be considered as a signal of MCS and reflects higher-level cognitive processing supported by higher functional connectivity in the brain regions supporting consciousness, as shown by MRI and EEG data (Carriére et al., 2020). In this context, EEG spectral features and coherence, combined with resting-state fMRI (rs-fMRI)

TABLE 6 The risk of bias assessment for case series.

Study	JBI case series items					
	Clear criteria for inclusion in the case series	DoC/consciousness state measured in a standard, reliable way	Valid methods used for identification of DoC	Evaluation test results clearly described	Consecutive inclusion of participants	Complete inclusion of participants
Aubinet et al. (2018)	Y	Y	Y	Y	Y	N
Aubinet et al. (2019)	Y	Y	Y	Y	N	N
Edlow and Fins (2018)	U	Y	Y	Y	N	N
Kanarsky et al. (2021)	Y	Y	Y	Y	N	Y
Plum et al. (1998)	Y	N	N	NA	N	N
Rousseau et al. (2008)	Y	U	U	N	N	N
Schiff et al. (2002)	Y	U	N	NA	N	N
Wijdicks et al. (2001)	Y	U	NA	NA	Y	N
Zanatta et al. (2012)	Y	Y	N	Y	U	U

Abbreviations: N, no; NA, not applicable; U, unclear; Y, yes.

[a]The percentages were calculated by dividing the number of high-risk items rated by the total number of the items rated, excluding the not applicable ones.

TABLE 6 (Continued)

Study	JBI case series items							
	Clear reporting of the demographics	Clear reporting of consciousness state of the participants and its changes	Final consciousness state or outcome results of cases clearly reported	Clear reporting of the site(s)/clinic(s) demographic information	Multimodal approach clearly described	Multimodal techniques integrated or compared	Takeaway lessons	No. of high (%)[a]
Aubinet et al. (2018)	Y	Y	N	N	Y	Y	Y	23%
Aubinet et al. (2019)	U	Y	N	N	Y	Y	Y	31%
Edlow and Fins (2018)	Y	Y	Y	N	Y	U	Y	23%
Kanarsky et al. (2021)	N	Y	Y	N	Y	N	Y	44%
Plum et al. (1998)	Y	Y	Y	N	Y	Y	N	50%
Rousseau et al. (2008)	Y	Y	Y	N	Y	Y	N	38%
Schiff et al. (2002)	Y	Y	N	N	Y	Y	Y	42%
Wijdicks et al. (2001)	N	U	Y	N	Y	Y	N	30%
Zanatta et al. (2012)	Y	Y	Y	N	Y	Y	Y	15%

Abbreviations: N, no; NA, not applicable; U, unclear; Y, yes.

[a]The percentages were calculated by dividing the number of high-risk items rated by the total number of the items rated, excluding the not applicable ones.

data and brain atrophy information coming from sMRI, have successfully improved the differential diagnosis between VS/UWS and MCS patients (e.g., Lutkenhoff, Nigri, et al., 2020). Similarly, a combination of fMRI and EEG brain response to thermal passive stimulation successfully predicted the outcome of VS/UWS and MCS patients, with a high degree of accuracy (Li et al., 2015). Regarding studies combining EEG with PET, the data showed that MCS patients preserved a coupling between electrical activity and glucose metabolism, especially in the best preserved hemisphere, which was not found in VS/UWS patients (Coleman et al., 2005; Hermann et al., 2021; Rudolf et al., 1999).

Other authors combined conventional EEG data acquisition with a motor imagery paradigm during fMRI or PET scanning (Braiman et al., 2018; Forgacs et al., 2014). For instance, Braiman et al. (2018) used EEG to demonstrate that the natural speech envelope (NSE) seems to be a passive approach able to better stratify DoC patients, since it does not require a high level of cognitive functions as compared to the more traditional active paradigms.

The modulations induced by neurostimulation techniques could also be a promising approach to better differentiating the DoC population. In this framework, 12 studies employed TMS and tDCS, analysing either the changes in various cortical excitability indexes (Lapitskaya et al., 2013; Naro, Leo, Filoni, et al., 2015; Naro, Calabrò, Russo, et al., 2015; Naro, Leo, Cannavò, et al., 2015; Naro, Leo, et al., 2016; Naro et al., 2018; Odinak et al., 2014; Zhang et al., 2020, 2022) or focusing on natural rhythms modulation (Naro et al., 2017; Naro, Bramanti, et al., 2016; Naro, Leo, Bramanti, & Calabrò, 2015; Pisani et al., 2015).

Regarding the first set of works, repetitive TMS (rTMS) applied over the motor cortex resulted in lower amplitude of motor and sensory evoked potentials in DoC patients (Lapitskaya et al., 2013; Odinak et al., 2014) with positive correlations between the magnitude of the TMS' induced effects and the CRS-R scores. Notably, tDCS and rTMS modulations differentiated DoC subgroups (Naro, Leo, Filoni, et al., 2015; Naro, Calabrò, Russo, et al., 2015; Naro, Leo, Cannavò, et al., 2015; Naro, Leo, et al., 2016; Naro et al., 2018; Zhang et al., 2020, 2022).

Studies focusing on natural brain rhythms modulation found slow-wave activity (SWA) perturbation in MCS patients but not in VS/UWS (Pisani et al., 2015). Other works found the same pattern of after-effects between DoC subgroups during painful stimulation (Naro, Leo, Bramanti, & Calabrò, 2015) or modulating θ (4–8 Hz) and γ (>30 Hz) EEG band oscillations with tACS over the dorsolateral prefrontal cortex (DLPFC) (Naro, Bramanti, et al., 2016). Furthermore, when compared to healthy controls, DoC patients showed abnormal short and long-range connectivity after rTMS over the left DLPFC (Naro et al., 2017). This result supports the feasibility of employing neuromodulation protocols to complement the clinical evaluation of DoC.

3.7 | Studies investigating the neural correlates of consciousness

Fourteen studies explored the underlying neuropathological mechanisms of consciousness by observing rs-fMRI (Kim et al., 2021; Mikell et al., 2015; Snider et al., 2022) or neurometabolic (Hildebrandt et al., 2007) data by testing patients' responsiveness to external auditory (Laureys et al., 2000), or noxious somatosensory (Laureys et al., 2002), or visual stimuli (Sattin et al., 2020, 2021) or by arousing cognitive active paradigms (Bekinschtein et al., 2011; Chennu et al., 2013; Curley et al., 2018; Edlow et al., 2017; Gibson et al., 2016). Most of these studies suggested that combining information from different approaches should help in detecting the brain networks required to support conscious processes. For instance, Gibson et al. (2016) observed the relationship between electroencephalographic and neuroimaging data as evidence of perceptual/cognitive preservation and markers of awareness.

Notably, patients able to follow commands, whether overtly during clinical assessment or covertly during fMRI, showed evidence of attentional orienting (Gibson et al., 2016). In line with these results, rs-fMRI and EEG coherence data seem to support a model in which multiple frontal networks are needed for command-following, an ability required to assess responsiveness during the behavioural evaluation of DoC patients and, more generally, of patients in the ICU (Mikell et al., 2015). Furthermore, Kim et al. (2021), combining computational models and empirical data from EEG and fMRI, observed the central role of criticality in generating the brain's ability to transition between internal and external stimuli. MCS patients appear to lose the ability to integrate internal information and show an abnormal relationship between synchronization and susceptibility in brain networks (Kim et al., 2021). The neurometabolic data also converged to show that a homoeostatic relationship between neuronal electrical function and cerebral metabolism is fundamental to the recovery of consciousness, when observed in frontoparietal regions (Hildebrandt et al., 2007).

Conversely, two studies reported no agreement between EEG and PET data in either acute or chronic VS/UWS, compared to healthy controls. During both

auditory (Laureys et al., 2000) and noxious somatosensory stimulation (Laureys et al., 2002), increases in the electrical activity were found only in the primary somatosensory cortices, although PET data showed a significant reduction in the brain metabolism.

Taken together, these results are mostly, even not fully, consistent in reporting the advantages of a multimodal approach to understanding neuropathologic pathways in DoC patients. Furthermore, they demonstrated that the combination of different techniques significantly improves the diagnosis of DoC and provides more information about the neural underpinnings of consciousness.

3.8 | TMS-EEG studies

As stated before, we opted for considering apart studies employing TMS-EEG for technical and theoretical reasons.

Regarding the former, despite combining two different instruments, TMS-EEG is a highly integrated system in which the final output, namely TMS-evoked potentials (TEPs), derives from the interaction of the two techniques. From this perspective, TMS-EEG can be considered *sui generis*, since it allows the direct perturbation of the cortex while probing the reactivity of a selected brain area, unveiling its electrophysiological features and causal interactions with the rest of the thalamocortical system.

Regarding the second reason, the idea of using TMS-EEG as a multimodal approach in the field of DoC is grounded on theoretical considerations of the neural underpinnings of awareness (Tononi, 2004; Tononi et al., 2016; Tononi & Edelman, 1998). These theoretical accounts affirm that a system suitable to sustain consciousness should be functionally segregated but also integrated. Each conscious experience is indeed highly informative but unitary at the same time. Conversely, consciousness cannot be sustained anymore, whether either a loss of information integration or differentiation occurs. Accordingly, at a brain level, consciousness depends on the ability of a large set of functionally and spatially different cerebral regions to integrate an extensive amount of information. In this perspective, TMS-EEG represents an optimal tool to measure brain complexity, since it allows to perturb any cortical area by TMS and to observe the induced effects all over the cortex and in real time with the EEG. According to the theoretical account, a system unable to sustain consciousness due to a lack of integration and differentiation should result in a simple, local response regardless of the stimulated site. In contrast, a system capable of sustaining consciousness should result in a highly variable response in time and space, hence complex.

In this framework, this 'perturb and measure' approach can provide essential information about the role of brain complexity in the emergence of consciousness, as postulated in many theoretical accounts (Sarasso et al., 2021). In healthy individuals, both connected (e.g., wakefulness) and disconnected (e.g., dreaming) consciousness are associated with a spatially and temporally complex TMS-EEG brain responses (Massimini et al., 2005), whereas during models of loss of consciousness (e.g., sleep and anaesthesia) lead to local, undifferentiated and stereotypical TMS-EEG response (Sarasso et al., 2015). Building on these evidence and premises, TMS-EEG represented an ideal tool to improve DoC diagnosis and prognosis, independently from the patient's behavioural capacity.

From our literature screening, 14 papers employed TMS-EEG to investigate the residual brain functional connectivity and improve the differential diagnosis in DoC patients (Table 2). These papers were published between 2012 and 2023 and involved a total of 409 patients. Most of the studies considered mixed groups of patients (e.g., VS/UWS and MCS and EMCS and LIS, or VS/UWS and MCS), while two papers considered only VS/UWS patients (Li et al., 2023; Rosanova et al., 2018). CRS-R was used for diagnosis by 12 out of 14 papers, while one paper used the Disability Rating Scale (Formaggio et al., 2016). Healthy participants were considered as controls by six out of 14 papers, while two papers used data from other groups of DoC patients, and four papers did not use a control group (Li et al., 2023; Lutkenhoff, Johnson, et al., 2020; Mensen et al., 2020; Sinitsyn et al., 2020). The time from the onset and the aetiology were mixed in all 14 studies.

The first group of studies focused on the TEPs characteristics in DoC patients (Formaggio et al., 2016; Ragazzoni et al., 2013; Rosanova et al., 2012). In this group, one paper examined event-related potentials (ERPs) before and after tDCS stimulation (Mensen et al., 2020). The second set of works computed the Perturbational Complexity Index (PCI; Casali et al., 2013; Casarotto et al., 2016; Rosanova et al., 2018; Sinitsyn et al., 2020; Wang et al., 2022), an index synthesizing the complexity of the deterministic components of TEPs. Finally, three additional papers used the TMS-EEG alone (Li et al., 2023) or supplemented the TMS-EEG assessments based on PCI with neuroimaging techniques to link a functional connectivity measure with brain structural integrity or preserved metabolic rates (Bodart et al., 2017, 2018; Lee, Sanz, et al., 2022; Lutkenhoff, Johnson, et al., 2020).

In the first group of works, VS/UWS patients showed a slower response confined to the stimulation site (Rosanova et al., 2012), indicating a breakdown of effective connectivity as in sleeping and anaesthetized healthy subjects. MCS patients, instead, showed a faster and bilateral propagation of the TEP (Ragazzoni et al., 2013; Rosanova et al., 2012). Furthermore, TMS in DoC patients failed to trigger the desynchronization of θ (4–8 Hz), α (8–12 Hz) and β (15–30 Hz) rhythms, emphasizing the impairment of this clinical population in engaging in complex brain interactions (Formaggio et al., 2016). Notably, SSEP and ERP lacked the same specificity in distinguishing MCS from VS/UWS patients (Ragazzoni et al., 2013), highlighting TEPs' effectiveness as a possible diagnostic tool for unresponsive patients. Moreover, the paper by Mensen et al. (2020) showed that tDCS applied over the dorsolateral prefrontal cortex reduced the slow-wave activity, as measured by TMS-EEG, while it did not alter the high-frequency activity. Thus, tDCS produced only small changes that were not sufficient to determine clinical changes. Recently, however, some doubts have been raised about drawing conclusion on tDCS efficacy the treatment of DoC patients when the analysis is performed at a group-level, due to the impact of the specific diagnosis and aetiology in the response to tDCS treatment (Thibaut et al., 2023). TDCS may still retain some efficacy at an individual level, in subgroups of patients with specific diagnosis and aetiology (e.g., MCS with traumatic aetiology). The second group of studies introduced the PCI (Casali et al., 2013; Casarotto et al., 2016; Rosanova et al., 2018; Sinitsyn et al., 2020; Wang et al., 2022). Normative data collection under different conditions of physiological awareness on healthy and brain-injured populations allowed the detection of an empirical cut-off (PCI* = 0.31), able to optimally (100% sensitivity and specificity) discriminate between consciousness and impaired consciousness in controlled experimental conditions. The computation of PCI in a cohort of DoC patients probed its sensitivity (94.7%) in detecting MCS patients and unveiled the chance of stratifying VS/UWS patients according to the complexity of their brain responses. Namely, VS/UWS patients can be stratified into three subgroups: no response (PCI = 0), where no brain response can be detected; low complexity (PCI < PCI*), where the brain response is comparable to that achieved in healthy population during propofol anaesthesia and dreamless sleep; high complexity, in which the brain response suggests the presence of residual capacity for consciousness despite the behavioural unresponsiveness. Finally, further analysis of the TEPs signal showed that low PCI scores are probably linked with pathological sleep-like off-periods, abolishing complex brain interactions (Rosanova et al., 2018).

The third set of studies observed a high inter-individual variation in functional connectivity among VS/UWS patients (Li et al., 2023). Moreover, by comparing FDG-PET and MRI measures with the PCI to find a link between functional connectivity and the metabolic and structural features of the brain, Bodart et al. (2017) found a strong correlation between PCI and FDG-PET findings. MCS patients showed higher PCI values and relative preservation of cerebral metabolism in the internal or external frontoparietal network, while VS/UWS patients showed low complexity responses to TMS and preserved metabolic activity only in the brainstem and/or the cerebellum. Interestingly, as in Casarotto et al. (2016), a subgroup of VS/UWS patients showed a PCI above the empirical cutoff and a preserved metabolic activity compatible with consciousness, meaning a possible case of CMD. Similar results were also found comparing the PCI and functional anisotropy (FA), showing relative structural integrity in MCS (Bodart et al., 2017) or in VS/UWS and MCS+/MCS− (Lutkenhoff, Johnson, et al., 2020) patients holding high complexity PCI.

In conclusion, these results highlight the potential of the TMS-EEG as a tool to detect covert complex brain activity in DoC patients, which depends on the level of impairment of functional connectivity and structural integrity. In this scenario, a multimodal approach combining neuroimaging, neurometabolic screening and a neurophysiological assessment, with both PCI and standard TEPs analysis, would be crucial to improve DoC diagnosis. The former allows the identification of patients with partially preserved metabolic activity and structural integrity, while the latter should provide an assessment of functional connectivity, giving together a broader overview of the patient's status.

3.9 | Non-EEG-based multimodal studies

The 14 non-EEG-based studies were published between 2003 and 2023 and included a total of 686 patients (Table 3). Most of these studies considered mixed groups of patients (e.g., VS/UWS and MCS or VS/UWS and MCS and EMCS), whereas two papers considered chronic VS/UWS individuals and only one paper focused on MCS− and MCS+ diagnosis. The time from the onset and the aetiology were mixed while the control groups, when present and specified, were composed of healthy participants, except for one work in which LIS and EMCS patients were also included as controls.

3.10 | Studies improving the diagnosis and prognosis of DoC

Four papers focused on improving DoC diagnosis and prognosis by integrating different neuroimaging and neurometabolic techniques (Annen et al., 2018; Qin et al., 2015; Sawamura et al., 2023; Soddu et al., 2016). Although F-FDG-PET has traditionally been considered the most reliable technique to assess DoC patients, these studies tested the possibility of integrating F-FDG-PET with MRI-derived measures to improve the diagnostic process, or to replace metabolic data in case of necessity. For instance, Annen et al. (2018) found that regional brain volume, as measured by structural MRI (sMRI), could provide additional information that may help to disentangle DoC diagnosis, whereas Soddu et al. (2016) managed to estimate the relative metabolic brain levels out from rs-fMRI data. These results should be particularly valuable in the case of clinical settings that may not have access to PET.

A different integration of PET and MRI data was performed by Qin et al. (2015), who investigated the role of $GABA_A$ receptors deficits in the recovery of consciousness. PET results suggested that $GABA_A$ receptor binding may be linked to the recovery of consciousness, thus indicating a possible biomarker of DoC outcomes. Conversely, although informative on connectivity alterations, fMRI data did not correlate with patients' behavioural improvements as evaluated at 3 months follow-up.

3.11 | Studies focusing on the differential diagnosis among DoCs

Four studies focused on improving the differential diagnosis between VS/UWS and MCS (Bedini et al., 2017; Hattori et al., 2003; Rosazza et al., 2016; Stender et al., 2014).

A general better suitability in discriminating DoC diagnosis was found for metabolic data when compared to MRI-derived measures. For instance, Rosazza et al. (2016) investigated whether a relationship between the metabolic, functional and structural DMN integrity and the clinical status of DoC patients may exist, integrating F-FDG-PET, rs-fMRI and sMRI. Evidence for a link between the activity of the DMN and the level of consciousness was detected, with VS/UWS patients showing lower DMN activity as compared to MCS. However, the best classification feasibility was found for FDG-PET followed by MRI and rs-fMRI. The last one was suitable only for those patients relatively stable during scanning. Differently from the other two, rs-fMRI was found to proficiently detect the DMN preserved synchronization activity in a subsample of cases that emerged from VS status in the few months following scanning. This finding suggests that rs-fMRI should be particularly valuable to detect those cases where possible conversion to MCS may motivate additional diagnostic investigations.

In a different study, a lower sensitivity was found when using an active fMRI paradigm in comparison to F-FDG-PET in performing both differential diagnosis and recovery prediction in a sample of VS/UWS and MCS patients (Stender et al., 2014). The diagnostic effectiveness of F-FDG-PET was also highlighted by Hattori et al. (2003), who successfully discriminated between comatose and non-comatose brain-injured patients, whereas an association among FDG-PET values and VS/UWS and MCS diagnosis was found by Bedini et al. (2017).

Regarding the differential diagnosis between MCS+ and MCS−, Aubinet et al. (2020) explored the neural underpinnings of language-related abilities in a sample of MCS. By applying FDG-PET and MRI with voxel-based morphometry (VBM) analysis, they found that brain metabolism, but not brain atrophy, differentiated MCS+ and MCS− diagnosis, suggesting that the recovery of language-related abilities could rely upon brain function, more than structural loss.

3.12 | Studies investigating the neural correlates of consciousness

Five studies multimodally integrated neuroimaging and metabolic-derived indexes to deepen the knowledge of the pathophysiological process of impaired consciousness (Annen et al., 2016; Di Perri et al., 2016; Ferraro et al., 2019; Juengling et al., 2005; Kassubek et al., 2003). For instance, Di Perri et al. (2016) paired rs-fMRI, sMRI and F-FDG-PET to explore DMN structural and functional connectivity within different levels of consciousness. They found that negative DMN connectivity may stand as a neurophysiological marker able to track the recovery of consciousness. In fact, relatively preserved DMN anticorrelations were found in EMCS patients, but not in MCS and VS/UWS. Furthermore, correlations between fMRI and PET were also detected, whereas no differences were found in the grey matter (GM) volume between VS/UWS and MCS.

Another example of integration of different techniques arises from Annen et al. (2016), who explored the link between functional and structural brain dysfunctions through the application of F-FDG-PET and MRI-diffusion-weighted images (DWI). Fractional anisotropy (FA) and metabolic standardized uptake value (SUV) were analysed, revealing low levels of metabolism and white matter (WM) integrity within the DMN in a sample

of VS/UWS and MCS patients. Furthermore, a direct relationship between metabolic function and structural integrity within the DMN was found.

Correlation between DTI-derived measures and metabolic values was also detected by Ferraro et al. (2019) while tracking a relation between corpus callosum integrity and DoC differential diagnosis.

Two different works (Juengling et al., 2005; Kassubek et al., 2003) focused on chronic VS/UWS patients to better characterize the structural and functional abnormalities patterns linked to this condition. In the study by Kassubek et al. (2003), functional PET with O-labelled water ($O–H_2O$ PET) was employed to investigate the neural activations during electrical nociceptive stimulation. Residual brain activity in some pain-related regions was found, despite the severely impaired brain condition of these patients, as further demonstrated by Juengling et al. (2005).

Taken together, these data suggest that neuroimaging and neurometabolic tools could be proficiently integrated into the clinical assessment of DoC patients. Indeed, the combination of functional and structural investigations of the neural underpinnings of impaired consciousness may allow a deeper understanding of the disease, thus supporting both the diagnostic and prognostic procedure.

3.13 | Case reports and case series

Among the 32 papers included, 23 were case reports and nine were case series, published between 1983 (Agardh et al., 1983) and 2022 (Nawfal et al., 2022) (Table 4). The articles included were highly heterogeneous in terms of patients' demographic characteristics, clinical evolution, aetiology and applied diagnostic techniques. Case reports and case series typically followed patients from admission to discharge. Therefore, they longitudinally tracked the patients' status, reporting the initial consciousness state, its changes throughout time and the outcome. However, not all studies reported the complete clinical history of patients.

The most frequent diagnosis was Coma and VS/UWS, followed by MCS. A unique case of a patient with a diagnosis of long-lasting coma (LLC) was described in Bagnato et al. (2014). A high variability can be observed in the trajectories that led individuals from the DoC onset to the recovery of consciousness or death. Five studies included healthy controls to compare the patient's brain activity or metabolism.

Twenty-four out of 32 papers reported the use of a clinical scale to evaluate the patient's consciousness state. Specifically, 14 of them used the GCS, five applied the CRS-R and five combined both scales. Concerning the neurological techniques employed, 17 studies combined neurophysiological and neuroimaging instruments, while 13 studies combined neurophysiological, neuroimaging, and metabolic instruments. The last two studies joined neuroimaging and metabolic instruments only.

3.14 | Studies improving the diagnosis and prognosis of DoC

Eighteen studies are in this group. Sixteen of them used only EEG-based and neuroimaging techniques, while six also used metabolic techniques, and one used neuroimaging techniques together with EEG and polysomnography (Rommel et al., 2001). Interestingly, one paper used metabolic and neuroimaging techniques, EEG and polysomnography (Kanarsky et al., 2021).

Papers that combined EEG-based and neuroimaging instruments focused their discussion on the prognostic or diagnostic value of only one of the techniques employed (e.g., Delamarre et al., 2020; Edlow et al., 2013; Fischer et al., 2020; Legouy et al., 2020; Nawfal et al., 2022; Pistoia et al., 2008; Sangare et al., 2020; Scarpino et al., 2021). Nonetheless, some papers highlighted that the use of a multimodal approach, even if incidental, improved the DoC diagnosis.

One study showed that the combination of EEG-based and neuroimaging techniques helped in explaining the data provided by each technique alone (Aboukasm & Barkley, 1995). Aboukasm and Barkley (1995), describing the case of an 85-year-old man with a unilateral α-coma, showed that EEG detected low voltage activity only over the left hemisphere, while MRI showed an old infarction in the right hemisphere, mostly affecting the basal ganglia. Authors postulated that the presence of unilateral α-coma was due to the pre-existing brain impairment.

Three papers found that MRI had a better prognostic value compared to neurophysiological examinations in comatose individuals (Moritz et al., 2001; Pfeiffer et al., 2014; Wijdicks et al., 2001). In a 38-year-old female patient in Coma due to ischaemic injury, median nerve stimulation indicated absence of thalamocortical processing, while BAEPs and VEPs suggested impaired auditory and visual processing (Moritz et al., 2001). However, despite large contusions in the temporal lobes, fMRI showed preserved cerebral activity in response to visual, auditory and tactile stimulation. These results led physicians to pursue an intensive medical treatment for the brain injury. Three months post-trauma, the patient recovered her linguistic and motor functioning, although retaining visual and both short- and long-term memory deficits.

Two studies (Nawfal et al., 2022; Zanatta et al., 2012) integrated EEG-based and neuroimaging techniques. Zanatta et al. (2012) investigated the prognostic value of painful electrical stimulation of median-nerves in three post-anoxic comatose patients. In their study, SSEPs and EEG were performed within 5 days from cardiac arrest and repeated, together with an fMRI, after 1 month. Results showed a correspondence between physiological reactivity to noxious stimulation, as indicated by the presence of the N20/P25 and middle latency SSEPs components, and the activation of brain areas involved in the processing of pain. Nawfal et al. (2022) reported the case of a 24-year-old woman, initially comatose after cardiac arrest. MRI performed 32 h after cardiac arrest showed restricted diffusion on both precentral gyri and both putamina. SSEPs showed preserved EP and N13 responses, but bilateral absence of the N20 potentials, which lead to the prognosis of persistent VS/UWS. Despite the poor prognosis, the family decided to insert a cardioverter-defibrillator device and to take the patient home. Four weeks later, the patient was readmitted to the hospital and showed signs of regained consciousness, concurrently with reappearance of the N20 component and disappearance of MRI abnormalities. The hypoxic injury shown by initial MRI may explain why the N20 was initially not detected and why its prognostic value can be made more accurate when combined with brain imaging findings.

Among the papers that performed metabolic analyses, two aimed exclusively at improving the diagnosis and prognosis (Achard et al., 2011; Schiff et al., 1999), while four also aimed at describing the neural correlates underlying DoC (Aubinet et al., 2018; Laureys et al., 2004; Owen et al., 2005; Rousseau et al., 2008). Achard et al. (2011) proposed the use of fMRI connectivity analysis in combination with PET and evoked potential (EP) data to further corroborate a diagnosis of DoC. They applied their method to a 36-year-old man in VS/UWS due to CA. Connectivity analyses identified global disconnections between primary and associative areas, confirming the VS/UWS diagnosis obtained with more traditional measures (i.e., PET and EP).

One study (Edlow & Fins, 2018) discussed the clinical and ethical implications of using a multimodal approach encompassing EEG and task-based fMRI measures to detect covert consciousness in patients in Coma after TBI.

3.15 | Studies focusing on the differential diagnosis among DoCs

Three papers aimed at providing the differential diagnosis. One combined EEG and neuroimaging techniques to identify the correct diagnosis (Carrai et al., 2009), founding a discrepancy between neurophysiological findings and the observational assessment of a 56-year-old male patient with a closed head injury who appeared to be in Coma. The EEG showed reactivity to acoustic stimuli, as well as posterior α activity. Median-nerve SSEPs showed bilaterally preserved early and middle-latency components. These results were in contrast with the low level of motor responses detected by the GCS. Therefore, the MRI revealed diffuse and midbrain axonal injuries involving both cerebral peduncles, consistent with tetraplegia, allowing physicians to conclude that the patient's diagnosis was LIS. ERPs further confirmed the diagnosis, providing evidence of cognitive activity. These evidences highlighted how the integration of neurophysiological and neuroimaging measures might have a crucial impact on the differential diagnosis between LIS and Coma.

Two papers (Bagnato et al., 2014; Vanhaudenhuyse et al., 2018) pointed out the relevance of using a multimodal approach including metabolic techniques to sharpen DoC differential diagnosis. In Vanhaudenhuyse et al. (2018), the bedside assessment through repeated CRS-R evaluation over 1 week indicated residual consciousness in a patient with a VS/UWS from 20 years. MRI highlighted a brainstem lesion typically found in individuals with LIS and relative preservation of WM connections. PET analysis showed that the global cerebral metabolism was almost entirely retained. Hypometabolism was observed in the mediofrontal region, the thalamus bilaterally, the brainstem and the cerebellum, consistent with a brainstem lesion. The EEG detected bilateral α activity in the 8–10 Hz band. The convergent results of behavioural and neurological assessment allowed clinicians to correctly change the patient's diagnosis to LIS.

3.16 | Studies investigating the neural correlates of consciousness

Ten studies aimed at better describing the neural correlates of DoC. One of them employed EEG-based and neuroimaging techniques (Tan et al., 2018), whereas the remaining papers combined EEG-based, neuroimaging and metabolic measures (i.e., Migdady et al., 2021).

One study (Voss et al., 2011) monitored changes in consciousness state before and after cranioplasty in a 19-year-old female shifting from Coma to MCS. Five papers included patients in VS/UWS (Agardh et al., 1983; Owen et al., 2005; Plum et al., 1998; Rousseau et al., 2008; Schiff et al., 2002) and four focused on patients in MCS (Aubinet et al., 2018, 2019; Laureys et al., 2004; Tan et al., 2018).

Schiff et al. (1999) observed that the production of random isolated words in a woman in VS/UWS for 20 years was not a sign of preserved consciousness, but it could be a preserved activity of neuronal groups, even in a severely impaired brain. Starting from these results, Schiff et al. (2002) extended their study to four more VS/UWS patients (including the case described in 1999). Three out of five patients manifested observable complex behaviours (e.g., chewing objects placed in the mouth). Using co-registered PET/MRI and MEG analysis, the authors identified islands of residual cortical activity in all patients. They argued that complex behaviours observed in VS/UWS patients can be an index of preserved activity of an isolated group of neurons, rather than a sign of preserved consciousness. These results are consistent with findings by Plum et al. (1998), who studied three VS/UWS patients exhibiting fragments of organized behaviour (including the one also described in Schiff et al., 1999). Similarly, based on MRI, PET and MEG analyses, Plum et al. (1998) found that extensively injured brains can still express partial, but not integrated, activity as it would be necessary to consciousness.

The studies described so far investigated different behaviours, including language production, in VS/UWS. In a complementary manner, one study (Owen et al., 2005) carried out two PET exams (9 months apart) and one fMRI session (the same day as the second PET scan) on a 30-year-old man in VS/UWS to focus on language comprehension. During PET, the patient underwent a spoken language comprehension task, while a semantic ambiguity study was performed during fMRI. Although both fMRI and PET identified activity in the left superior and middle temporal gyri, consistent with advanced speech comprehension, researchers could not conclude whether this was a sign of preserved consciousness or a residual cognitive function that can characterize individuals in VS/UWS.

Laureys et al. (2004) also investigated the presentation of auditory stimuli with emotional valence on a 42-year-old man in MCS. Auditory stimuli, particularly the patient's own name, produced a more widespread activation compared to VS/UWS, including the precuneus, anterior cingulate/mesiofrontal, right temporoparietal, left dorsolateral prefrontal and bilateral angular gyri. ERPs showed preserved P300 component in response to the presentation of patient's own name. The authors did not provide an explicit interpretation of their findings in terms of signalling residual consciousness. However, the areas with greater activity in response to the auditory perception of one's name seem to be involved in consciousness, as already observed in previous studies (e.g., Kjaer et al., 2002).

Two papers employed a multimodal approach to detect the presence of overall residual cognitive functioning (Aubinet et al., 2018) and of command following (Aubinet et al., 2019) in MCS patients. The most recent study by Aubinet et al. (2019) pointed out how the reappearance of previously silent cognitive functions, namely, command following, was concomitant with a recovery of metabolism and GM structure in language-related areas. Inclusion criteria required patients to be diagnosed as MCS− during the first week of assessment (T1), and as MCS+ during the second week (T2), in accordance with their recovery in following commands. Based on these criteria, three patients were enrolled and underwent FDG-PET and sMRI exams that showed increased metabolism from MCS− to MCS+ in areas related to language (left temporal lobule and cortex and cerebellum), executive functions (medial frontal gyrus) and extrapyramidal functions (left/right caudate). Only Case 2 showed a significant increase of GM volume at T2 in the bilateral caudate and the left fusiform, angular and middle/inferior temporal gyri.

Tan et al. (2018) focused instead on the cerebral transformations that happen in the event of a clinical evolution from VS/UWS to MCS. Twenty-four-hour EEG over multiple nights and MRI with connectome try analysis were performed on a 23-year-old man in transition from VS/UWS to MCS after a TBI. EEG showed an absence of spindling activity and low θ activity during VS/UWS. During the transition to MCS, EEG detected spindling activity and an increase in wave amplitude, especially in the right temporal and right posterior occipital lobe. At the onset, the MRI showed that the left hemisphere was mostly impaired. Consistently, individual fibres analysis showed that WM fibres density was reduced overall in the left hemisphere. While the patient was in MCS, fibres density increased in the right hemisphere. The temporoparietal junction exhibited the largest (more than 30%) increase in density. Whole-brain analysis indicated that the largest increase in density happened in vision-related areas (i.e., the cuneus and calcarine fissure) and auditory-related areas (i.e., the middle temporal gyrus). In this case, both EEG-based and neuroimaging results pointed towards the role of the temporoparietal junction and of the visual and auditory systems in the spontaneous recovery from VS/UWS to MCS.

4 | DISCUSSION

Nowadays, in the panorama of DoC diagnosis, the assessment of the residual level of consciousness is a crucial issue to address, for both clinical and ethical reasons. As the limits of the behavioural DoC diagnosis emerged,

research seemed to address this issue by employing neuroimaging, neurophysiological, neurometabolic and neurostimulation techniques to explore covert brain activity indicative of residual consciousness not observable from overt behaviour. Since each technique alone entails certain limitations and greater information can be achieved by their integration, in this systematic review, we collected the evidence provided by studies that employed a multimodal approach, defined as the use of at least two different instrumental techniques (i.e., neurophysiological, neuroimaging, neurostimulation or neurometabolic), to support DoC diagnosis and prognosis and to spread light on the neural correlates of impaired consciousness.

In clinical practice, the use of EEG-based measurements for diagnosing DoC appears to be the most prevalent approach, to the extent that it is currently reviewed and recommended in both the American and European guidelines for DoC (Giacino, Katz, Schiff, Whyte, Ashman, Ashwal, Barbano, Hammond, Laureys, Ling, Nakase-Richardson, et al., 2018; Kondziella et al., 2020). It is not surprising, considering that EEG equipment is more cost-effective, portable and easy to use compared to other techniques. For instance, MRI presents many contraindications that are common in brain-injured patients, such as metal inserts and quality of recording is heavily affected by motion artefacts. Moreover, the American guidelines currently recommend the use of advanced imaging and electrophysiological techniques whenever the behavioural presence of conscious awareness is ambiguous. In an attempt to systematize and rationalize the use of all available tools, in a recent review on the use of neurophysiology in the prognostic and diagnostic evaluation of DoC, Comanducci et al. (2020) draw an operational stepwise workflow, in which conventional EEG-based assessment is defined as a first step to better stratify patients with prolonged DoC and to increase the effectiveness of differential diagnosis between chronic VS/UWS and MCS, according to the expectations of recovery and tailoring their rehabilitation pathway (Comanducci et al., 2020).

Another result emerging from our review is the impact of adopting multimodal approaches in improving the outcome prediction of DoC patients. This is particularly true when EEG-based measurements are combined with neuroimaging or metabolic data (e.g., Bosco et al., 2014; Forgacs et al., 2014; Scarpino, Lolli, Lanzo, Carrai, Spalletti, Valzania, Lombardi, Audenino, Celani, Marelli, et al., 2019; Scarpino, Lolli, Lanzo, Carrai, Spalletti, Valzania, Lombardi, Audenino, Celani, Marrelli, et al., 2019; Soldner et al., 2001; Velly et al., 2018) or with neurostimulation, namely, TMS-EEG (e.g., Bodart et al., 2017, 2018; Casarotto et al., 2016; Formaggio et al., 2016; Ragazzoni et al., 2013; Rosanova et al., 2012, 2018). For instance, the integration of EEG and PET data results in improved prognosis, as well as in an earlier diagnosis compared to the single instrumental approach (Chennu et al., 2017). Furthermore, some studies successfully tested the possibility of integrating MRI-derived measurements to improve the F-FDG-PET diagnostic assessment (e.g., Annen et al., 2018; Soddu et al., 2016). These findings highlighted the existent correlation between the metabolic, functional and structural DMN integrity and the clinical DoC diagnosis, as well as the importance to associate metabolic, functional and structural data in the same cohort of patients (Rosazza et al., 2016).

Most of these studies suggested that combining information from different techniques would help in better identifying the brain networks required to support conscious processes. This is crucial not only to understand the neuropathological underpinnings of consciousness but also for differentiating VS/UWS from MCS in cases of uncertain diagnosis (e.g., Aubinet et al., 2020; Bekinschtein et al., 2011; Chennu et al., 2013; Curley et al., 2018; Di Perri et al., 2016; Edlow et al., 2017; Stender et al., 2014). The challenge of a differential diagnosis between these two groups of patients is that some of them might recover awareness but still be significantly impaired in their ability to reproduce goal-directed behaviours, leading to up to 40% of misdiagnosis (Giacino et al., 2002; Schnakers et al., 2009). However, MCS patients seem to retain some cognitive processing capability and the possibility to activate brain networks like those of control patients (e.g., Boly et al., 2008; Laureys et al., 2002). Patterns of EEG coherence and spectral features (e.g., Lutkenhoff, Nigri, et al., 2020), as well as concurrent preservation of electrical activity and glucose metabolism (e.g., Coleman et al., 2005; Rudolf et al., 1999), and more functional and structural integrity of DMN (e.g., Bedini et al., 2017; Hattori et al., 2003; Rosazza et al., 2016; Stender et al., 2014), seem to be brain-based information able to differentiate MCS patients from VS/UWS, demonstrating their potential capability to sustain awareness. Thus, the multimodal data integration from active paradigms or passive stimulation, with auditory or painful stimuli, allowed the detection of signs of covert consciousness (e.g., Gibson et al., 2016). This became even more evident when passive paradigms, such as NSE (Braiman et al., 2018) or thermal painful stimulation (Li et al., 2015), were used.

Another relevant consideration prompted by our review concerns the rationale for which different techniques are usually combined. We observed that, across the studies reviewed, three main reasons can be identified to justify the employment of multimodal measures.

First, in many cases, the use of more techniques occurred without an a priori explicit intention to integrate them to take advantage of the complementary information provided by the two types of measures. It is particularly noticeable in the case reports and case series section. In these works, the peculiar aetiology often required different types of measures to deepen the knowledge of the underlying pathological mechanisms. As well as the longitudinal monitoring of the patients' evolutionary trajectory resulted in the collection of different neurophysiological, metabolic or neuroimaging measures. Here, despite a multimodal approach being employed, the several measures often were not integrated, but rather analysed, reported and discussed separately. In most of these studies, the multimodal approach was not designed a priori with a precise diagnostic purpose and a reasoned choice on the types of measures to be collected and integrated.

In a similar vein, in many studies, the use of a multimodal approach aimed to compare the diagnostic and prognostic value, in terms of sensitivity and specificity, of each technique alone. For instance, Scarpino, Lolli, Lanzo, Carrai, Spalletti, Valzania, Lombardi, Audenino, Celani, Marelli, et al. (2019); Scarpino, Lolli, Lanzo, Carrai, Spalletti, Valzania, Lombardi, Audenino, Celani, Marrelli, et al. (2019) compared the accuracy of EEG, SSEPs and CT for predicting the neurological outcome at 6 months in comatose survivors after cardiac arrest. The pattern of bilaterally absent/absent-pathological amplitude of cortical SSEP patterns showed greater sensitivity (57.3%) in predicting a poor outcome than the Grey Matter/WM (GM/WM) density ratio from brain CT (48.8%) and the isoelectric/burst-suppression EEG patterns (34.5%). Crucially, the combination of the three markers (at least one pathological) reaches 61.2% of sensitivity, confirming the added value of a multimodal approach. The GM and WM volume atrophy (s-T1-MRI) was also compared to DoC classification using cerebral glucose uptake from FDG-PET to understand its role in differentiating VS/UWS and MCS patients (Annen et al., 2018). The authors observed that GM atrophy occurred faster in VS/UWS patients compared to MCS, with a congruency between MRI data and CRS-R diagnosis of at least 87%. Moreover, when structural T1-weighted MRI and PET-based diagnoses information are combined, they found a false-negative rate of 2% for the GM and 4% for the WM, suggesting that combining different diagnostic modalities is a powerful tool in detecting residual consciousness (Annen et al., 2018).

With the rationale of correlating clinical, neurophysiological and neuroimaging measures, a recent study (Lutkenhoff, Nigri, et al., 2020) tested the relevance of EEG spectral features for the differential diagnosis between VS/UWS and MCS. Specifically, EEG components, together with demographic information (i.e., gender and age), could correctly classify patients across the conscious/unconscious line (as behaviourally defined) with ~87% success, leveraging demographic information, overall brain atrophy and EEG features. With a different purpose, only tangentially affecting DoC diagnosis, in a series of studies, Wedekind et al. (1999); Wedekind, Hesselmann, and Klug (2002); Wedekind, Hesselmann, Lippert-Grüner, and Ebel (2002) tested the accuracy of MRI and EEG protocols in detecting brainstem lesions in traumatic injuries and compared their prognostic value. Electrophysiological and MRI testing were both significant for prognostic purposes, but MRI data turn out to be more relevant. Similarly, Soldner et al. (2001) compared the prognostic value of MRI based atrophy, BAEP and SSEP in acute brain injured patients. The volume of brainstem lesions, but not callosal ones, correlated with the worst outcome and with SSEP. The results suggested that MRI does not improve the prognostic reliability compared to SSEP, whereas BAEP seemed not reliable as a prognostic method. With similar aims but opposite results, Velly et al. (2018) compared EEG and MRI-based assessment in the ability to predict the long-term neurological outcomes in patients after cardiac arrest by comparing the receiving operating characteristic (ROC) curve of clinical assessment, EEG-based and MRI-based measures. ROC for EEG alone or clinical assessment was less specific and sensitive than quantitative MRI ROC (FA). Crucially, the combination of the two techniques increased the area under the ROC curve to 0.99 (0.98–1.00), with a specificity of 100% (95% CI 86–100) and a sensitivity of 98% (95% CI 93–100). On top of highlighting the relevance of quantitative MRI methods, these results indicate the added value of a multimodal approach integrating different techniques.

Some studies also compared the sensitivity and specificity of FDG-PET and MRI data to understand if the MRI could substitute the FDG-PET (e.g., Soddu et al., 2016; Stender et al., 2014). F-FDG-PET results in higher sensitivity for MCS diagnosis (93%, 95% CI 85–98), as well as in higher congruency with CRS-R score (85%, 77–90), compared with fMRI imaging active paradigm (MCS diagnosis accuracy: 45%, 30–61; CRS-R congruency: 63%, 51–73). Moreover, PET data predicted the VS/UWS patients' outcome more correctly (74%, 64–81) than fMRI (56%, 43–67). Metabolic data seem to be more suitable in complement bedside behavioural evaluation and in predicting the long-term recovery in VS/UWS patients (Stender et al., 2014). At the same time, interesting results emerged from Soddu et al. (2016), demonstrating the possibility for rs-fMRI to estimate relative levels of activity in a metabolic map starting from the

constructed rs-fMRI functional connectivity maps. This is a crucial aspect to consider in those cases when FDG-PET is not available.

Rosazza et al. (2016) investigated the correlation between the DMN integrity and the level of consciousness by comparing rs-fMRI information with sMRI and FDG-PET data. The results showed that rs-fMRI has a low diagnostic accuracy (area under curve [AUC] = 0.65) and that it did not provide additional information when compared to sMRI and FDG-PET. Nevertheless, rs-fMRI could be informative in detecting residual DMN activity for those VS/UWS patients who remain relatively still during scanning. SMRI data were less sensitive to head movement than rs-fMRI, with a greater diagnostic accuracy (AUC = .72). The importance of assessing structural integrity is further underlined by recent DTI results demonstrating a correlation between WM damage in DMN regions and the level of consciousness (i.e., Fernández-Espejo et al., 2012). However, sMRI data alone cannot replace functional and metabolic measures. FDG-PET, indeed, yielded the best diagnostic accuracy (AUC = 0.75) and a higher correlation with CRS-R scores. Additionally, it is less sensitive to head movement, confirming that FDG-PET can robustly differentiate MCS from VS/UWS patients at the group level (Rosazza et al., 2016).

Taken together, the data described so far seems to converge in demonstrating that a multimodal approach, including at least two different technical instruments, seems advantageous for balancing the limits of each single modality, even if there is no significant superiority of one technique on the other.

As a third reason, the multimodal approach was seldom adopted with the explicit aim of benefit of the added value of integrating two complementary approaches, chosen a priori. In this sense, TMS-EEG studies represent a particular case as the concurrent use of TMS and TMS-compatible EEG allows not only to sum up the respective advantages of the two techniques alone but also to create new advantages from their integration. Indeed, this kind of multimodal approach gives us information that cannot be gathered just by comparing data from the two techniques separately. Namely, the concurrent EEG recording permits to track in real time the spread of the activity induced by the focal and direct perturbation of cortical neurons by TMS, thus unveiling effective connectivity (e.g., King et al., 2013; Massimini et al., 2009; Ragazzoni et al., 2013; Rosanova et al., 2012; Solovey et al., 2015; Tononi et al., 2016; Tononi & Koch, 2008). In this perspective, as reported previously, the combination of TMS and EEG appears to be particularly useful, since it permits an objective evaluation of the residual capacity of specialized brain regions to work in synergy to integrate information from highly specific functional thalamocortical networks (e.g., Koch et al., 2016; Massimini et al., 2009, 2010; Ragazzoni et al., 2013; Sarasso et al., 2015). Building on these bases, the use of TMS-EEG provided a substantial advancement in the field of DoC diagnosis. Recently, a synthetic index accounting for brain complexity as measured by TMS-EEG, called PCI, has been computed and validated (Casali et al., 2013; Casarotto et al., 2016; see also in Comolatti et al., 2019, a computationally different measure of perturbational complexity that holds for other types of brain signals beyond TMS-EEG recordings), showing the ability to discriminate the presence of consciousness with high accuracy, sensitivity, and specificity also for prognostic purposes (Casali et al., 2013; Casarotto et al., 2016; Rosanova et al., 2018). In this regard, the use of TMS-EEG in acute DoC patients offers an intriguing new perspective (Edlow et al., 2023). The application of TMS-EEG, as well as of other multimodal approaches, in acute DoC patients is indeed limited due to obvious logistical, technical and methodological issues. However, the stakes are high, since an early application of TMS-EEG (probably also other multimodal approaches) in acute phase will increase prognostic accuracy, in turn improving goal-concordant care and preventing premature withdrawal of life-sustaining therapy.

To summarize these considerations for the future direction of both research and clinical trials in patients with DoC, we would like to highlight the use of the CRS-R instead of the GCS (see Bodien et al., 2021) in behavioural assessment as a relevant starting point. Considering the inherent limitations of behavioural assessment, which have also been highlighted in this review, we believe it is appropriate to maximize diagnostic efficacy in this essential first step by proposing the use of the CRS-R as a specifically validated test for the diagnosis of DoC according to the different possible diagnostic profiles. Another point that we consider relevant, especially in research settings, is the presence of a control group. In this paper, we have considered the absence of a control group as a high-risk factor when assessing the risk of bias. However, given the complexity of working with this type of patient and the research conducted to improve the diagnostic and prognostic practice of such patients, we consider this limitation to be secondary. All studies based on differential diagnosis and comparing different clinical profiles (Coma, VS/UWS, MCS−; MCS+; EMCS) are equally informative to guide clinical practice. Regarding the multimodal approach, which is the focus of our

work, we believe that it should be designed ad hoc to effectively combine different clinical data. An a priori designed multimodal diagnostic approach could also maximize the effectiveness of technique integration by reducing mutual limitations.

According to these considerations, we believe that it should be the starting point for future studies with the aim of improving DoC diagnosis, prognosis and our understanding of consciousness mechanisms.

AUTHOR CONTRIBUTIONS

All authors contributed significantly to the study conception and design. Material preparation, data collection and analysis were performed by Alessia Gallucci, Erica Varoli, Lilia Del Mauro, Gabriel Hassan, Margherita Rovida and Leonor J. Romero Lauro. The first draft of the manuscript was written by Alessia Gallucci, Erica Varoli, Lilia Del Mauro, Gabriel Hassan, Margherita Rovida and Leonor J. Romero Lauro. The final revisions of the manuscript were performed by Angela Comanducci, Silvia Casarotto, Vincenzina Lo Re and Leonor J. Romero Lauro, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. No other contributors assisted the authors in this work.

ACKNOWLEDGEMENTS

This work was supported by the project 'Dealing with patients with consciousness disorders: a multimodal approach to support the diagnosis and prognosis' (Project code: GR-2016-02361494) funded by the Italian Ministry of Health (RF 2016 Ministero della Salute).

A.C. is supported by the Italian Ministry of Health – RicercaCorrente 2022 and by Fondazione Regionale per la Ricerca Biomedica (Regione Lombardia), Project ERAPERMED2019-101, GA 779282. A.C. is also a PhD student enrolled in the National PhD in Artificial Intelligence, XXXVII cycle, course on Health and life sciences, organized by Università Campus Bio-Medico di Roma.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/ejn.16149.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/supporting information. Further inquiries can be directed to the corresponding author.

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How to cite this article: Gallucci, A., Varoli, E., Del Mauro, L., Hassan, G., Rovida, M., Comanducci, A., Casarotto, S., Lo Re, V., & Romero Lauro, L. J. (2024). Multimodal approaches supporting the diagnosis, prognosis and investigation of neural correlates of disorders of consciousness: A systematic review. *European Journal of Neuroscience*, *59*(5), 874–933. https://doi.org/10.1111/ejn.16149