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Residual implicit and explicit language abilities in patients with disorders of consciousness: A systematic review

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ABSTRACT

Language assessment in post-comatose patients is difficult due to their limited behavioral repertoire; yet associated language deficits might lead to an underestimation of consciousness levels in unresponsive wakefulness syndrome (UWS) or minimally conscious state (MCS; -/+) diagnoses. We present a systematic review of studies from 2002 assessing residual language abilities with neuroimaging, electrophysiological or behavioral measures in patients with severe brain injury. Eighty-five articles including a total of 2278 patients were assessed for quality. The median percentages of patients showing residual implicit language abilities (i.e., cortical responses to specific words/sentences) were 33 % for UWS, 50 % for MCS- and 78 % for MCS + patients, whereas explicit language abilities (i.e., command-following using brain-computer interfaces) were reported in 20 % of UWS, 33 % of MCS- and 50 % of MCS + patients. Cortical responses to verbal stimuli increased along with consciousness levels and the progressive recovery of consciousness after a coma was paralleled by the reappearance of both implicit and explicit language processing. This review highlights the importance of language assessment in patients with disorders of consciousness.

1. Introduction

One of the most frequent and fundamental questions professionals are faced with when taking care of patients with severe brain injury is: “Can they understand us?” Language assessment is a crucial aspect in these patients, but it is complicated by their limited behavioral repertoire (Majerus et al., 2009).

Post-comatose patients evolve through different states of altered consciousness (disorders of consciousness; DoC). As soon as they recover eye-opening and reflexive behaviors, patients are no longer considered in coma but in a state of unresponsive wakefulness (UWS, i.e. vegetative state; Laureys et al., 2010; Multi-Society Task Force on P.V.S, 1994). Reappearance of inconsistent but reproducible signs of consciousness characterizes the minimally conscious state (MCS; Giacino, 2004; Giacino et al., 2002). The most frequent behaviors observed in MCS patients are visual fixation and pursuit, reproducible movement to command, localization to noxious stimulation and automatic motor response (Wannez et al., 2017). Previous neuroimaging studies showed the presence of residual cognitive abilities such as language processing in some MCS patients (e.g., Coleman, Bekinschtein et al., 2009; Coleman, Davis et al., 2009; Schiff et al., 2005). MCS has subsequently been subcategorized as “MCS+” and “MCS- “depending on the presence or absence of language-related signs of consciousness (i.e., command-following, intelligible verbalization and/or non-functional communication; Bruno et al., 2011). The emergence of MCS (EMCS) is finally defined by the recovery of higher-level cognitive and motor abilities such as functional communication and/or use of objects (Giacino et al., 2002). Importantly, a differential diagnosis has to be made between DoC and states of profound paralysis with preserved cognitive functions, namely the locked-in syndrome (LIS; Bruno et al., 2013).

Standardized and validated scales have been developed to optimize the bedside assessment of consciousness. Among them, the Coma Recovery Scale-Revised (CRS-R; Giacino et al., 2004) is currently the most-used behavioral scale, which has shown good validity, sensibility and reliability (Seel et al., 2010). A shorter version of the CRS-R, the Simplified Evaluation of CONsciousness Disorders (SECONDs) also

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recently showed good psychometric properties (Aubinet et al., 2020a; Sanz et al., 2021). Nevertheless, the diagnosis of consciousness in patients with severe brain lesions is affected by many issues such as motor impairment or fluctuating arousal level (Schnakers et al., 2009). Importantly, associated language deficits might prevent consistent responses to verbal items, leading to an underestimation of levels of consciousness in DoC patients (Majerus et al., 2009). This "bias of aphasia" for behavioral assessment tools such as the CRS-R has been demonstrated in conscious stroke-related aphasic patients (some of whom never experienced a comatose state): 54 % of aphasic patients can be characterized by CRS-R assessment as being in an MCS while these patients clearly have no impaired consciousness (Schnakers et al., 2014).

During the past two decades, an increasing amount of studies attempted to detect residual language abilities in post-comatose patients. Recent research suggested the reappearance of language processing in the absence of consciousness, by employing implicit measures of brain reactivity to verbal stimuli during passive listening tasks either based on neuroimaging or electrophysiological techniques (e.g., Gui et al., 2020; Sokoliuk et al., 2020). Implicit responses classically imply reduced controllability or awareness, lack of intention or highly efficient processing, whereas explicit responses are considered as controllable, aware and requiring cognitive resources (Bargh, 1994; Nosek, 2007). Explicit assessment of language abilities therefore requires active participation from the patient, which is particularly challenging in the DoC population, not only due to variable levels of consciousness and attention, but also due to motor impairment. Apart from behavioral bedside testing, explicit abilities such as command following may be observed in some DoC patients only covertly via a brain-computer interface (again using neuroimaging or electrophysiology in most cases), highlighting a cognitive-motor dissociation (CMD; Schiff, 2015; Edlow et al., 2017).

In this systematic review, we aim to analyze the literature on residual language processing (i.e., speech comprehension and/or production) in DoC patients, as assessed by neuroimaging, electrophysiological and behavioral techniques. Our main goal is to (1) identify the level and quality of language residual abilities as a function of DoC diagnosis; and (2) examine how, when and where implicit and explicit language abilities reappear after severe brain injury associated with impaired consciousness.

2. Methods

The review protocol was preregistered in the PROSPERO (CRD42020139361) database, prior to the beginning of the study, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2015).

2.1. Inclusion criteria

Studies were included in the systematic review if they met the following criteria: (1) population sample composed of adult or close-to-adult patients ($>$ 16 years old) with DoC following severe acquired brain injury; (2) reporting of language-related neuroimaging, electrophysiological or behavioral measurements (e.g., linguistic stimulations, assessment of language networks/areas); (3) study targets the detection of residual language abilities (speech comprehension and/or production); (4) study published in international peer-reviewed journals and written in English; and (5) study using the 2002 consensus-based criteria for diagnosing MCS (Giacino et al., 2002). Only empirical studies were included.

2.2. Search method

We selected all relevant studies published between January 2002 and May 2021 from the following electronic bibliographic databases: PubMed (Medline), Ovid (Medline) and Scopus. Primary search terms were *consciousness disorders, vegetative state, unresponsive wakefulness, minimally conscious, coma* and *severe brain injury*. These primary terms were paired with secondary terms: *language (disorders), comprehension, auditory, speech, command-following, semantics, phonology, lexical, sentence* and *syntactic*. A full description of the search strategy is presented in Supplementary Material 1. The last search was done on May 11, 2021. Ad-hoc sources were also considered (e.g., references mentioned in field-specific papers but not directly appearing via our literature search).

2.3. Study selection and data extraction

The RAYYAN QCRI web application (https://rayyan.qcri.org/) was used to merge all search results and remove duplicates. As a first step, two investigators (CA and CC) independently reviewed titles and abstracts. Next, the same blinded investigators performed a second selection on the basis of the full-texts of the papers. Our main review question was: *Which residual language abilities were observed in patients with disorders of consciousness following severe acquired brain injury using neuroimaging, electrophysiological and behavioral bedside assessment methods?* All publications not meeting this criterion were removed. Any discrepancies were resolved by consensus, and a third investigator (MC) intervened when no agreement could be reached.

The extracted data included: study design, number of included patients and healthy subjects, patient diagnosis, etiologies, age, gender and time post-onset, diagnostic scale, language assessment techniques, and main outcomes – including the percentages of UWS, MCS and EMCS patients with evidence of implicit or explicit residual language abilities. Data extraction was performed by the same two blinded investigators. Any disagreements were discussed and the same third investigator was involved when necessary.

2.4. Quality assessment

All selected studies were assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 criteria (QUADAS-2; https://www.bristol.ac.uk/population-health-sciences/projects/quadas/quadas-2/). Again, the same two main investigators independently conducted this assessment, which was then submitted for consensus. This checklist estimates the risk of bias and applicability concerns over four domains:

i) "Patient selection" was regarded to be at high risk of bias if the study included a single case or convenience sample of patients.
ii) The "index test" (i.e., the language assessment technique) risk of bias was considered as "unclear" if the investigators performing the language-related analyses were not specified to be blinded of patients' diagnosis of DoC. A high risk of bias was estimated as soon as non-blinding was reported.
iii) The "reference standard" (i.e., behavioral diagnostic tool used for diagnosis of DoC) led to high risk of bias when the resulting DoC diagnosis did not comply with established consensus-based diagnostic criteria for UWS and MCS (Giacino et al., 2002; Multi-Society Task Force on P.V.S, 1994). We also attributed a high risk of bias when the behavioral assessor was not blinded to the results of language assessment.
iv) The "flow and timing" (i.e., patient flow and study timing) presented a high risk of bias when the patient flow could have introduced bias (e.g., no appropriate interval between index test and reference standard or patients assessed by different reference standard).

Furthermore, the "applicability concerns" referred to the representativeness of the studies as regards to the review question (i.e., target population, relevance of language assessment techniques, adherence to diagnostic criteria for DoC).

2.5. Data synthesis

Selected studies were organized in a table including a comparative synthesis of their characteristics and main results. Data were synthesized according to the PRISMA guidelines and checklist. We organized the different studies depending on the implicit and/or explicit language measurements that were involved (i.e., use of passive versus active tasks). For all studies revealing proportions of UWS, MCS (-/+) or EMCS patients with either implicit or explicit residual language abilities (e.g., similar brain reactivity compared to healthy control subjects), we reported them in percentages. The medians of the percentages were calculated for each DoC diagnosis as shown in Supplementary Material 2. Percentage values relative to only one patient were not included in our calculation to avoid any risk of bias. Differences between median percentages for implicit vs. explicit language abilities were analyzed using χ^2 tests and considered as significant when $p < 0.05$. The presence of dependent studies conducted in the same populations of DoC patients was taken into account, by considering the study with the largest patient sample.

3. Results

3.1. Study characteristics

As shown in Fig. 1 (flow diagram), a total of 884 records were initially identified and 85 articles were retained in the present systematic review. Study characteristics are detailed in Table 1. We found both prospective and retrospective studies, cross-sectional and cohort studies, as well as single and multiple case studies. All studies followed standard ethical requirements (e.g., informed consent obtained by the patient or their legal representative).

Forty-eight studies included implicit language measurement and thus detected brain activity in response to various language stimuli: 18 of them used functional magnetic resonance imaging (fMRI), two of them employed positron emission tomography (PET) and 29 included electroencephalography (EEG) and event-related potentials. Moreover, 51 studies examined residual explicit language, either by using fMRI (i.e., 20 studies) and/or EEG (i.e., 16 studies) as brain-computer interfaces to detect covert explicit language and consciousness, or by presenting bedside behavioral assessments (i.e., 9 studies based on CRS-R assessments and 6 on other more "language-specific" scales) possibly in line with their neural correlates.

3.2. Quality assessment

Table 1 also reports the quality assessment of all individual studies. Given that DoC patients constitute a rare population, all the studies included convenience samples, leading to a high risk of bias regarding the population according to the QUADAS-2 checklist. Additionally, some studies reporting behavioral communication abilities (Borer-Alafi et al., 2002; Rasmus et al., 2019) only used the Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1976) to estimate the level of consciousness, leading to uncertain DoC diagnoses and high concern regarding the applicability of the population. Besides the use of convenience samples, studies investigating the neural correlates of CRS-R language-related items mostly required from the examiner to categorize the patients on the basis of CRS-R scores (i.e., UWS or MCS- vs. MCS + patients) without mentioning any blinding procedure. They were consequently considered with high concern regarding the index test as well. In the same line, most studies also did not specify if the assessors of language abilities were blinded regarding the reference standard scores. The risk of bias regarding the index test was therefore considered as "unclear". All studies that did not use the recommended CRS-R assessment were deemed as presenting high risk of bias for the reference standard. Here again, most studies did not specify if there was any blinding regarding the index test (i.e., language measurement). The flow and timing risk of bias was also often unclear given that the interval between the behavioral reference standard assessment and the residual language measurement was regularly not specified. Finally, most studies presented low applicability concerns as they involved the target population, language assessment techniques and reference standard measurement corresponding to the review question.

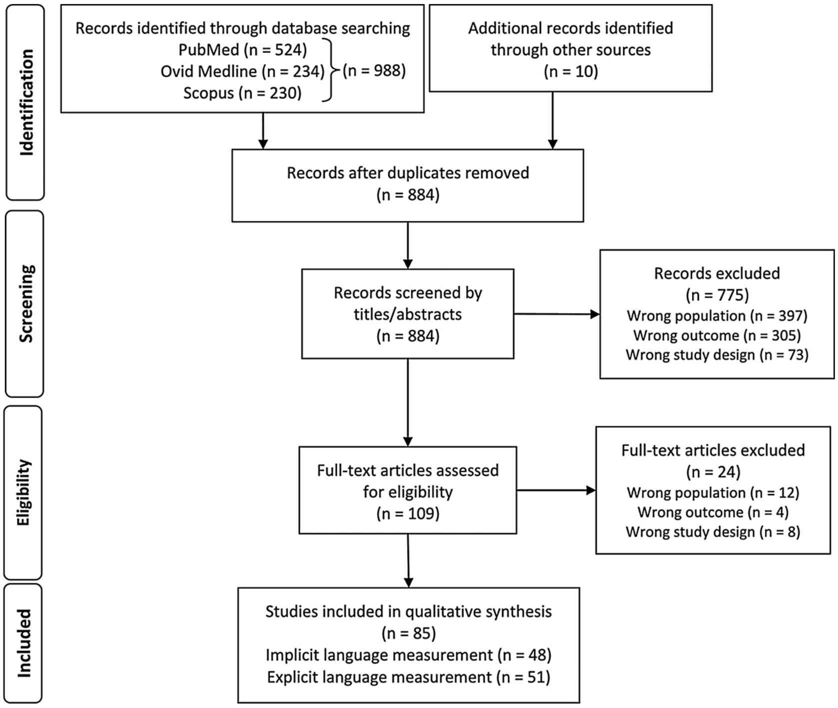

Fig. 1. Flowchart of the selection of articles. PRISMA 2009 flow diagram.

Table 1
Characteristics, main outcome and quality assessment of the included studies.

									Risk of bias			
REFERENCE	N (and diagnoses)	ETIOLOGY	AGE (years)	GENDER	TIME POST-ONSET	SCALE	TECHNIQUE	MAIN OUTCOME	POPULATION	INDEX TEST	REFERENCE STANDARD	FLOW & TIMING
Prospective cross-sectional studies												
Annen et al. (2018)	12 (8UWS, 4MCS-) HCS: 34 (PET)	5TBI, 6anoxia, 1hemorrhage	*Mdn* = 47.5, IQR = 20 MCS-: *M* = 47.5, *SD* = 20 UWS: *M* = 43.5, *SD* = 25.5	5F	*Mdn* = 7.5, IQR = 7.75 MCS-: *M* = 7.5, *SD* = 7.75 UWS: *M* = 50, *SD* = 30.5 months	CRS-R	Active EEG (counting), PET	Explicit: 0%UWS, 25%MCS-	+	?	?	?
Balconi et al. (2013)	18 (10UWS, 8MCS) HCS: 20	5TBI, 10 anoxia, 3stroke	*M* = 50, *SD* = 10.11, R = 25–69	8F	*M* = 52, R = 6–70 months	CNC, DRS, GCS	Passive EEG (N400)	Implicit : 100% UWS, 100% MCS, 100%HCS (but delayed peaks in DoC)	+	?	+	?
Balconi and Arangio (2015)	18 (7UWS, 11MCS)	6TBI, 9anoxia, 3stroke	*M* = 49.5, *SD* = 11.7, R = 25–64	10F	*M* = 48, R = 6–63 months for initial sample of 22patients	CNC, DRS			+	+	+	?
Bekinschtein et al. (2011)	5 (UWS) HCS: 3	4TBI, 1mixed	*M* = 29.4, *SD* = 7.8, R = 20–40, Mdn = 30	?	*M* = 10.4, *SD* = 7.1, R = 5–20, *Mdn* = 6 months	CRS-R	Passive EEG (speech detection), active fMRI (moving hand)	Implicit : 100%UWS Explicit : 40%UWS	+	?	–	?
Beukema et al. (2016)	16 (8UWS, 8MCS) HCS: 17	8TBI, 8NTBI	*M* = 38.5, *SD* = 17.2, R = 16–69	4F	*M* = 42.8, *SD* = 50.8, R = 5–202 months	CRS-R	Passive EEG (N400)	Implicit : 37.5%UWS, 50% MCS	+	?	?	+
Bodien et al. (2017)	10 (1coma, 4UWS, 2MCS-, 3MCS+) HCS: 10	10TBI	*M* = 27.9, *SD* = 9.1, R = 18–51	4F	*M* = 242.9, *SD* = 586.9, R = 3–1900, Mdn = 10 days	CRS-R, CAP	Active fMRI (imagery)	Explicit : 0%coma, 25%UWS, 0%MCS-, 67%MCS + for hand squeezing, 0%coma, 25%UWS, 50%MCS-, 0% MCS + for tennis playing	+	+	+	–
Braiman et al. (2018)	21 (3UWS, 12MCS, 6EMCS) HCS: 13	18TBI, 3NTBI	*Mdn* = 27, IQR = 9	7F	*Mdn* = 64, IQR = 40 months	CRS-R	Passive EEG (narrative), fMRI (motor imagery)	Implicit: Progressive delay in natural speech envelope latencies across diagnostic categories Explicit: 0%UWS, 58%MCS (including MCS-)	+	?	?	?
Charland-Verville et al. (2014)	25 (11UWS, 14MCS)	15TBI, 10NTBI	*M* = 33, *SD* = 13	10F	*M* = 31, *SD* = 27 months	CRS-R	Breathing-based “sniff controller”	Explicit: 0%UWS, 7%MCS	+	?	?	?
Chatelle et al. (2018)	10 (4coma, 1UWS, 4MCS, 1LIS) HCS: 10	2TBI, 3anoxia, 4hemorrhage, 1stroke	*M* = 56.7, *SD* = 12.2, *Mdn* = 56, R = 37–72	2F	*M* = 15.7, *SD* = 11.4, *Mdn* = 15, R = 3–38 days	CRS-R	Active EEG (counting, motor imagery)	Explicit: 0%UWS, 0%MCS	+	?	–	–
Chatelle et al. (2020)	17 (1coma, 2UWS, 3MCS-, 5MCS+, 6EMCS) HCS : 16	17TBI	*M* = 27, *SD* = 7	4F	*Mdn* = 11.5, R = 2–1173 days	CRS-R, fMRI	Passive EEG (speech detection), active fMRI	Implicit: 100%coma, 100% UWS, 66%MCS-, 80% MCS+, 100%EMCS Explicit: 0%coma, 100% UWS, 33%MCS-, 80%MCS+, 100%EMCS	+	–	–	–
Cheng et al. (2013)	86 (47UWS, 39MCS)	53TBI, 33NTBI	*M* = 46, *SD* = 17	19F	*Mdn* = 5, R = 3–13 months	CRS-R	Behavioral (SON)	Implicit: 10%UWS, 30%MCS	+	?	?	?
Crivelli et al. (2019)	21 (UWS)	6TBI, 8stroke, 7anoxia	*M* = 59.1, *SD* = 9.1, R = 29–86	8F	*M* = 37.2, *SD* = 29.9, R =	CNC, DRS	Passive EEG (SON), physiology	Implicit : 100% UWS?	+	?	+	?

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Table 1 (*continued*)

REFERENCE	N (and diagnoses)	ETIOLOGY	AGE (years)	GENDER	TIME POST-ONSET	SCALE	TECHNIQUE	MAIN OUTCOME	Risk of bias			
									POPULA-TION	INDEX TEST	REFERENCE STANDARD	FLOW & TIMING
Curley et al. (2018)	28 (3UWS, 17MCS, 8EMCS) HCS: 15	18TBI, 10NTBI	*M* = 31.6, R = 19–56	7F	12–117 months *M* = 6.5, *SD* = 6.1, R = 0–30 years	CRS-R	Active EEG, active fMRI	Explicit : 66%UWS, 65% MCS, 100%EMCS using EEG; 0%UWS, 29%MCS, 50% EMCS using fMRI	+	?	?	?
Coleman et al. (2007)	14 (7UWS, 5MCS, 2EMCS) HCS: Previous study	7TBI 3anoxia 4stroke	*M* = 42.9, *SD* = 15.0, R = 22–67	5F	*M* = 26.5, *SD* = 39.4 months	GCS, CRS-R	Passive fMRI (speech detection)	Implicit : 43%UWS, 40% MCS, 100%EMCS	+	?	+	?
Coleman, Bekinschtein et al., 2009; Coleman, Davis et al., 2009)	41 (22UWS, 19MCS) HCS: Previous study	26TBI, 11 anoxia, 4stroke	*M* = 40, R = 17–68	13F	*M* = 17.9, *SD* = 26.2, R = 2–122 months	CRS-R, SMART		Implicit : 32%UWS, 63%MCS from extensive bilateral superior temporal area to reduced posterior part of the temporal lobes	+	?	?	?
Erlbeck et al. (2017)	19 (13UWS, 3MCS, 3EMCS) HCS: 45	3TBI, 10 anoxia, 3stroke, 2other	*M* = 50.7, *SD* = 13.7, R = 31–69	8F	*M* = 72.3, *SD* = 39.8, R = 3–141 months	CRS-R	Passive EEG (N400)	Implicit : 8%UWS, 0%MCS, 0%EMCS showed an N1 (prerequisite for N400)	+	?	?	–
Ferraro et al. (2020)	11 (4UWS, 5MCS-, 2MCS+) HCS: 20	4TBI, 5hemorrhage, 2anoxia	*Mdn* = 57, R = 19–69	7F	*Mdn* = 27, R = 5–252 months	CRS-R	Behavioral, structural MRI (DTI), passive fMRI (speech detection), PET	Explicit : 18%DoC brainstem auditory pathways, left superior temporal gyrus and arcuate fasciculus, neural activity elicited by passive listening of language, and left hemispheric glucose metabolism	+	–	+	–
Gibson et al. (2016)	14 (7UWS, 4MCS, 2EMCS, 1LIS) HCS: 15	6TBI, 4anoxia, 4other	*M* = 40.8, *SD* = 12.3, R = 19–58	7F	*M* = 7.8, *SD* = 6.7, R = 0.9–20.4 years	CRS-R	Active EEG (counting), active fMRI	Explicit(bottom-up attention-orienting EEG responses): 35%UWS, 75% MCS, 100%EMCS, 100%LIS, 100%HCS, all with behavioral/fMRI evidence of command-following	+	?	?	+
Guger et al. (2018)	12 (UWS) HCS: 3	4TBI, 2stroke, 4anoxia, 2other	*Mdn* = 53.3, R = 19–91	3F	*Mdn* = 2, R = 1–28 months	CRS-R	Active EEG (counting)	Explicit : 17%UWS	+	?	–	+
Habbal et al. (2014)	38 (10UWS, 8MCS-, 20MCS+) HCS: 18	23TBI, 15NTBI	*M* = 39, *SD* = 14	18F	25 patients: R = 1.08–11.83 years 13 patients: R = 51–347 days	CRS-R	EMG (moving hand, leg, mouth)	Explicit: 10%UWS, 0%MCS-, 20%MCS+	+	?	?	–
Hauger et al. (2015)	20 (11MCS-, 9MCS+) HCS: 20	13TBI, 3anoxia, 2stroke, 2other	*M* = 39.7, *SD* = 14.2, R = 19–66	9F	*M* = 32.7, *SD* = 35.3, R = 3.6–117 months	CRS-R	Passive vs. active EEG (SON detection or counting)	Implicit: “Listen for pitch change” 9%MCS-, 33% MCS+ vs. Explicit: “count your name” 45%MCS-, 44%MCS+	+	+	?	–
Haugg et al. (2018)	15 (9UWS, 4MCS-, 2MCS+) HCS: 13	5TBI, 10anoxia	R = 18–60	?	*M* = 105, *SD* = 36, R = 3–445 months	CRS-R	Active & passive fMRI (counting, movie scene)	Explicit : 33%UWS, 100% MCS-, 50%MCS+, with implicit: heightened differentiation between default mode and dorsal attention networks	+	?	–	–
		?		?	?	None		Explicit : 20%UWS	+	?	+	?

(*continued on next page*)

Table 1 (*continued*)

									Risk of bias			
REFERENCE	N (and diagnoses)	ETIOLOGY	AGE (years)	GENDER	TIME POST-ONSET	SCALE	TECHNIQUE	MAIN OUTCOME	POPULA-TION	INDEX TEST	REFERENCE STANDARD	FLOW & TIMING
Hinterberger et al. (2005)	5 (UWS) HCS: 5		*M* = 47, *SD* = 14, R = 19–70				Active EEG (hand moving)					
Höller et al. (2013)	14 (9UWS, 5MCS) HCS: 22	4TBI, 3anoxia, 5hemorrhage, 2other	*M* = 51.2, *SD* = 14.1, R = 31–73	6F	*M* = 21.1, *SD* = 32.6, R = 2–119	CRS-R, WHIM	Active EEG (hand moving)	Explicit : 22%UWS, 60%MCS (without correction)	+	?	?	?
Kempny et al. (2018)	16 (5UWS, 11MCS) HCS: 12	4TBI, 5anoxia, 6stroke, 1other	*M* = 46, *SD* = 11, R = 18–68	6F	*M* = 17.3, *SD* = 22.6, R = 1.8–80.9 months	SMART	Passive EEG (SON)	Implicit : 20%UWS, 27%MCS	+	?	+	–
Kotchoubey et al. (2009)	30 (15UWS, 12MCS, 3LIS) HCS: 16	10TBI, 7hemorrhage, 3stroke, 7anoxia, 3other	*M* = 43, *SD* = 15, R = 18–68	9F	*M* = 19.1, *SD* = 29.6, R = 1,5–108 months	None	Passive EEG (affective prosody), MEG	Implicit : 27%UWS, 17% MCS, 100%LIS	+	?	+	?
Kotchoubey et al. (2013)	55 (29UWS, 26MCS) HCS: 21	14TBI, 23 anoxia, 11 hemorrhage, 7other	*M* = 48.6, *SD* = 15, R = 16–73	23F	*M* = 25.9, *SD* = 33.9, R = 1–132 months	CRS-R	Passive fMRI (semantics)	Implicit : 38%UWS, 19%MCS	+	+	?	+
Lechinger et al. (2016)	15 (8UWS, 7MCS) HCS: 24	3TBI, 5anoxia, 4hematoma, 1hemorrhage, 2other	*M* = 47.8, R = 20–73) UWS: *M* = 48.13, *SD* = 11.24 MCS: *M* = 47.43, *SD* = 16.19	5F	*M* = 70.7, *SD* = 52, R = 8–152 months	CRS-R	Passive EEG (SON)	Implicit: 0%UWS, 0%MCS	+	?	?	?
Li et al. (2018)	19 (10UWS, 9MCS)	?	UWS: *M* = 51.1, *SD* = 10.2 MCS: *M* = 39.3, *SD* = 11.9	4F	UWS: *M* = 4.05, *SD* = 1.38 MCS: *M* = 3.10, *SD* = 1.92 months	CRS-R, GCS	Passive EEG	Implicit : SON > habit > music detection in UWS and MCS	+	+	?	?
Liang et al. (2014)	5 (3UWS, 2MCS) HCS: 11	4TBI, 1 unclear	*M* = 42,8, *SD* = 14,6, R = 24–60	2F	*M* = 46.6, *SD* = 40.2, *Mdn* = 34, R = 14–118 months	GCS, GOS, WHIM	Passive fMRI (semantics), active fMRI (imagery tasks)	Implicit: 0%UWS, 0%MCS Explicit: 33%UWS, 100% MCS	+	?	+	?
Lulé et al. (2013)	18 (3UWS, 13MCS, 2LIS) HCS: 16	UWS: 2anoxia MCS: 5TBI	UWS: *M* = 61, *SD* = 17 MCS: *M* = 42, *SD* = 21	UWS: 1F MCS: 4F	UWS: *M* = 10, *SD* = 15 MCS: *M* = 70, *SD* = 109 months	CRS-R	Active EEG (counting)	Explicit: 0%UWS, 8%MCS, 50%LIS	+	?	?	?
Naci et al. (2018)	11 (6UWS, 4MCS, 1LIS) HCS: 16	5TBI, 4anoxia, 2other	*M* = 37.4, *SD* = 12.9, R = 19–55	6F	*M* = 84.7, *SD* = 87.6, R = 3–248 months	CRS-R	Active & passive fMRI (counting, movie scene)	Explicit : 33%UWS, 75% MCS, 100%LIS with implicit: down-regulation of the auditory and fronto-parietal networks connectivity	+	?	–	–
Nigri et al. (2017)	11 (4UWS, 7MCS) HCS: 18	4TBI, 2anoxia, 5hemor-rhage	*M* = 50.6, *SD* = 17, *Mdn* = 57, R = 19–69	7F	*M* = 63.4, *SD* = 81.7, *Mdn* = 27, R = 5–252 months	CRS-R	Passive fMRI (speech detection, lexical, semantic processing), passive EEG, PET	Implicit: fMRI: speech detection in 75%UWS, 57% MCS, pseudo-word effect in 25%UWS, 43%MCS (superior temporal gyri, left	+	?	?	+

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Table 1 (*continued*)

									Risk of bias			
REFERENCE	N (and diagnoses)	ETIOLOGY	AGE (years)	GENDER	TIME POST-ONSET	SCALE	TECHNIQUE	MAIN OUTCOME	POPULA-TION	INDEX TEST	REFERENCE STANDARD	FLOW & TIMING
								middle temporal gyrus, inferior frontal gyri), lexical effect in 25%UWS, 14%MCS (right inferior frontal gyrus, left middle temporal gyrus), semantics in 25%UWS, 0% MCS (inferior frontal and temporal gyri, middle temporal gyrus, angular gyrus), 100% with EEG auditory responses, 75% UWS and 100%MCS with residual brain metabolism in the same regions.				
Pan et al. (2014)	8 (4UWS, 3MCS, 1LIS), HCS: 4	3TBI, 3anoxia, 2stroke	*M* = 38, *SD* = 19, R = 16–70	4F	*M* = 10.2, *SD* = 11.9, R = 1–37 months	CRS-R	Active EEG (visual task)	Explicit : 25%UWS, 33% MCS, 100%LIS	+	?	?	+
Perrin et al. (2006)	15 (5UWS, 6MCS, 4LIS), HCS: 5	4TBI, 11NTBI	*M* = 54.9, *SD* = 17.2, R = 24–83	3F	*M* = 14.1, *SD* = 25.6, R = 0.4–84 months	CRS-R, GLS	Passive EEG (SON)	Implicit : 60%UWS, 100% MCS, 100%LIS	+	?	?	–
Rodriguez Moreno et al. (2010)	10 (3UWS, 5MCS, 1EMCS, 1LIS) HCS: Previous study	5TBI, 1anoxia, 3stroke, 1other	*M* = 34.4, *SD* = 15.9, R = 18–58	5F	*M* = 20.5, *SD* = 25.2, R = 2–84 months	CRS-R	Active fMRI (silent picture naming)	Explicit: 33%UWS, 40%MCS, 100%EMCS, 100%LIS in superior temporal gyrus, inferior frontal gyrus and medial frontal gyrus	+	?	?	–
Schabus et al. (2011)	14 (10UWS, 4MCS) HCS: 14	7TBI, 3anoxia, 3stroke, 1other	R = 20–73 UWS: *M* = 44.10, *SD* = 12.32 MCS: *M* = 52.25, *SD* = 17.8	6F	*M* = 78.1, *SD* = 49.3, R = 8–152 months	CRS-R	Passive EEG (semantics)	Implicit : 0%UWS, 100%MCS	+	?	?	–
Schnakers et al. (2015)	26 (10UWS, 8MCS-, 8MCS+), HCS: 14	9TBI, 12 anoxia, 3stroke, 2other	*M* = 38, *SD* = 12, R = 18–68	8F	*M* = 39.9, *SD* = 36.5, R = 0.47–124.8 months	CRS-R	Active EEG (SON)	Explicit: “Listen for pitch change” 10%UWS, 38%MCS-, 63%MCS+	+	+	?	–
Schoenle and Witzke (2004)	120 (35.8 % vegetative state, 19.2 % ‘near vegetative state’, 45 % ‘not vegetative state’) HCS: Brain-damaged but no UWS	41.7 % TBI, 25.8 % anoxia, 32.5 % stroke	*M* = 44.2, *SD* = 14.7, R = 18–75	30 %F	?	Unclear	Passive EEG (N400)	Implicit: 39% vegetative state, 77% ‘near vegetative state’, 90% ‘not vegetative state’	+	?	+	?
Sergent et al. (2017)	13 (4UWS, 8MCS, 1EMCS) HCS: 15	6TBI, 6stroke, 1anoxia	*M* = 46.1, *SD* = 14.6, R = 25–63	3F	*M* = 19.6, *SD* = 29.7, R = 0.5–96 months	CRS-R	Passive EEG (SON)	Implicit : 25%UWS, 50% MCS, 0%EMCS	+	?	–	–
Vassilieva et al. (2019)	48 (41 ‘neurological patients’, 1MCS-,	2TBI, 5stroke, 3hemor-rhage, 38other	*Mdn*(IQR) : 60.5(51–68) ; 50(41–70) ;	31F	?	None	Automated pupillometry	Explicit : 100%MCS-, 40% of neurological patients	+	–	+	?

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									Risk of bias			
REFERENCE	N (and diagnoses)	ETIOLOGY	AGE (years)	GENDER	TIME POST-ONSET	SCALE	TECHNIQUE	MAIN OUTCOME	POPULATION	INDEX TEST	REFERENCE STANDARD	FLOW & TIMING
	1EMCS, 5 sedated-comatose) HCS: 20		34(34–34) ; 62(55–64)									
Zheng et al. (2017)	25 (10UWS, 7MCS-, 8MCS+)	17TBI, 8NTBI	*M* = 39.5, *SD* = 14.2, R = 17–67	6F	*M* = 11.8, *SD* = 5.5, R = 3–30 months	CRS-R	MRI (DTI)	Explicit: 32%DoC UWS: reduced connectivity in thalamo-cortical circuits, MCS-: less thalamo-premotor and thalamo-temporal connectivity than MCS+	+	+	?	+
Prospective longitudinal cohort studies												
Borer-Alafi et al. (2002)	42 (UWS and MCS)	42TBI	*M* = 30.6, *SD* = 13.9, R = 17–72	15F	*M* = 43.6, *SD* = 31.2, R = 12–212 days	GCS	Loewenstein Communica-tion Scale (LCS)	Explicit: better LCS scores in those with potential for further recovery with rehabilitation compared to vegetative patients	+	?	+	?
Claassen et al. (2019)	104 (56coma, 23UWS, 25MCS) HCS: 10	15TBI, 33 Anoxia, 39 hemorrhage	*M* = 61, *SD* = 17	46F	*Mdn*=6, R = 3–10 days	GCS, CRS-R, GOS-E	Active EEG (hand moving)	Explicit : 11%coma, 13% UWS, 17%MCS-⟶ 15% CMD 50 % of CMD vs. 26 % of no responders were MCS + before discharge, after 1 year 44 % of CMD vs. 14 % of no responders were able to function independently for 8h	+	?	?	–
Edlow et al. (2017)	16 (2coma, 3UWS, 3MCS-, 4MCS+, 4EMCS) HCS: 16	16TBI	*M* = 28.9, *SD* = 9.2, R = 18–51	4F	*M* = 9.2, *SD* = 5, R = 1–17 days	CRS-R, CAP, GOSE	Passive & active fMRI, passive & active EEG	Implicit : Language: fMRI 0% coma, 33%UWS, 100%MCS-, 100%MCS+, 25%EMCS, EEG : 0%coma, 0%UWS, 33% MCS-, 75%MCS+, 83%EMCS (more superior temporal gyrus activation to forward compared to backward language, Heschl's gyrus and superior temporal gyrus activation to language) Explicit(motor imagery): fMRI: 0%coma, 100%UWS, 33%MCS-, 50%MCS+, 33% EMCS, EEG: 0%coma, 0% UWS, 0%MCS-, 25%MCS+, 40%EMCS Measures with prognostic value	+	+	–	–
Forgacs et al. (2014)	44 (8UWS, 36MCS/EMCS)	28TBI, 6anoxia, 6stroke, 1mixed, 3other	*M* = 32, R = 16–57	13F	*M* = 78, R = 6–312 months	CRS, CRS-R	EEG, PET, active fMRI (imagery)	Explicit : 0%UWS, 20%MCS/EMCS with preserved EEG organization during wakefulness, spindling activity during sleep, relatively preserved brain glucose metabolism	+	+	+	?
Gui et al. (2020)					R = 0.5–180		Passive EEG		+	+	+	?

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									Risk of bias			
REFERENCE	N (and diagnoses)	ETIOLOGY	AGE (years)	GENDER	TIME POST-ONSET	SCALE	TECHNIQUE	MAIN OUTCOME	POPULATION	INDEX TEST	REFERENCE STANDARD	FLOW & TIMING
	Resting-state: 54 Linguistic: 60 External validity: 25 (57UWS, 69MCS) HCS: 27	55TBI, 62stroke, 9anoxia	Resting-state: *M* = 49.3, R = 17–75 Linguistic: *M* = 47.8, R = 19–68 External validity: *M* = 39.9, R = 18–69	Resting-state: 6F Linguistic: 8F External validity: 12F		CRS-R, GCS		Implicit : 7%UWS, 16%MCS, of whom 25%UWS and 45% MCS with good outcome				
Kotchoubey et al. (2005)	98 (50UWS, 34MCS, 4unclear, 10 severely brain-damaged conscious patients) HCS: 22	36TBI, 27 anoxia, 32 hemorrhage, 3other	*M* = 44, R = 15–76	27F	*M* = 8.7 R = 1.2–127 months	DRS	Passive EEG (N400)	Implicit: cortical activity in 38%UWS with background EEG activity >4 Hz, correlated with the 6-month outcomes, semantics in UWS patients with preserved thalamocortical feedback connections	+	?	+	?
Rasmus et al. (2019)	18 (MCS)	?	*M* = 25, *SD* = 5	?	1month to 7months	GCS	Individual Nonverbal Communication Rating Scale (ICSS)	Explicit: Preverbal communication (in primal and sensory areas) increases between Stage II (GCS = 6–8 points) and Stage III (GCS = 9–12 points). After a time: high level of primal communication, communication attempts from the behavior organization level, increase in the nonverbal communication level	+	?	+	?
Risetti et al. (2013)	11 (8UWS, 3MCS)	4TBI, 6stroke, 1anoxia	*M* = 38.3, *SD* = 15.1, R = 20–63	5F	*M* = 8.6, *SD* = 5.6, R = 3–19.5 months	CRS-R	Passive (SON) & active (counting) EEG	Implicit: 100%UWS, 100% MCS Explicit: 14%UWS, 71%MCS increase of nP3 amplitude and wider spatial distribution, correlation with patient outcome	+	?	?	–
Rohaut et al. (2015)	29 (15UWS, 14MCS) HCS: 19	7TBI, 8anoxia, 9stroke, 5other	*M* = 44.4, *SD* = 15.3, R = 18–78	9F	*M* = 159, *SD* = 365, R = 7–1593 days	FOUR, GCS, CRS-R, GOSE	Passive EEG (N400)	Implicit : 7%UWS, 36%MCS (N400), 7%UWS, 50%MCS (late positive component), 20%MCS with both (including 14% who recovered consciousness and language)	+	+	–	–
Salvato et al. (2020)	15 (12UWS, 2MCS-, 1MCS+) HCS: 35	5TBI, 9hemorrhage, 1infection	*M* = 63.9, *SD* = 8.3, R = 43–77	9F	*M* = 18, R = 5–38	CRS-R, GOSE	Electrodermal skin conductance, resting state fMRI	Implicit: autonomic response for words > pseudo-words in outcome-positive patients, correlated with resting-state activity in the posterior cingulated cortex	+	?	–	–
		TBI		3F		GCS			+	–	+	–

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									Risk of bias			
REFERENCE	N (and diagnoses)	ETIOLOGY	AGE (years)	GENDER	TIME POST-ONSET	SCALE	TECHNIQUE	MAIN OUTCOME	POPULATION	INDEX TEST	REFERENCE STANDARD	FLOW & TIMING
Sokoliuk et al. (2020)	17 (behaviorally unresponsive patients) HCS: 20		$M = 58$, R = 26–86		$Mdn = 3$ months + 4.5 days and $Mdn = 6$ months + 4 days		Passive EEG (sentences)	Implicit: strength of language cortical tracking (inter-trial phase coherence) correlated with patient outcome				
Steppacher et al. (2013)	92 (53UWS, 39MCS)	43TBI, 25 anoxia, 24other	UWS: $M = 44.5$, $SD = 14.5$ MCS: $M = 45.0$, $SD = 16.9$	28F	UWS: $M = 1.9$, $SD = 1.6$ MCS: $M = 6.8$, $SD = 8.5$ months	CRS, Barthel	Passive EEG (N400)	Implicit : 16–32%UWS, 21–32%MCS, N400 correlated with patient outcome	+	?	+	+
Steppacher et al. (2020)	102 (59UWS, 43MCS)	49TBI, 25anoxia, 28others	$M = 45$, R = 17–75	26F	$M = 8.49$, $SD = 3.31$, R = 2–17 years	CRS	Passive EEG (N400)	Implicit: 97% predicted chance of recovery for MCS with N400 & P300 vs. 10% for UWS without N400 nor P300 ⟶ model reaching 80% of the correct classifications	+	?	+	+
Wu et al. (2011)	37 (21UWS, 16MCS) HCS: 30	32TBI, 5NTBI	R = 19–80 UWS: $M = 46.9$, $SD = 17.5$ MCS: $M = 45.7$, $SD = 10.1$	10F	UWS: $M = 92.9$, $SD = 46.4$ MCS: $M = 106.6$, $SD = 51.7$ days	GCS, CNC, CRS-R	Passive EEG (music)	Implicit : nonlinear indices in UWS < MCS<HCS Painful stimuli > music to predict patient outcome	+	?	?	?
Zhang et al. (2017)	18 (2coma, 9UWS, 5MCS-, 2MCS+) HCS: Previous study	8TBI, 3anoxia, 7hemorrhage	$M = 43.7$, $SD = 13.5$, R = 17–71	6F	$M = 6.1$, $SD = 4.9$, R = 1.5–21 months	CRS-R	Passive EEG (SON)	Implicit: 44%UWS, 100% MCS, P300 correlated with patient outcome	+	–	–	?
Retrospective cross-sectional and cohort studies												
Aubinet et al. (2018a)	19 (9MCS-, 10MCS+) HCS: 35	13TBI, 3anoxia, 2stroke, 1other	MCS-: $M = 37$, $SD = 14$ MCS+: $M = 39$, $SD = 12$	4F	$M = 23.3$, $SD = 28.9$, R = 1.5–96 months	CRS-R	fMRI	Explicit : resting state connectivity in left frontoparietal network (left dorsolateral prefrontal and fusiform cortex)	+	+	?	?
Aubinet et al. (2020)	87 (16MCS-, 41MCS+ [PET]; 17MCS-, 49MCS+ [MRI]) HCS: 34 (PET), 36 (MRI)	47TBI, 40NTBI	PET MCS-: $M = 42$, $SD = 18$ MCS+: $M = 39$, $SD = 16$ MRI MCS-: $M = 38$, $SD = 14$ MCS+: $M = 43$, $SD = 17$	PET 23 F MRI 27F	PET MCS-: $M = 543$, $SD = 571$ MCS+: $M = 825$, $SD = 901$ MRI MCS-: $M = 541$, $SD = 509$ MCS+: $M = 860$, $SD = 1025$ Days	CRS-R	PET, structural MRI (VBM)	Explicit: glucose metabolism in left middle temporal cortex, left angular gyrus, left middle frontal gyrus, left prefrontal cortex	+	+	?	–
Bruno et al. (2012)	27 (13MCS-, 14MCS+) HCS: 39	9TBI, 18NTBI	$M = 45$, $SD = 16$	10F	MCS-: $M = 21$, $SD = 23$ MCS+: $M =$	CRS-R	PET	Explicit : glucose metabolism in caudate, sensory-motor areas, premotor, inferior frontal gyrus, middle frontal	+	+	?	–

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REFERENCE	N (and diagnoses)	ETIOLOGY	AGE (years)	GENDER	TIME POST-ONSET	SCALE	TECHNIQUE	MAIN OUTCOME	Risk of bias POPULATION	INDEX TEST	REFERENCE STANDARD	FLOW & TIMING
					19, $SD = 26$ months			gyrus, superior temporal gyrus, middle temporal gyrus				
Claassen et al. (2016)	83 (‘comatose’, ‘arousable’ or ‘aware’)	83 hemorrhage	$M = 57$, R = 46−66	58F	?	Unclear	EEG	Explicit : increase in central gamma and posterior (centro-occipital) alpha power, as well as in complexity measures such as alpha permutation entropy	+	+	?	?
Day et al. (2018)	27 (?)	21TBI, 3anoxia, 2stroke, 1other	$M = 36.5$, $SD = 14.7$, R = 18−69	11F	$M = 88.1$, $SD = 134.5$, R = 13−610 days	CRS-R	Individualized Quantitative Behavioral Assessments (IQBA)	Explicit: more consistent and earlier evidence using IQBA dual command protocols (4–8 command trials depending on informal assessment of arousal)	+	?	?	+
Formisano et al. (2019)	15 (7UWS, 3MCS-, 5MCS+) HCS: 10	7TBI, 1anoxia, 7stroke	$M = 50$ $SD = 16.4$ R = 25−73	5F	$M = 123.1$, $SD = 32$, R = 66−189 days	CRS-R, GCS	Passive EEG (N400)	Implicit : 57%UWS, 63%MCS correlation with patient outcome	+	?	–	?
Guldenmund et al. (2016)	61 (16UWS, 8MCS-, 37 MCS+) HCS: 28	30TBI, 31NTBI	R = 16−87 UWS: $M = 49$, $SD = 20$ MCS-: $M = 37$, $SD = 13$ MCS+: $M = 42$, $SD = 21$	20F	R = 5−3342 UWS: $M = 112$, $SD = 174$ MCS: $M = 792$, $SD = 1041$ days	CRS-R	Structural MRI	Explicit : left middle temporal gyrus, superior temporal gyrus (primary auditory cortex and Wernicke’s area) and inferior frontal gyrus (Broca’s area).	+	+	?	?
Thibaut et al. (2019)	120 (63UWS, 57MCS- at admission)	68TBI 52NTBI	$M = 46.68$, $SD = 18.85$	46F	$M = 43.85$, $SD = 13.42$ days at admission	CRS-R	DRS	Explicit : reappearance of command-following vs. intelligible verbalization vs. intentional communication = same level of disability	+	+	?	?
Yamaki et al. (2018)	45 (1coma, 8UWS, 20MCS, 16 severe neurological disability)	TBI	$M = 36.5$, $SD = 15.6$, R = 17−71	11F	$M = 782$days	CRS-R, GCS	PET, behavioral ‘Chiba score’	Explicit: recovery of language abilities (especially in expression) associated with accelerated glucose metabolism change	+	?	?	?
Single and multiple case studies												
Aubinet et al. (2018b)	5 (2MCS-, 1MCS+, 2EMCS) HCS: 34 (PET), 36 (MRI)	2TBI, 2stroke, 1anoxia	R = 20−66	1F	$M = 21.6$, $SD = 10.7$, R = 13−36 months	CRS-R	PET, structural MRI	Explicit : MCS- : both 23% at CAVE (left hemisphere), MCS+: 67% at CAVE (bilateral hippocampi & precentral cortices), EMCS: 73% at CAVE (left hemisphere) and 925% (left angular gyrus)	+	?	?	?
Aubinet et al. (2019)	3 (MCS- then MCS+) HCS: 34 (PET), 36 (MRI)	2TBI, 1hemorrhage	R = 23−37	1F	R = 10−60 months	CRS-R	PET, structural MRI	Explicit:increased metabolism and/or grey matter in precuneus, angular gyri (case 1), left temporal lobule, angular gyrus, superior medial frontal gyrus, occipital cortex, bilateral caudate (case 2), fronto-parieto-temporal	+	+	?	?

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Table 1 (*continued*)

REFERENCE	N (and diagnoses)	ETIOLOGY	AGE (years)	GENDER	TIME POST-ONSET	SCALE	TECHNIQUE	MAIN OUTCOME	Risk of bias			
									POPULATION	INDEX TEST	REFERENCE STANDARD	FLOW & TIMING
								areas & left temporal lobule (case 3)				
Aubinet et al. (2021)	4 (1MCS-, 2MCS+, 1EMCS) HCS: 34 (PET), 10 (MRI)	4 TBI	*M* = 42, R = 30–63	0F	*M* = 848, R = 150–2340 days	BERA CRS-R	PET, fMRI	Explicit : MCS- : 53% at BERA (left hemisphere), MCS+: 53% at BERA (left temporal lobule) and 70% (frontal lobules, left temporo-occipital fusiform gyrus), EMCS: 73% at BERA (left frontal pole, premotor & fronto-orbital cortex, left temporo-parietal cortex)	+	+	–	–
Bardin et al. (2011)	6 (5MCS, 1LIS) HCS : 14	5TBI, 2stroke, 2anoxia	*M* = 34.3, *SD* = 14.3	?	*M* = 33.3, *SD* = 22.7 months	CRS-R	Active fMRI (motor imagery)	Explicit : 40%MCS, 100%LIS	+	?	?	?
Coleman, Bekinschtein et al., 2009; Coleman, Davis et al., 2009)	1 (MCS-) HCS: Previous study	TBI	19	0F	7 months	CRS-R, SMART	Passive (semantics) & active (motor imagery, visual recognition) fMRI, EEG, DTI	Implicit: yes, Explicit: no, EEG: preserved neural axis supporting vision, hearing, creation of a basic memory trace, DTI: loss of inferior temporal and inferior frontal pathways	+	–	?	?
Fernández-Espejo et al. (2010)	1 (UWS) HCS: 19 for DTI	TBI	48	0F	33 days (then 7 months)	GCS, DRS, LCFS, BDAE	DTI, passive fMRI (narratives)	Implicit: yes, DTI: preserved arcuate fasciculus and global white matter, recovery of receptive linguistic functioning by 12-months post-ictus.	+	+	+	?
Fernández-Espejo et al. (2015)	2 (1UWS, 1EMCS) HCS: 15	2TBI	38 and 49	1F	149 and 146 months	CRS-R	Active fMRI (motor imagery vs. execution), DTI	Explicit: 0%UWS, 100% EMCS, DTI: connection between thalamus and primary motor cortex.	+	+	?	?
Forgacs et al. (2016)	1 (MCS) HCS: 10 (PET)	Anoxia	± 20	F	33 months	CRS-R	Active EEG (hand opening), PET	Explicit: yes, normal brain glucose metabolism and electrical activity across the entire anterior forebrain	+	?	?	?
Goldfine et al. (2011)	3 (2MCS, 1LIS) HCS: 5	2TBI, 1stroke	25, 19, 24	?	25, 6 (then 10), 31 (then 43) months	Unclear	Active EEG (motor imagery)	Explicit : 50%MCS, 100%LIS	+	?	?	?
Kazazian et al. (2020)	1 (from UWS to EMCS) HCS: Previous study	TBI	34	0F	0 to 9 months	GCS	Structural MRI, passive (speech detection, semantics) & active (imagery) fMRI	Implicit: yes (both time points), Explicit: yes (at 9 months post-injury)	+	?	+	–
Laureys et al. (2004)	1 (MCS) HCS: Previous study	Intra-cerebral hemorrhage	42	0F	6 months	WHIM, CRS-R, WNSSP	Passive EEG (SON) & PET	Implicit : yes (bilateral inferior parietal lobules including angular gyri, left dorsal prefrontal regions and Broca area,…)	+	?	?	–
Monti et al. (2009)	1 (MCS+) HCS: 12	Anoxia	?	?	?	CRS-R	Passive & active fMRI (counting target words)	Implicit: yes, Explicit: yes (fronto-parietal network).	+	?	?	?
Monti et al. (2013)		TBI	?	0F	18 months	CRS-R		Explicit: yes	+	?	?	?

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REFERENCE	N (and diagnoses)	ETIOLOGY	AGE (years)	GENDER	TIME POST-ONSET	SCALE	TECHNIQUE	MAIN OUTCOME	Risk of bias			
									POPULA-TION	INDEX TEST	REFERENCE STANDARD	FLOW & TIMING
	1 (MCS-) HCS: 13						Active fMRI (visual recognition)					
Naci and Owen (2013)	3 (1UWS, 2MCS) HCS: 15	2TBI, 1anoxia	34 25 38	0F	184, 67, 147 (then 152) months	CRS-R	Passive & active fMRI (counting target words)	Implicit: 100%UWS, 100% MCS, Explicit: 100%UWS, 50%MCS	+	?	–	?
Owen et al. (2005)	1 (UWS) HCS: Previous study	Ictus	30	0F	4 then 9 months	None	Passive PET & fMRI (semantics, sentences)	Implicit: yes, speech detection (bilateral superior temporal lobules) and comprehension (left superior & middle temporal gyri)	+	?	+	?
Owen et al. (2006)	1 (UWS) HCS: 12	TBI	23	1F	5 months	WHIM	Passive (semantics, sentences) & active (motor imagery) fMRI	Implicit: yes (bilateral middle & superior temporal gyri, left inferior frontal area), Explicit: yes	+	?	?	?
Schiff et al. (2005)	2 (MCS) HCS: 7	1TBI, 1stroke	21 and 33	0F	18 and 24 months	Unclear	Passive fMRI (semantics, narratives)	Implicit: 100% MCS (bilateral middle & superior temporal gyri)	+	?	+	?
Staffen et al. (2006)	1 (UWS) HCS: 3	Anoxia	50	0F	?	Unclear	Passive fMRI (SON)	Implicit: yes (bilateral medial prefrontal cortices, left temporo-parietal and superior frontal cortex)	+	+	+	?
Tomaiuolo et al. (2016)	1 (from UWS to EMCS)	TBI	23	0F	?	CRS-R	Passive fMRI (semantics, narratives)	Implicit: yes, left angular gyrus activation to forward speech, increased response in language-related network & greater deactivation in the default mode network following progression to MCS.	+	?	–	?

Behavioral scales: Coma Recovery Scale-Revised (CRS-R), Wessex Head Injury Matrix (WHIM; Shiel et al., 2000), Full Outline of UnResponsiveness (FOUR; Wijdicks et al., 2005), Sensory Modality Assessment and Rehabilitation Technique (SMART; Gill-Thwaites et al., 2018), Disability Rating Scale (DRS; Gouvier et al., 1987), Coma/Near Coma (CNC; Rappaport, 2005), Confusion Assessment Protocol (CAP; Sherer et al., 2005), Glasgow Outcome Scale (Extended; GOS[E]; Weir et al., 2012) Glasgow Coma Scale (GCS; Teasdale and Jennett, 1976, 1974), Rancho Los Amigos Level of Cognitive Functioning Scale (LCFS; Gouvier et al., 1987), Individual Communication Skills Scale (ICSS ; Rasmus et al., 2019) ; Coma Remission Scale (CRS ; (Steppacher et al., 2013), Brief Evaluation of Receptive Aphasia (BERA; Aubinet et al., 2021), Boston Diagnostic Aphasia Examination (BDAE; Fernández-Espejo et al., 2010); Western Neuro Sensory Stimulation Profile (WNSSP; Laureys et al., 2004). Other abbreviations: Unresponsive Wakefulness Syndrome (UWS), Minimally Conscious State (MCS), Emergence from MCS (EMCS), Healthy Control Subjects (HCS), Locked-In Syndrome (LIS), Cognitive-Motor Dissociation (CMD), Traumatic Brain Injury (TBI), Non Traumatic Brain Injury (NTBI), Female (F), electroencephalography (EEG), Event-Related Potentials (ERP), functional Magnetic Resonance Imaging (fMRI), Positron Emission Tomography (PET), Diffusion Tensor Imaging (DTI). Quality assessment: High risk of bias (+) was reported in all studies regarding the population (i.e., convenience samples and case reports), and regarding the reference standard when DoC diagnosis was not based on the recommended CRS-R. Low risk of bias (-) was notably reported when a blinding procedure and clear timeline were presented. Such aspects were most often unclear (?). The applicability concerns were low for all studies, except two of them were it was high for the population and reference standard (Borer-Alafi et al., 2002; Rasmus et al., 2019).

3.3. *Residual language abilities observed in patients with disorders of consciousness*

Our first objective was to identify the level and quality of language residual abilities as a function of DoC diagnosis. Overall, 56 studies (66 %) reported a proportion of patients with residual implicit and/or explicit language abilities in one or several DoC entities, and results are summarized in Fig. 2. Note that eleven single-case studies were excluded from our statistical analysis, and one study from Coleman et al. (2007) was also removed due to the inclusion of patients that were also examined in Coleman, Bekinschtein et al., 2009; Coleman, Davis et al., 2009.

3.3.1. *Unresponsive wakefulness syndrome*

Implicit language abilities were examined in UWS patients by means of passive fMRI, PET and EEG paradigms. According to the reviewed studies, UWS patients can show preferential responses to language with emotional content, such as affective prosody (Kotchoubey et al., 2009), their own name (e.g., Perrin et al., 2006; Sergent et al., 2017; Staffen et al., 2006; Zhang et al., 2017) or songs (Li et al., 2018; Wu et al., 2011). Neural sensitivity to different phonological, lexical and even higher-level semantic variables was also highlighted, by contrasting intelligible vs. less intelligible speech or noise (Beukema et al., 2016; Coleman et al., 2007, Coleman, Bekinschtein et al., 2009; Coleman, Davis et al., 2009; Edlow et al., 2017; Erlbeck et al., 2017; Kotchoubey et al., 2005; Owen et al., 2005; Sergent et al., 2017), words vs. pseudo-words (Nigri et al., 2017; Salvato et al., 2020), semantically related vs. unrelated words (Beukema et al., 2016; Erlbeck et al., 2017; Kotchoubey et al., 2005; Nigri et al., 2017), sentences of low vs. high ambiguity (Coleman et al., 2007; Coleman, Bekinschtein et al., 2009; Coleman, Davis et al., 2009; Owen et al., 2005), factually correct vs. incorrect short sentences (Kotchoubey et al., 2013) and congruous vs. incongruous sentences (Balconi et al., 2013; Balconi and Arangio, 2015; Formisano et al., 2019; Kotchoubey et al., 2005; Schoenle and Witzke, 2004). For instance, Kotchoubey et al. (2013) proposed the use of factually correct vs. incorrect short sentences in an fMRI research. Significant brain responses to the incorrect compared to the correct sentences were found in 11/29 UWS patients and mainly recorded in left-sided language-related (e.g., Broca or Wernicke areas). Two of these patients were considered as "full responders" as they showed significant contrast activations in the inferior frontal gyrus *and* the superior/middle temporal gyrus. Using EEG, Formisano et al. (2019) recently investigated brain activity in response to congruous (i.e., semantically related final word) vs. incongruous (i.e., unrelated final word) sentences and reported an N400 effect in 4/7 UWS patients. According to the median of percentages of responding UWS patients in these 28 studies, we estimated that 33 % of UWS patients would show implicit language abilities, at either phonological or semantic levels.

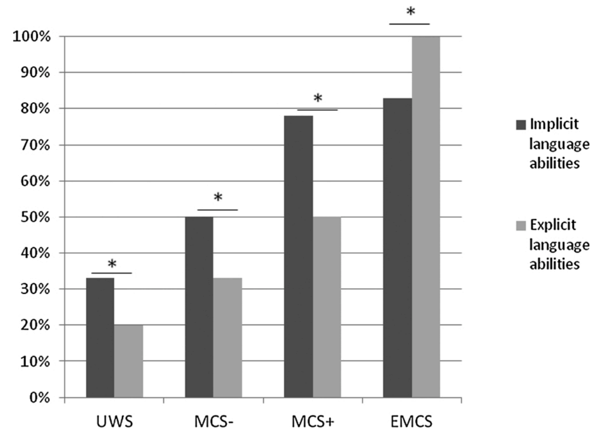

Fig. 2. Median percentages of patients with residual implicit vs. explicit language abilities. More implicit abilities were shown in the unresponsive wakefulness syndrome (UWS), the minimally conscious state minus (MCS-) and the minimally conscious state plus (MCS+), compared to the explicit abilities (*$p < 0.05$). The opposite was observed for patients emerging from the minimally conscious state (EMCS).

In addition, several studies used brain-computer interfaces and reported the presence of residual explicit language in behaviorally unresponsive patients. Among the 24 included studies, the median percentage of UWS patients with covert command-following was 20 %. Note that these patients should consequently be classified as having a CMD or MCS* (Thibaut et al., 2021; Gosseries et al., 2014; cf. discussion).

3.3.2. *Minimally conscious state*

Implicit language abilities have been investigated in MCS using the same neuroimaging and EEG paradigms as for UWS reported above. Stronger neural responses to the manipulation of lexical and semantic variables were observed during passive speech processing in MCS as compared to UWS patients (e.g., Balconi and Arangio, 2015; Kempny et al., 2018; Lechinger et al., 2016; Risetti et al., 2013; Rohaut et al., 2015; Schabus et al., 2011; Schnakers et al., 2015; Steppacher et al., 2013; Wu et al., 2011). More extended cortical responses to intelligible compared to backward speech were also particularly highlighted in MCS patients, encompassing higher areas such as superior temporal and angular gyri (e.g., Schiff et al., 2005; Tomaiuolo et al., 2016). Still, a few studies failed to distinguish UWS and MCS patients based on implicit language processing abilities (e.g., Beukema et al., 2016; Kotchoubey et al., 2013, 2009). The median percentage (from 24 studies) of MCS patients with implicit language abilities was 50 %, which is not much higher than the percentage reported above for UWS patients. Three studies however considered the clinical sub-categorization of the MCS (Chatelle et al., 2020; Edlow et al., 2017; Hauger et al., 2015) and involved a total of 17 MCS- and 18 MCS + patients, reporting a residual implicit language processing in 50 % of MCS- patients and 78 % of MCS + patients.

Explicit language abilities were mostly assessed by means of brain-computer interfaces or using command-following, intelligible verbalization and intentional communication items of the CRS-R. The use of other behavioral scales, requiring patients to look at a specific picture that corresponds to a specific word or sentence, was also reported (e.g., Aubinet et al., 2021, 2018b). Picture-based explicit speech recognition was further examined using EEG and fMRI paradigms. A single-case study from Monti et al. (2013) for example involved language assessment in the form of explicit verbal commands; the patient was repeatedly asked to execute two different commands such as "look at the house" vs "look at the face". This study revealed the expected differential brain activations in either the place selective parahippocampal area or the face selective fusiform area for the two commands, showing that the patient understood the verbal commands and was able to implement the appropriate actions. Moreover, Rodriguez-Moreno et al. (2010) employed fMRI during covert picture-naming with 10 patients with and without behavioral evidence of awareness. They observed complete network activations in the superior temporal gyrus (including Wernicke area), inferior frontal gyrus (including Broca area) and medial frontal gyrus for 2/5 MCS patients (both MCS + patients), and at least partial activation for 5/5 MCS patients (including 1 MCS- patient). According to 16 of the included studies, the median percentage of MCS patients with explicit language abilities as assessed by active paradigms was 50 %. For 9 studies distinguishing between MCS- and MCS+, the median percentages for explicit language abilities were 33 % and 50 %, respectively.

3.3.3. *Emergence from the minimally conscious state*

Implicit and explicit language abilities were measured in this patient category using the same paradigms as described before. We should expect much higher percentages for both implicit and explicit language processing abilities as the ability to functionally use a "yes"/"no" for responding to verbal questions is the main defining criterion for reaching this state of consciousness by using the CRS-R (Giacino et al., 2004, 2002). Some studies also used more general communication scales such as the Loewenstein Communication Scale (Borer-Alafi et al., 2002) or the Individual Nonverbal Communication Rating Scale (Rasmus et al., 2019), both of them reporting specific abilities such as preverbal, verbal, interpersonal or alternative communication. Five of the studies investigating residual explicit language involved a total of 21 EMCS patients, with a median percentage of 100 % showing such abilities. As expected, this is much larger in comparison to UWS but also MCS. Nevertheless, this median percentage decreased to 83 % for residual implicit language, as reported by 4 studies including a total of 15 EMCS patients.

3.4. *Reappearance of implicit vs. explicit language processing*

Our second objective was to examine how, when and where implicit and explicit language abilities reappear after a severe brain injury. Overall, while an implicit language processing may reappear at an early stage, in patients considered as having an UWS (Gui et al., 2020; Sokoliuk et al., 2020), by definition explicit language abilities may only be recovered at stage MCS+ (CMD or MCS*; see discussion below).

Using neuroimaging techniques, the main neural correlates associated with implicit vs. explicit residual language abilities in DoC patients are illustrated in Fig. 3. Brain regions involved in implicit and explicit residual language processing showed an important overlap. Studies reported the bilateral superior temporal gyrus, left middle temporal gyrus and left angular gyrus for implicit language (Coleman, Bekinschtein et al., 2009; Coleman, Davis et al., 2009; Ferraro et al., 2020; Nigri et al., 2017; Owen et al., 2005, 2006; Schiff et al., 2005; Tomaiuolo et al., 2016), while the left superior and middle temporal gyrus and left medial/middle frontal cortex were highlighted for measurements associated to explicit language (Aubinet et al., 2021, 2020b, Aubinet et al., 2019; Bruno et al., 2012; Edlow et al., 2017; Guldenmund et al., 2016; Rodriguez Moreno et al., 2010). Thalamo-frontal and thalamo-temporal connections were mainly related to explicit language measures (Coleman, Bekinschtein et al., 2009; Coleman, Davis et al., 2009; Fernández-Espejo et al., 2015; Zheng et al., 2017). Apart from these tracts, implicit and explicit language could essentially reappear within comparable brain substrates, and the observed differences between neural correlates of implicit vs. explicit language may also reflect differences in their measurements (i.e., passive paradigms vs. association with language behavioral scales).

According to EEG studies, increased N400 peak amplitudes within the fronto-central cortical areas were particularly related to residual implicit semantic processing in DoC patients (Balconi et al., 2013; Balconi and Arangio, 2015; Formisano et al., 2019; Steppacher et al., 2013), whereas increased central gamma and posterior alpha power, as well as complexity measures, were more specifically observed in patients with residual explicit language abilities (Claassen et al., 2016).

4. Discussion

This review reveals that neural signs of residual language abilities can be observed in all DoC entities, and the proportion of patients showing sensitivity to language stimuli increases along with the level of consciousness. The early recovery is particularly true for implicit language processing abilities, such as neural responses elicited by the manipulation of phonological, lexical or semantic variables in passive listening tasks. Indeed, such responses were reported in one third of behaviorally unresponsive patients. Explicit language abilities, as documented by neural or behavioral responses to explicit language processing tasks such as verbal commands or word-picture matching tasks, are observed mostly in MCS + and EMCS patients. In line with Kondziella et al. (2016; 15 %), 20 % of patients diagnosed as UWS also presented this type of explicit responses to speech stimuli when using brain-computer interfaces, suggesting misdiagnosis as these explicit responses reflect intentional responses which is incompatible with UWS. These patients rather belong to the MCS+, CMD or MCS* category as we will discuss below. On the other hand, only 50 % of MCS(+) patients show explicit language using such brain techniques, compared to 100 % of EMCS.

4.1. *Implicit vs. explicit language processing and levels of consciousness*

Both implicit and explicit language processing would reappear in parallel with the progressive recovery of consciousness after a coma (Fig. 4). As suggested by Gui et al. (2020), we hypothesize an early recovery of implicit language processing, the depth of which (e.g., from word to sentence processing) would increase along with patients' level of consciousness. Explicit language abilities would also be gradually reestablished but later in the course of consciousness recovery (i.e., from the MCS), as further supported by our main results (Fig. 2) as well as the lower frequency of explicit compared to implicit language responses in DoC patients highlighted in diverse individual studies (Bekinschtein et al., 2011; Coleman, Bekinschtein et al., 2009; Coleman, Davis et al., 2009; Edlow et al., 2017). The paralleled trajectory of recovery between language and consciousness is finally confirmed by various longitudinal data (Aubinet et al., 2019; Kazazian et al., 2020; Risetti et al., 2013; Tomaiuolo et al., 2016).

Moreover, the results highlight the importance of explicit language assessment for allowing for more accurate DoC diagnosis, detecting the presence of CMD (e.g., Edlow et al., 2017; Schiff, 2015) and consequently helping to reduce the well-documented risk of DoC misdiagnosis

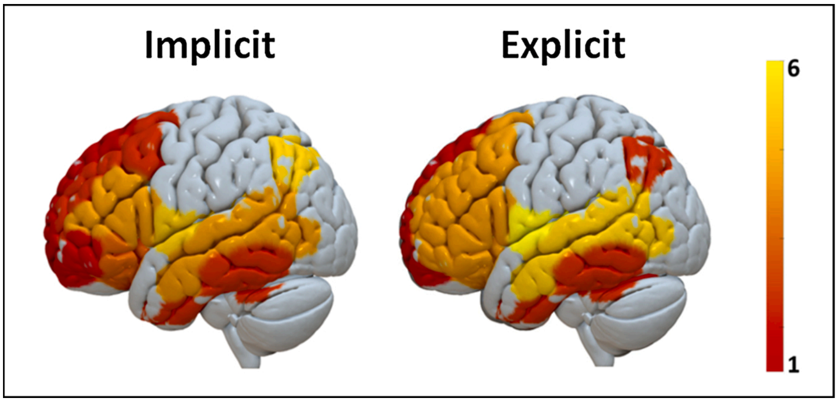

Fig. 3. Similarity of neural correlates involved in residual implicit and explicit language abilities in DoC patients. The colors represent the number of neuroimaging studies which either highlighted residual activity during passive language listening tasks (i.e., implicit processing), or which showed preserved brain function in patients with preserved (covert) command-following (i.e., explicit processing). Note that this figure is only descriptive and has no statistical value.

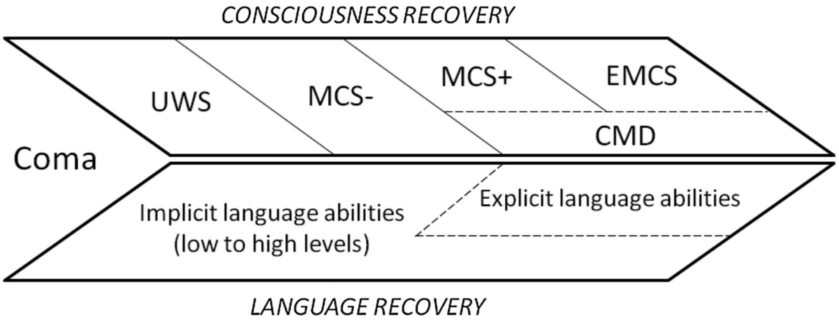

Fig. 4. Classical consciousness recovery path after a period of coma, paralleled with the hypothesized language recovery path. "Implicit language abilities" refer to the reappearance of language in absence of conscious behaviors, whereas "explicit language abilities" involve conscious receptive and productive language abilities.

(Schnakers et al., 2009; van Erp et al., 2015). Yet, so far, implicit language assessment is not specifically taken into account as regards the current diagnosis and taxonomy of post-comatose DoC (although some authors proposed the "higher-order cortex motor dissociation" category; Edlow et al., 2017). Diverse theoretical issues may here be highlighted.

According to the above-mentioned definitions of implicit and explicit responses, the presence of implicit language processing would reflect automatic processing in preserved linguistic areas and connections, whereas residual explicit language processing would be considered as a sign of consciousness. Nevertheless, some studies based on passive paradigms showed complex implicit language processing in the lowest consciousness levels: even deep semantic processing (e.g., distinction of factually correct vs. incorrect sentences; Kotchoubey et al., 2013) has been observed in patients who were behaviorally diagnosed as UWS. Such findings raise the following question: is the presence of complex language processing in the absence of "consciousness" possible?

According to Naci et al. (2018), implicit responses to narrative listening may be shown in healthy subjects with deep anesthesia compared to a wakeful condition, but these responses would be limited to sensory (and not fronto-parietal) regions. We may mention here the current controversy between first-order and higher-order theories of consciousness (Melloni et al., 2021). According to the former, spreading activity in sensory areas would be sufficient for consciousness, therefore raising the possibility to consider UWS patients with implicit sensory brain responses as "conscious". The latter theories claim that higher-order activity must point to the first-order sensory activity for allowing conscious experience. The earlier re-occurrence of implicit language abilities in DoC patients may also speak for a more pre-cognitive approach such as suggested by the Temporo-spatial Theory of Consciousness (Northoff and Huang, 2017), where the external stimuli have to interact with ongoing spontaneous brain activity to be integrated into the current stream of consciousness (Northoff and Lamme, 2020). Further studies on anesthesia should clarify whether passive paradigms can be used to detect 'conscious responses' or not.

One may finally consider that behaviorally unresponsive patients with evidence of complex implicit language processing should rather be diagnosed as having a CMD, which would consequently question the definition of CMD as only involving covert "command-following and/or communication" abilities.

On the other hand, similarly to explicit language differentiating the MCS- vs. MCS+, implicit language abilities should be taken into account in order to distinguish consciousness levels, as also supported by their capacity to predict patients' functional outcome (see results in Table 1). Both implicit and explicit language performance indeed demonstrated a prognostic value regarding patients' subsequent functional recovery (e.g., Claassen et al., 2019; Coleman, Bekinschtein et al., 2009; Coleman, Davis et al., 2009; Edlow et al., 2017; Formisano et al., 2019; Rohaut et al., 2015; Sokoliuk et al., 2020; Steppacher et al., 2020; Wu et al., 2011; Zhang et al., 2017), and the strength of comprehension brain response may interestingly improve the accuracy of prognosis (Sokoliuk et al., 2020).

4.2. Methodological issues

The studies reported in this systematic review were particularly heterogeneous as regards to the language measures, even within the implicit or explicit language domains. There was also a large variability of dependent variables (e.g., behavioral detection of command-following, neural responses to speech or visual recognition capacity), techniques (i.e., neuroimaging, electrophysiological or behavioral measures), as well as verbal stimuli (e.g., subject's own name, songs, words, narratives). Such diversity renders comparisons between studies difficult and precluded more advanced quantitative analyses of reported data.

Moreover, we assessed data quality using the QUADAS-2 criteria, which revealed a lack of blinding procedures and clarity regarding the timing of data acquisition in numerous studies. According to these criteria all studies also present a high risk of bias with regard to the population as they include convenience samples or single cases. It has to be noted that the QUADAS-2 criteria can be easily applied to populations that are frequent and easy-to-enroll, allowing for the recruitment of consecutive or random samples. These criteria are however much more difficult to apply to DoC patients due to their lower frequency and large heterogeneity.

4.3. Implications for future studies

We here hypothesize that implicit language processing would be reestablished earlier than explicit language processing in the course of post-comatose cognitive recovery. Further studies using longitudinal design should however be conducted to assess the timing of recovery of both implicit and explicit language functions in a more systematic manner. The neural correlates of residual implicit language processing should also be specifically investigated in future studies including quantitative neuroimaging analyses. This is however currently difficult to achieve due to the highly heterogeneous nature of existing studies, both in terms of experimental design and statistical power.

The investigation of residual language functions in post-comatose patients might also contribute to a more accurate taxonomy of DoC. Bayne, Hohwy and Owen (2017) indeed consider that the current CRS-R-based taxonomy of DoC would not be sufficient to account for patients' residual abilities and recovery. They suggest the use of a multi-dimensional framework including a comprehensive modeling of the intricate interactions between patients' behavioral and neural capacities (Bayne et al., 2017). Such a new taxonomy was recently proposed by Kondziella et al. (2021), but no specific emphasis was brought regarding residual language abilities, which is also probably due to the lack of language-specific examinations in this challenging population.

In line with this, our results stress the importance of developing and validating bedside language behavioral assessments. If the CRS-R allows the detection of language-related signs of consciousness, this scale cannot be used to assess language abilities at a more detailed and specific level (Schnakers et al., 2014). There is currently a lack of standardized tools for assessing residual language abilities in DoC patients. The CAVE (Murphy, 2018) and BERA (Aubinet et al., 2021) instruments have been proposed and they are well adapted to MCS (and EMCS) patients with intact visual abilities as the items require looking at a target picture among distractors, but these scales need further validation in larger samples of DoC patients. Moreover, the presence of residual language abilities in DoC patients also needs to be assessed and to be assessable in non-sighted patients, requiring the development of alternative assessment methods such as language-related brain-computer interfaces.

In a nutshell, multimodal assessment protocols combining behavioral evaluations, neuroimaging and electrophysiology should be provided to document the presence of residual language abilities in DoC patients, as previously suggested by Majerus et al. (2009). In the future, such protocols would need to include measures of both implicit and explicit language abilities (using EEG and/or fMRI passive and/or active paradigms) and cover diverse domains, with a panel of various linguistic stimulations. This aspect would greatly help clinicians when trying to answer the critical question of “Can they understand us?” While detected residual language abilities may support patient rehabilitation, the absence of language-related brain activity may reflect the presence of severe global aphasia, which further needs to be taken into account for therapeutic strategies.

4.4. Conclusion

Residual language abilities have been documented in DoC patients by means of neuroimaging, electrophysiological and behavioral assessments. Implicit language abilities were shown in 33 % of UWS, 50 % of MCS-, 78 % of MCS + and 83 % of EMCS patients, and encompassed domains such as language recognition, detection of intelligibility, lexical and semantic processing of words and sentences. These abilities raise various theoretical and clinical issues and should be taken into account when diagnosing post-comatose DoC. Evidence of explicit language processing was further reported in 20 % of UWS and 33 % of MCS- (in the context of a CMD), as well as in 50 % of MCS + and 100 % of EMCS patients. Future studies need to validate standardized and sensitive language assessment protocols for DoC patients, targeting both behavioral and neural responses to language stimuli.

Data availability

Data will be made available on request.

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Declaration of Competing Interest

The authors declare no conflict of interests regarding the publication of this paper.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2021.12.001.

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