# *Language assessment in patients with disorders of consciousness*

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Number of words in the body of the manuscript: 3546

Number of figures and tables: 1

## ABSTRACT

The assessment of residual language abilities in patients with disorders of consciousness (DoC) after severe brain injury is particularly challenging due to their limited behavioral repertoire. Moreover, associated language impairment such as receptive aphasia may lead to an underestimation of actual consciousness levels. In this review, we examine past research on the assessment of residual language processing in DoC patients, and we discuss currently available tools for identifying language-specific abilities and their prognostic value. We first highlight the need for validated and sensitive bedside behavioral assessment tools for residual language abilities in DoC patients. As regards neuroimaging and electrophysiological methods, the tasks involving higher level linguistic commands appear to be the most informative about level of consciousness and have the best prognostic value. Neuroimaging methods should be combined with the most appropriate behavioral tools in multimodal assessment protocols to assess receptive language abilities in DoC patients in the most complete and sensitive manner.



**Keywords**:

Language, disorders of consciousness, behavioral assessment, aphasia.

## INTRODUCTION

Patients with severe brain injury may evolve through different states of altered consciousness (disorders of consciousness; DoC) following a coma. They are considered as being in an unresponsive wakefulness syndrome (i.e., vegetative state, VS/UWS) when they recover eye-opening and reflexive behaviors.[1,2] The minimally conscious state (MCS) is defined by the reappearance of inconsistent but reproducible signs of consciousness.[3,4] Due to the heterogeneity of this clinical entity, a sub-categorization was suggested: MCS minus (MCS-) mainly characterizes patients with visual pursuit and/or fixation, oriented movements and localization to pain,[5] whereas MCS plus (MCS+) describes patients who have recovered command-following, intelligible verbalization, and/or intentional communication.[6] The emergence of MCS (EMCS) is diagnosed when patients recover higher-level cognitive and motor abilities such as functional communication and object use.[3]

An accurate diagnosis is crucial for daily management of these patients (e.g., pain treatment),[7] prognosis[8] and end-of-life decisions.[9] In this respect, several standardized and validated scales were developed to optimize the bedside assessment of consciousness. Among them, the well-known Coma Recovery Scale-Revised (CRS-R)[10] and the recently validated Simplified Evaluation of CONsciousness Disorders (SECONDs)[11,12] showed good validity and sensitivity.[11,13] The diagnosis of consciousness in patients with severe brain injury is, however, affected by many issues such as motor impairment or fluctuating arousal level.[14]

Language impairments like receptive aphasia (i.e., involving language comprehension deficits) represent a further major issue for the assessment of consciousness.[15] Indeed, the presence of language deficits may prevent consistent responses to verbal instructions, leading to an underestimated level of consciousness in aphasic patients. This “bias of aphasia” is attested by a study showing that 54% of fully conscious patients with aphasia would obtain a diagnosis of MCS following the administration of the CSR-R.[16]

In this review, we analyze the literature that has investigated residual language abilities (i.e., speech comprehension and/or production) in DoC patients suffering from severe brain lesions. Our goal is threefold: (1) report currently available assessment tools for assessing language abilities in this challenging population; (2) identify the language-specific abilities (e.g., phonological versus semantic processing) that were identified as a function of DoC diagnostic category; and (3) examine the prognostic value of observed residual language abilities.

## LANGUAGE ASSESSMENT TOOLS IN POST-COMATOSE PATIENTS

### *a) Behavioral scales*

Three items of the CRS-R allowing the sub-categorization of the MCS (i.e., command-following, intelligible verbalization and intentional communication items)[6] particularly require language processing abilities. For example, patients need to understand verbal commands to respond adequately. A recent study reported that any (combination) of those three language-related items (i.e., MCS+ diagnosis) was associated to similar level of disability using the Disability Rating Scale,[17] whereas their absence (i.e., MCS- diagnosis) was related to higher functional impairment.[18] Other scales also assess basic language abilities via verbal command items such as the Individualized Quantitative Behavioral Assessments (IQBA), which involves the administration of 4 to 8 command trials,[19] and the more recent SECONDs scale.[12] As illustrated in Figure 1, if the CRS-R and similar scales allow the detection of language-related signs of consciousness, performance on these command-following items is nevertheless co-determined by many other motor and/or cognitive factors such as auditory selective attention or verbal short-term memory.[20]

[INSERT FIGURE 1 AROUND HERE]

As reported in Table 1, other studies developed new behavioral tools to more specifically assess language abilities in post-comatose patients. For example, Yamaki et al.[21] included an estimation of residual language based on the patient's bedside observation in their "Chiba score". This scale comprises 11 items: level of wakefulness, motor activity, language comprehension (from no evidence to ability to understand language adequately for use in normal daily life), language expression (from no evidence to ability to communicate using sentences in normal daily life), visual cognition (from no eye movement following a moving object to evidence that the patient can communicate using visual information), auditory cognition (from no blink in response to a loud sound to evidence of verbal comprehension such as following verbal commands), nutrition, facial expression of emotion, excretion, position change and movement. Another tool is the Cognitive Assessment by Visual Election (CAVE),[22,23] which is comprised of six subscales evaluating recognition of objects, pictures, numbers, letters, written words and colors. CAVE involves language comprehension, as patients have to understand the pronounced words and look at the corresponding item. However, both scales do not specifically assess psycholinguistic effects nor various domains of language as shown in Figure 1, which can be differentially affected in patients with aphasia, and orient the strategies of language rehabilitation.[24]

[INSERT TABLE 1 AROUND HERE]

The Brief Evaluation of Receptive Aphasia (BERA) was recently developed to target residual language abilities in a specific and comprehensive manner by distinguishing receptive phonological, semantic and morphosyntactic abilities, based on visual fixation of target stimuli among phonologically or semantically related distractors.[25] The language-level specificity of this scale was validated in a group of aphasic patients, but full validation in patients with DoC is still lacking (note that four single case assessments of post-comatose patients were also conducted and reported).

Two other bedside assessments focus on a listing of “communication abilities”. First, the Loewenstein Communication Scale[26] scores the patient’s mobility, respiration, visual responsiveness, presence of auditory comprehension, verbal communication and alternative communication. Second, the Individual Nonverbal Communication Rating Scale[27] combines patient observation, family interviews and scores of the Glasgow Coma Scale.[28] This rating scale provides an estimation of preverbal, verbal and interpersonal communication as well as creative expression, and considers the emotional, language and cognitive or social levels. We are, however, not aware of any concrete definition or examples for the specific items of this rating scale.

### *b) Neuroimaging and electrophysiological measures*

Given the extent of brain lesions in DoC patients, the persistence of severe motor impairment is almost unavoidable, possibly preventing patients from demonstrating residual language abilities or other communicative abilities. A number of studies therefore directly examined neural signs of language processing via neuroimaging and electrophysiological techniques.

[INSERT FIGURE 2 AROUND HERE]

Shortly after the definition of the MCS diagnostic entity,[3] three neuroimaging studies showed residual language processing in DoC patients using purely passive listening tasks (Figure 2). Laureys et al.[29] first employed $H_2^{15}O$-positron emission tomography (PET) in one MCS patient and showed more widespread activation in parietal and prefrontal areas induced by auditory stimuli with emotional valence (i.e., infant cries and the subject’s own name) compared to noise. Using the same technique in a VS/UWS patient who was presented either normal spoken language or “speech in noise” (i.e., distortion generated by adding a continuous pink-noise background), Owen et al.[30] revealed preserved consistent responses in the left superior and middle temporal gyri in response to intelligible speech as compared to unintelligible speech. Using functional magnetic resonance imaging (fMRI), Schiff et al.[31] finally investigated cortical responses to speech in two MCS patients. Comparably to healthy subjects, more extended cortical responses were found to normal speech as compared to reverse replay of the same speech stimuli, encompassing the middle temporal gyrus as well as higher areas such as the superior temporal and angular gyri.

Since then, other studies based on neuroimaging or electroencephalography (EEG) adapted similar passive listening paradigms to examine neural reactivity to different levels of receptive language processing in DoC patients.[32–41] The results of these studies will be detailed in the next section. It is important to note that such passive paradigms only focus on *implicit* language processing as involuntary and uncontrolled,[42] and hence "conscious" processing of the language stimuli is required in these paradigms.

More recently, active paradigms using fMRI and EEG methodologies have been developed, and allow the assessment of residual *explicit* language abilities in DoC patients by requiring their active participation. In these studies, patients are required to exert mental responses to command, in contrast to a control group, passive paradigms or rest.[42,43] These paradigms most often involve motor imagery tasks, which require rehearsing or simulating a given action (e.g., imagine playing tennis). Such residual command-following ability was also reported using functional near infrared spectroscopy, a neuroimaging technique estimating local hemodynamic response variations using near-infrared light.[44–46] Note that other electrophysiological measures may be used, such as electromyography[47] or automated pupillometry.[48] These techniques, however, need to be further investigated to support their validity in the assessment of DoC patients.

## LANGUAGE ABILITIES IN THE DIFFERENT DOC ENTITIES

### Unresponsive wakefulness syndrome

### *a) Distinction of speech versus non-speech*

A number of studies implicitly measured the ability to distinguish speech from non-speech stimuli in VS/UWS patients by means of passive listening tasks.[49–51] Coleman et al.[49,50] used fMRI and compared responses to sentence versus noise listening, and found neural correlates of speech comprehension in a subset of unresponsive patients (i.e., significant temporal lobe responses in the speech versus noise perception contrast). The authors revealed a wide variation in the extent of these neural responses, from extensive bilateral superior temporal area to reduced posterior part of the temporal lobes (Figure 3). In some patients, neural signs of low-level auditory processing were observed, but neural responses were either too weak or too variable to be statistically reliable.

[INSERT FIGURE 3 AROUND HERE]

Moreover, several studies showed contrasts between noise and speech by means of EEG.[51–54] For example, Beukema et al.[55] showed that the event-related potentials (ERPs) elicited by words were significantly more negative than the ERPs elicited by noises across midline fronto-central-parietal scalp in several VS/UWS patients, similar to healthy subjects.

According to Edlow et al.,[56] this type of fMRI or EEG responses in associative cortices during passive processing of language or music stimuli indicates the presence of *covert cortical processing*. These findings reveal the possibility to observe speech detection capacity (i.e., low-level language processing) in patients who initially have a VS/UWS diagnosis. They suggest a relative preservation of (at least) the earliest language component (i.e., auditory phonological analysis; Figure 1),[20] which would be in line with involvement of mainly the superior temporal gyri.

### *b) Phonological and lexical processing*

In 2010, Fernandez-Espejo et al.[57] examined a VS/UWS patient and showed higher activity to forward speech as compared to backward speech, involving the left superior and middle temporal gyrus, by means of fMRI. The presence of covert cortical processing was therefore observed in this VS/UWS patient.

Residual lexical processing was further specifically assessed in an innovative multimodal study using neuroimaging and EEG techniques by Nigri et al.[58] The authors investigated the neural correlates of lexical residual abilities in DoC patients by means of an fMRI priming task, and found a pseudoword effect (i.e., greater activation in the left superior temporal gyrus for pseudoword compared to word listening) or lexical effect (i.e., greater activation in the right inferior frontal and left middle temporal gyri for word compared to pseudoword listening) in half of VS/UWS patients.

According to these studies, a significant proportion of behaviorally unresponsive patients may present residual phonological and lexical processing abilities, as indicated by response of neural cortices in the left middle and superior temporal gyri to language stimuli. At the psycholinguistic level, a relative preservation of the phonological input lexicon,[20] allowing identification of familiar words, could therefore be hypothesized (Figure 1).

### *c) Semantic processing*

Several studies have assessed semantic levels of processing in VS/UWS patients. Nigri et al.[58] reported a "semantic relatedness effect" in one VS/UWS patient: this patient showed specific activity in the middle temporal and angular gyri when listening to semantically related versus unrelated word pairs. Kotchoubey et al.[53] demonstrated a cortical semantic differentiation in about one-fourth of VS/UWS patients, again using presentation of related word pairs. Other authors however failed to show residual semantic word processing responses using EEG in this diagnostic entity.[52,55]

Various neuroimaging studies contrasted sentences of low versus high ambiguity (i.e., including homonyms/homophones or not, such as: there were *dates* and *pears* in the fruit bowl). In their case study, Owen et al.[30] used this type of approach and found significant neural responses in the posterior inferior temporal lobe to semantically ambiguous stimuli. Coleman and coworkers also showed that this part of the temporal lobe and the left inferior frontal gyrus reacted to similar semantic contrasts, indicating higher levels of semantic processing.[49,50] Kotchoubey et al.[59] alternatively compared factually correct versus incorrect short sentences and observed differential brain responses in VS/UWS patients, involving fronto-parietal cortices.

Similar results were observed with EEG methodologies. For example, Formisano et al.[60] recently reported an N400 response in several VS/UWS patients, by contrasting semantically congruent versus incongruent sentences. According to Schoenle et al.,[61] up to 39% of VS/UWS patients may show some form of N400 response, indicative of residual semantic capacities. An increased N400 peak amplitude within fronto-central cortical areas in response to incongruous sentence endings was further found by Balconi et al.[32,62] in all VS/UWS patients in their study. The peaks were, however, delayed compared to both healthy subjects and MCS patients. This is also in line with the study of Kotchoubey et al.,[53] which showed that neural responses to semantically incongruous sentences may occur in DoC patients, but they are less reliable than in conscious patients with severe brain injury.

In sum, the presence of neural signs of residual semantic abilities has been observed in many patients diagnosed as VS/UWS. These neural signs involved brain responses of the left inferior frontal gyrus, temporal lobe and angular gyrus, characterized by an N400 component in EEG studies, although this component may be delayed and less reliable than in conscious patients. Residual processing within the semantic system (Figure 1) can therefore be hypothesized in VS/UWS patients.

**Minimally conscious state**

***a) MCS- versus MCS+ distinction***

A series of studies have examined the extent to which neural structures and pathways associated with language processing show spontaneous recovery in patients with MCS by further distinguishing between MCS- and MCS+ patients (Figure 4).

[INSERT FIGURE 4 AROUND HERE]

Using fluorodeoxyglucose (FDG)-PET, higher brain glucose metabolism was observed in left-sided language-related cortical areas in MCS+ patients compared to MCS- patients.[63–65] Stronger brain connectivity in a left frontoparietal network was also observed using both resting state fMRI and FDG-PET in MCS+ compared to MCS-.[63,64,66] A recent study also supports the association between the level of preservation of the language network and the CRS-R auditory subscale scores (including the command-following item).[67] By examining white matter integrity, Zheng et al.[68] showed an increased structural connectivity for thalamo-premotor and thalamo-temporal pathways in MCS+ compared to MCS- patients. No significant grey matter volume, in language-related or other cortical areas, could however distinguish MCS- from MCS+ groups.[64,69] Studies using EEG methodology to distinguish DoC patients able to respond to commands from those who are not[70] observed an increase in central gamma and posterior (centro-occipital) alpha power as well as in complexity measures such as alpha permutation entropy (i.e., assessing the dynamics of a time series).

A few studies focused more directly on language-related behavior, beyond the simple MCS+ versus MCS- distinction. Using their “Chiba score”, Yamaki et al.[21] observed that higher language abilities were associated with increased left-sided brain glucose metabolism in MCS patients. Residual abilities involving the recognition of pictures, letters or words after their oral presentation were observed using CAVE in an MCS+ patient, along with preserved glucose metabolism in language-related brain areas.[23] Similarly, the language deficits that were identified using the BERA in some post-comatose patients (including three MCS patients) were in line with a decrease of grey matter volume and/or brain glucose metabolism in several language processing areas.[25] These two measures of language comprehension were further shown to be consistent with CRS-R-based diagnoses, with higher scores for CAVE and BERA in EMCS compared to MCS patients.[23,25]

### *b) Language-related cortical responses*

The different passive listening paradigms that were presented in the previous section regarding VS/UWS patients have also been used in MCS patients, contrasting speech versus non-speech or employing phonological, lexical and semantic verbal stimuli (Figure 3). Overall, similar responses to such aspects of speech for words and sentences were observed in MCS patients, though in a higher proportion compared to VS/UWS patients; responses were also faster, stronger and spatially more extended compared to VS/UWS patients (e.g., [32–40,71]). Using EEG, Gui et al.[71] recently investigated the neural dynamics associated with language tasks of increasing complexity. They showed that as the language task became more complex, associated neural dynamics became more reliable in differentiating VS/UWS from MCS patients. The authors suggested that language-related neural dynamics as measured by EEG might separate sensory from higher-level linguistic functions, and that only the latter distinguish consciousness levels (see also [55,59,72]). Other studies have shown that the recovery from VS/UWS to a MCS was associated with more selective recruitment of the left angular gyrus during listening to speech, increased responses in the language network and greater deactivation of the default mode network, as revealed by fMRI,[73] and an increment of the P3 component elicited by own name listening, as revealed by EEG.[35] Finally, several studies also showed the presence of residual language processing in a higher proportion of EMCS compared to MCS or VS/UWS patients, with responses that are more similar to healthy subjects (e.g., [74–77]).

On the other hand, command-following was explicitly identified in several MCS patients by means of fMRI or EEG (i.e., ERPs), as well as active tasks involving imagery (e.g., command "imagine playing tennis", "imagine walking into your house" or "imagine moving your left hand"),[75,78–82] counting (e.g., command "count the target word")[35,38,79,83–87] or visual recognition (e.g., command "look at the house" or "look at your own photo"),[88,89] which may also allow communication attempts (Figure 3). The presence of covert command-following is observed when the resulting pattern of brain activity in behaviorally unresponsive patients (i.e., VS/UWS or MCS- patients) is similar to those of healthy control subjects, furthermore revealing the presence of a cognitive-motor dissociation.[51,90] For example, Owen et al.[91] used fMRI in a patient who was initially misdiagnosed as VS/UWS and showed appropriate activation to motor imagery in the supplementary motor area, whereas activation to spatial imagery was found in the parahippocampal gyrus, posterior parietal lobe and lateral premotor cortex. Claassen et al.[82] more recently used the commands "keep/stop opening the hand" and obtained appropriate EEG responses in 16/104 behaviorally unresponsive acute patients. These patients with cognitive motor dissociation should therefore be considered as MCS+ or MCS*.

Overall, residual sensory responses to higher-level language processing were more frequently and strongly observed in the EMCS than in MCS, and in MCS more than in VS/UWS. The recovery of language abilities as assessed by active tasks, such as (covert) command-following capacity, should only correspond to the MCS+, EMCS or MCS*.

**LANGUAGE PROCESSING AND PROGNOSIS DATA**

Although still limited, a few studies indicate that early neural reactivity to passive and active tasks involving linguistic stimuli may predict a favorable outcome at the level of functional recovery (e.g., [36,39,40,51,60,71,82,92–94]).

As regards passive language listening paradigms, Coleman et al.[49,50] showed that the level of auditory processing revealed by fMRI correlated strongly with subsequent behavioral recovery six months later. Indeed, most of the included VS/UWS patients who were behaviorally diagnosed as EMCS at follow-up initially showed a mid-level response to speech stimuli or high-level response to semantic aspects of speech. Using EEG, N400 responses to sentence listening in acute and chronic DoC patients were reported as very good predictors of further recovery.[95] In this study, patients with both an N400 and a P300 component had 97% chances of a favorable outcome, with the presence of an N400 component being associated with the biggest change in predictive power. The authors concluded that electrophysiological indicators of high-level cognitive processing are important outcome predictors, whereas lower-level sensory and perceptual processing would add no further information to the outcome classification. Likewise, Formisano et al.[60] showed that the absence of a semantic N400 component during the acute stage predicted poorer outcomes and was associated with subsequent aphasia for patients reaching the EMCS stage. Sokoliuk et al.[93] recently investigated the cortical tracking of phrases and sentences (quantified by inter-trial phase coherence) in acute patients and showed a significant correlation between their functional outcome at three and six months and the strength of comprehension response, which also improved the accuracy of prognosis relative to clinical characteristics alone (e.g., Glasgow Coma Scale, computed tomography). Finally, a study assessing autonomic responses to emotionally salient words compared to pseudowords via electrodermal skin conductance responses observed that positive outcome (i.e., from consciousness recovery with severe disability to good recovery) VS/UWS patients had an earlier, higher autonomic response to words than negative outcome (i.e., death or persistent unresponsiveness) VS/UWS patients.[96]

Regarding active language paradigms such as command-following tasks, Edlow et al.[51] showed that, except for one patient who died in the intensive care unit due to withdrawal of life-sustaining therapy, all patients with cognitive motor dissociation and covert cortical processing recovered beyond a confusional state by six months. In the study of Claassen et al.[82] the presence of appropriate EEG responses to verbal commands predicted recovery of behavioral command-following before discharge as well as level of autonomy at one year post-injury.

Overall, these data demonstrate the importance of neural signs of residual language processing abilities signal the potential for a favorable functional outcome.

## CONCLUSION

The identification of residual cognitive and linguistic abilities after severe brain injury is crucial for optimal diagnosis and treatment of DoC patients. In this review, we discussed the behavioral and neural assessment methods that are currently used, the specific language abilities they detect, as well as their prognostic value. As regards to purely behavioral assessment methods, the CAVE and BERA tools appear to be well adapted to MCS (and EMCS) patients who have recovered vision, as the verbal command items require looking at a target picture next to a distractor. However, these scales need further validation in larger samples of DoC patients. Moreover, it is important that the presence of residual language processing abilities in post-comatose patients can be examined in the absence of residual vision. The neural assessment paradigms reviewed here seem to be very promising for this purpose. Multimodal assessment protocols should combine behavioral, neuroimaging and electrophysiological methods to assess receptive language abilities in DoC patients in the most complete and sensitive manner.[15] In our opinion, the level of consciousness of post-comatose patients should first be estimated using behavioral tools such as the CRS-R or SECONDs. Their residual language abilities should then be assessed using language-specific behavioral tools (Table 1). These protocols should include both passive and active linguistic paradigms and cover low-level (sensory) and higher-level (i.e., judgment and (mental) execution of sentence meaning) linguistic processes. As shown in this review, the tasks involving higher level linguistic commands appear to be the most informative about level of consciousness and have the best prognostic value, even if studies regarding the latter aspect remain scarce.

**CONFLICT OF INTEREST**

The authors declare that there is no disclosure or conflict of interests regarding the publication of this paper.

**ACKNOWLEDGEMENT**

This study was supported by the University and University Hospital of Liege, the Belgian National Funds for Scientific Research (FRS-FNRS), the European Union's Horizon 2020 Framework Programme for Research and Innovation under the Specific Grant Agreement No. 945539 (Human Brain Project SGA3), the European Space Agency (ESA) and the Belgian Federal Science Policy Office (BELSPO) in the framework of the PRODEX Programme, the Center-TBI project (FP7-HEALTH- 602150), the Public Utility Foundation 'Université Européenne du Travail', "Fondazione Europea di Ricerca Biomedica", the BIAL Foundation, the Mind Science Foundation and the European Commission, the fund Generet, the King Baudouin Foundation, the Mind-Care foundation, DOCMA project [EU-H2020-MSCA–RISE–778234]. SM is research director at FRS-FNRS.

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**TABLES AND FIGURES**

**Table 1. Behavioral tools allowing language assessment in post-comatose patients**

| Tool | Required level of consciousness | Advantages | Disadvantages |
|---|---|---|---|
| CRS-R (SECONDs, IQBA) language-related items | MCS+, EMCS | Included in validated scales allowing diagnosis of DoC | Multi-determinate, no distinction of language domains (Figure 1) |
| Chiba score[21] | MCS, EMCS | Distinction between language comprehension, expression, and communication, with reported level of severity | No available validation data, based on basic clinical observation |
| CAVE | MCS-, MCS+, EMCS | Assessment of item recognition, based on visual fixation (adapted to most MCS- patients), validated scale with high levels of inter-rater and test–retest reliability | Based on visual fixation (not adapted to patients with impaired vision and oculo-motricity), no distinction of language domains and no assessment of psycholinguistic effect |
| BERA | MCS-, MCS+, EMCS | Assessment of item recognition, based on visual fixation (adapted to most MCS- patients), good psychometric properties in aphasic conscious patients, distinction of language domains and assessment of some psycholinguistic effects | Based on visual fixation (not adapted to patients with impaired vision and oculo-motricity), no validation group study on DoC patients |
| Loewenstein Communication Scale | EMCS | Validated scale to assess communication abilities with very good reliability and good inter-rater agreement | No characterization of residual language abilities per see, no concrete definition nor examples |
| Individual Nonverbal Communication Rating Scale | EMCS | Combination of patient observation, family interviews and scores of the Glasgow Coma Scale to estimate patients' communication abilities | No characterization of residual language abilities per see, no concrete definition nor examples, no available validation data |

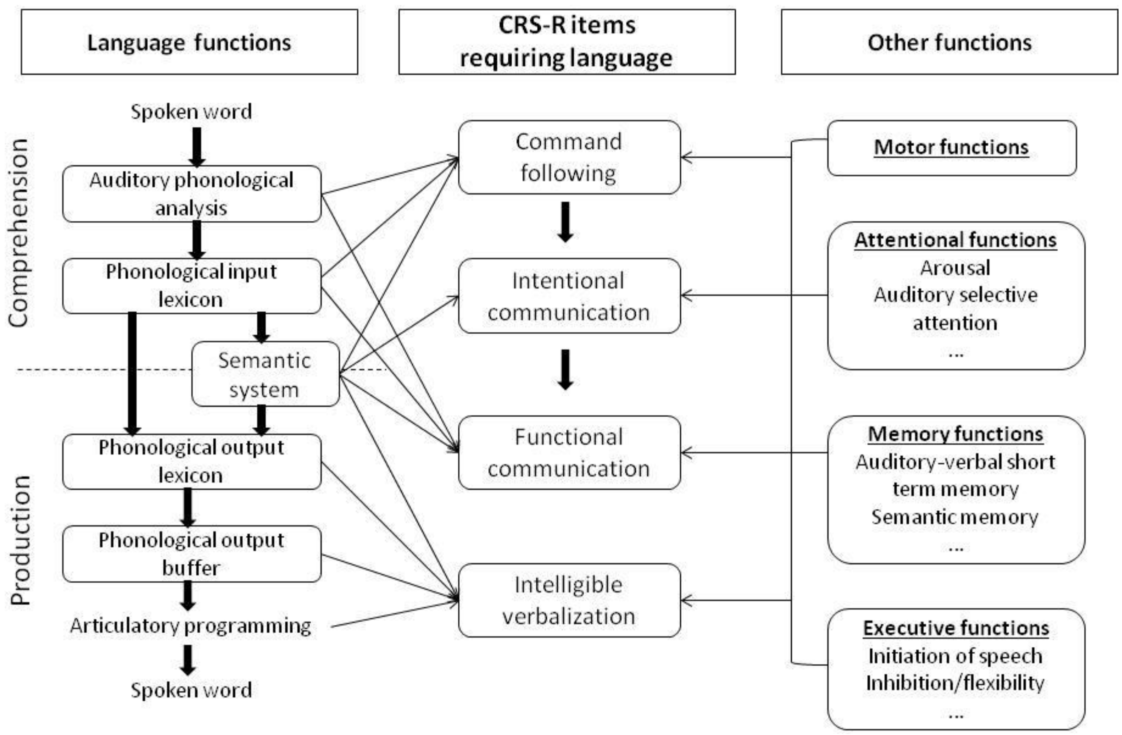


**Figure 1. Influence of specific language and motor/cognitive functions on CRS-R language-related items.** On the left: language model adapted from Patterson and Shewell (1987); in the center: the four CRS-R items directly requiring language residual abilities; on the right: motor and cognitive functions impacting patients' CRS-R performance.

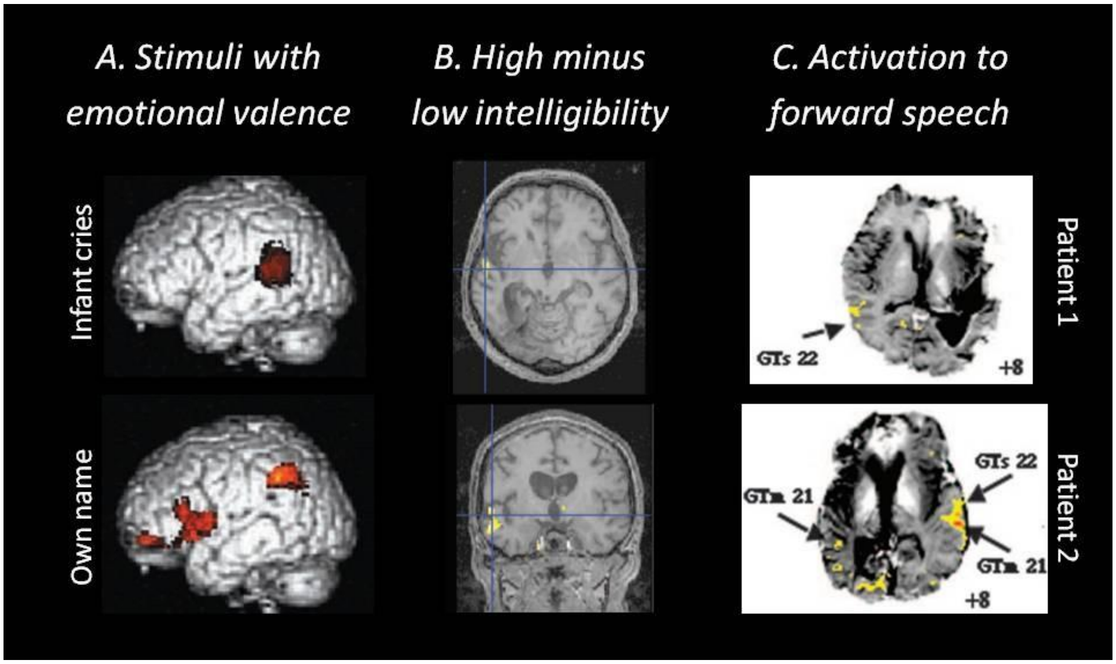


**Figure 2. Residual language processing in MCS patients using passive listening tasks,** employing (A) patient's own name (adapted from [29])**, (B)** intelligible versus unintelligible speech (adapted from [30]), and (C) narratives (adapted from [31]); GTs: superior temporal gyrus; GTm: middle temporal gyrus..

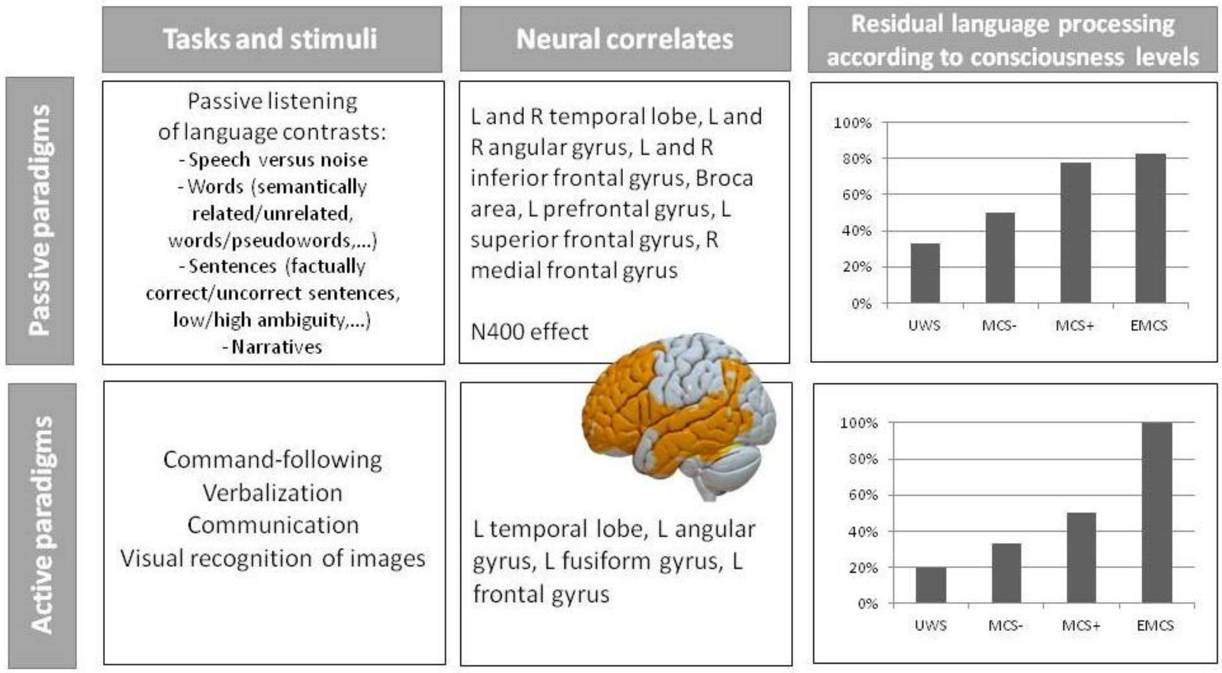


**Figure 3. Overview of active and passive language assessment paradigms and associated results for neuroimaging and electrophysiological study designs,** based on a systematic literature review .[42] On the right, the median percentages of patients showing residual active or passive language abilities are presented. L: left; R: right, UWS: unresponsive wakefulness syndrome; MCS-: minimally conscious state minus; MCS +: minimally conscious state plus; EMCS: emergence from the minimally conscious state.

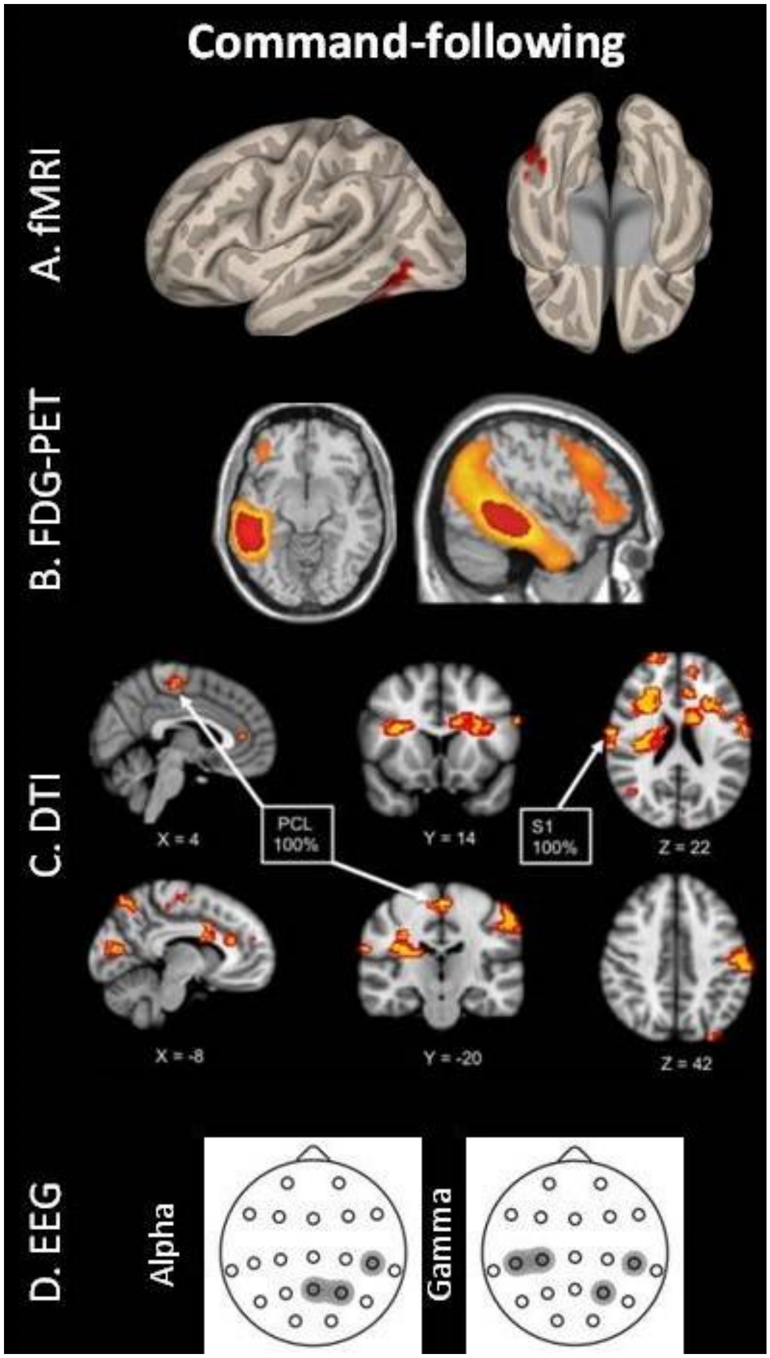


**Figure 4. Distinction between MCS- and MCS+ for different neuroimaging paradigms**. (A) Resting state fMRI results showing residual functional connectivity in MCS+ (but not MCS-) patients between the left dorso-lateral prefrontal cortex and the left fusiform gyrus (adapted from[66]); (B) FDG-PET results showing left-sided metabolic differences between the two MCS categories (adapted from [97]); (C) Diffusion tensor imaging (DTI) results showing tracks originating from the thalamus and projecting to the cortex that successfully distinguished MCS- and MCS+ (adapted from [68]); (D) Increase of EEG wave amplitude when patients recovered command-following capacity (adapted from [70]).