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CHAPTER 5

The problem of aphasia in the assessment of consciousness in brain-damaged patients☆

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Abstract: The assessment of the level and content of consciousness in brain-damaged patients relies to a large extent on behavioral assessment techniques. The limited behavioral repertoire displayed by vegetative and minimally conscious states requires the use of highly sensitive and reliable behavioral assessment methods, allowing the detection of subtle changes in behavior and associated level of consciousness. This situation is further complicated when patients with such disorders of consciousness have underlying deficits in the domain of communication functions, such as aphasia. The present paper examines the consequences of receptive and/or productive aphasia on the already limited behavioral repertoire presented in these patients and discusses a number of behavioral and neuroimaging assessment procedures designed to: (1) detect the presence of aphasia in patients with disorders of consciousness, and (2) reliably assess the level of consciousness of brain-damaged patients while taking into account the existence of receptive and/or expressive language deficits. The combined use of behavioral and neuroimaging assessment techniques appears to be particularly promising for disentangling impaired consciousness and aphasia.

Keywords: minimally conscious state; vegetative state; aphasia; dysphasia; communication; consciousness; responsiveness; behavioral assessment; neuroimaging

Introduction

The assessment of level of cognition in patients with altered states of consciousness such as vegetative state (VS) and minimally conscious state (MCS) is primarily based on the observation of spontaneous behaviors and those that occur in response to verbal, visual, or tactile stimulation. A number of consensus-based criteria have been proposed to distinguish MCS from VS. These criteria entail the observation of a number of behaviors considered to be inconsistent with VS and indicating the presence of minimal signs of consciousness, such as (1) visual fixation and pursuit, (2) response to verbal commands,

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(3) intelligible verbalization, (4) localization to noxious stimuli (Giacino, 2004; Giacino and Whyte, 2005; Majerus et al., 2005; Working Party of the Royal College of Physicians, 2003). Many of these behaviors require language comprehension or a response to verbal stimulation. The possible existence of unrecognized language disorders might, in some patients, prevent consistent behavioral responses to these verbal items, leading to an underestimation of the patient's level of consciousness. The present chapter examines the likelihood of the co-occurrence of language disturbance and alteration in consciousness, presents specific assessment procedures for detecting language impairment in patients with disorders of consciousness and discusses a number of precautionary measures when determining level of consciousness in patients likely to have associated language disorders.

A brief overview of the cognitive architecture of language processing and underlying neuroanatomical correlates

Before considering the likelihood of language disorders in patients with impaired consciousness, we will provide here a brief overview of the cognitive architecture of language processing and underlying neuroanatomical correlates, since this knowledge will be determinant when trying to delineate the nature of possible language disorders in patients with alterations in consciousness.

At the receptive level, different levels have to be distinguished, starting with sound-based analysis processes, involving acoustic and phonetic analysis. Acoustic processing, common to verbal and nonverbal sounds, involves the bilateral primary auditory cortex and surrounding lateral superior temporal cortex, with a dominance of left superior temporal cortex for temporal analysis, and right superior temporal cortex for spectral analysis (Formisano et al., 2003; Wessinger et al., 2001; Zatorre and Belin, 2001). Phonetic processing, that is, the extraction of temporal and spectral acoustic features necessary for identifying the basic verbal units (phonemes), involves the same neural substrates in the superior temporal lobes (Binder et al., 2000; Joanisse and Gati, 2003; Scott et al., 2000; Shestakova et al., 2004; Zatorre and Belin, 2001). The next level, phonological processing, involves the mapping of phonetic information to abstract representations of the speech sounds defining the phonology of a language (the vowels and consonants of a given language); this type of processing is subtended by the bilateral posterior superior temporal gyri and the superior temporal sulci (Binder et al., 2000; Scott et al., 2000). Finally, at the lexico-semantic stage, sounds are mapped to existing word forms and their associated semantic features, resulting in speech comprehension. The neural substrate involved in lexico-semantic stages are much more distributed, involving anterior temporal, middle and inferior temporal, medial temporal, inferior parietal as well as anterior inferior prefrontal regions (Binder et al., 2000; Longoni et al., 2005; Majerus et al., 2002; Martin et al., 1996). The precise role of these different areas involved in lexico-semantic processes has been proposed to vary as a function of semantic content, more abstract representations activating preferably the inferior prefrontal regions, animal categories activating the inferior temporo-occipital cortex and the tool category activating premotor regions (Martin et al., 1996; Noppeney and Price, 2004).

At the level of speech production, the starting point will be the lexico-semantic network, followed by the activation of phonological codes in the superior temporal lobe which, via the arcuate fasciculus, will activate corresponding articulatory patterns for speech motor production (Hickok and Poeppel, 2007). Speech motor production is subtended by a network involving the left frontal operculum (Broca's area), the left insula and adjacent sensori-motor cortex, subcortical nuclei (thalamus, putamen, pallidum) as well as the cerebellum (Hickok and Poeppel, 2007; Riecker et al., 2005). Finally, the precise neural substrate of sentence-level processing is less clearly understood. However, many studies have shown that Broca's area and adjacent inferior prefrontal cortex is critical for syntactic processing while the anterior temporal pole has also been frequently shown to be involved in sentence comprehension processes (e.g., Longoni et al., 2005; Vigneau et al., 2006).

Language disorders as a result of brain lesion (i.e., aphasia) can concern any combination of these different language processes, depending on the type and extent of brain lesions. However, for the issue of interest here, it is important to note that, except for very large lesions involving approximately two-thirds of the left hemisphere, aphasic patients rarely present global aphasia for a prolonged time (Kirshner, 1995; Laska et al., 2001). Global aphasia refers to the situation where both expressive and receptive language processing are severely impaired, leading to near complete loss of language comprehension and production. Global aphasia is frequent at the acute stage (25%) but its incidence rapidly decreases to a few percent after 18 months (Laska et al., 2001). The more typical and lasting situation is characterized by selective difficulties involving speech perception, lexical retrieval (word form access — anomia), semantic access (word meaning access), speech production (articulation — dysarthria, apraxia of speech), sentence comprehension and sentence production (agrammatism), patients presenting difficulties in one or several of these domains, but often retaining the capacity to understand high frequency and highly familiar words, to perceive words that are phonetically quite distinctive (e.g., car — bike, as opposed to bike — pike), to understand simple sentences and to utter single words.

The likelihood of aphasia in altered states of consciousness

The type of brain lesion causing an alteration of consciousness levels provides a first indication of the likelihood of associated language problems. Overall, in the light of the results presented above, any brain lesion involving the left superior, middle and/or inferior temporal lobes is likely to be associated with receptive aphasia, as well as word finding difficulties during language production; any brain lesion involving Broca's area and surrounding cortical and subcortical areas is indicative of possible speech output difficulties. More specifically, lesions in these regions are most frequent in patients presenting a left-hemisphere ischemic or hemorrhagic pathology, most frequently due to thrombosis or aneurysms in the territory of the left-middle cerebral artery (Kirshner, 1995). Cerebral vascular pathologies are among the most frequent etiologies of aphasia; the prevalence of aphasia after an ischemic stroke ranges between 15 and 30% (Inatomi et al., 2008; Laska et al., 2001). Traumatic brain injury less often leads to focal brain injury that could result in aphasic type language disorders (15% of all patients presenting traumatic brain injury; Chapman et al., 1995; Eisenberg et al., 1990). At the same time, it should be noted that for focal lesions in severe traumatic brain injury, they tend to be most widely distributed in the fronto-temporal area (Chapman et al., 1995; Levin et al., 1988; Newton et al., 1992). Severe aphasia is however very rarely reported as a result of traumatic brain injury. The most frequent language impairment at acute stages of closed traumatic brain injury is anomia (Heilman et al., 1971). Receptive language difficulties are most often related to sentence complexity, comprehension of simple sentence structures being in general preserved. However, discourse level deficits are a very common consequence of traumatic brain injury (Chapman et al., 1995). Given the limited and simplified verbal instructions used during assessment of levels of consciousness, this type of language disturbance should however be of little consequence in the accurate assessment of consciousness in these patients. Finally, carbon monoxide intoxications and herpes simplex encephalitis are other causes leading to altered states of consciousness (e.g., Schnakers et al., 2008a, b). Given that these pathologies preferentially lead to brain lesions in medial temporal and hippocampal areas, they very rarely lead to severe aphasic syndromes, but semantic impairments can nevertheless be a frequent consequence of these pathologies.

With respect to functional brain imaging findings in patients with altered states of consciousness such as MCS and VS, Laureys et al. (2000a, b, 2004a, b) showed that the regions that are most hypometabolic in patients presenting a VS or a

MCS involve posterior parietal areas, including the precuneus and posterior cingulate cortex, and that recovery of activation in these areas is what best differentiates patients in a VS and those in a MCS. At the same time, this does not necessarily imply that language-processing regions show preserved brain metabolism in MCS patients. In order to investigate this question, we explored the level of glucose metabolism in 36 MCS patients (minimum inclusion criterion: patients had to show visual fixation; Giacino, 2004) and 40 age-matched healthy controls using [18F]2-fluoro-2-deoxy-D-glucose positron emission tomography (PET FDG) brain imaging. These patients either had suffered from anoxia, traumatic brain injury, hemorrhagic, stroke, or other lesions (see Table 1). The images were spatially normalized into standard stereotactic space, smoothed using a smoothing kernel width at a half maximum of 14 mm owing to the severely damaged brains of the patients in minimally conscious state (MCS) (Friston, 1997). The images were then analyzed using an ANOVA design (SPM8b, www.fil.ion.ucl.ac.uk/spm), with participant group as group factor. Global scaling by proportional scaling was used. We focused the analyses specifically on main language-processing regions. This was achieved by applying an inclusive mask covering major language-processing regions in the left superior, middle and inferior temporal gyri, and the left inferior frontal gyrus, as well as the right inferior temporal gyri, based on the coordinates published in the functional neuroimaging studies of language processing reported earlier (Binder et al., 2000; Joanisse and Gati, 2003; Longoni et al., 2005; Majerus et al., 2002; Martin et al., 1996; Noppeney and Price, 2004; Scott et al., 2000; Shestakova et al., 2004; Vigneau et al., 2006; Zatorre and Belin, 2001). As shown in Fig. 1, the estimated metabolism of regions included in this mask volume was significantly lower in all MCS patients relative to the control group, and this irrespective of type of insult. Furthermore, as shown by the individual metabolic values in Fig. 1, there was a remarkably comparable level of hypometabolism in language-processing regions, despite the fact that the patients within each group varied greatly in terms of lesion site and lesion extent (see Table 1). This means that reduced levels of metabolism in language-processing areas might be a common characteristic of patients in a MCS.

In sum, the possibility of co-occurrence of severe aphasia and an alteration of consciousness should be considered especially in the context of left hemisphere cerebro-vascular pathologies or any other pathology leading to direct focal lesions in the left perisylvian area (e.g., focal traumatic brain injury). However, resting metabolic levels in language-processing areas cannot be used to directly infer the existence of possible language impairment given that hypometabolism in these regions appears to be a wide-ranging characteristic of minimally conscious patients.

Detection of aphasia in altered states of consciousness

Given the data presented in the previous section, the first important information to gather is structural information about the existence of focal brain lesions, and the extent and localization of these lesions, using CT or structural MRI scans. However, although structural brain imaging will

Table 1. Characteristics of 36 minimally conscious patients under going PET-FDG resting state brain imaging for determining metabolism levels in language processing areas

Brain injury type	Focal lesion in left hemisphere language processing areas	Other focal lesions	Diffuse or non-specified lesions	Age range (years)	Time post-onset
Anoxia	0	1	11	26–64	1 month-7 years
Traumatic brain injury	2	3	12	16–43	2 months-22 years
Hemorrhagic lesions, stroke, other	3	4	0	45–88	1 month-5 years

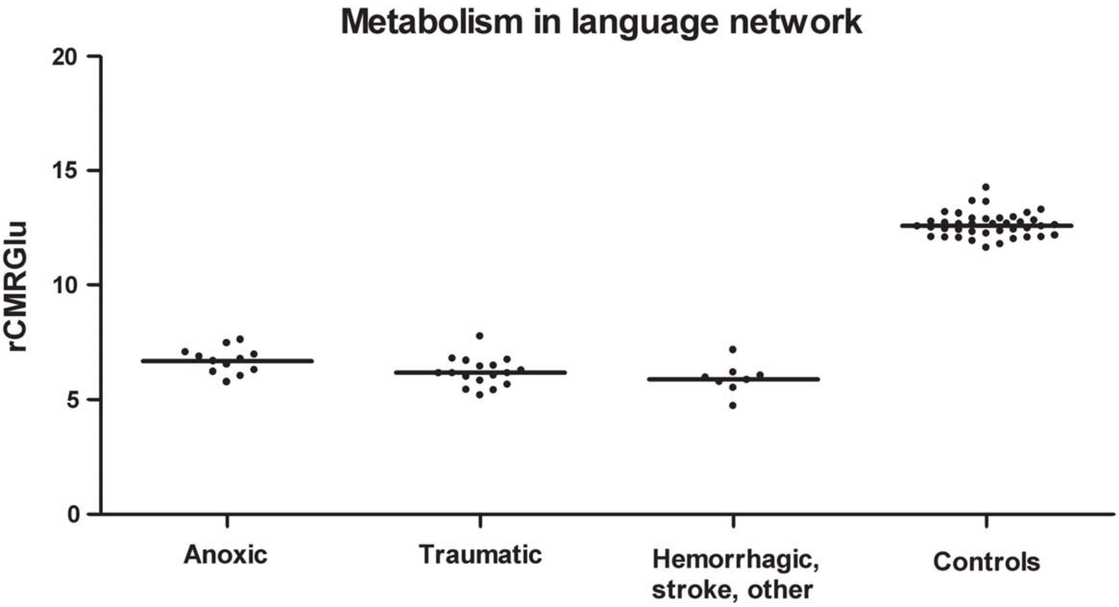

Fig. 1. Resting state metabolism (PET-FDG) in main fronto-temporal language-processing areas, in minimally conscious state patients as a result of anoxia, traumatic brain injury, or hemorrhagic, stroke, and other lesion types, and in age-matched healthy controls (first eigenvariate of main group effect for the volume of interest as defined by an inclusive mask covering major language-processing areas; see text for further details).

reveal potential lesions in temporal and inferior prefrontal language-processing areas, they give no information about the functionality of lesional and peri-lesional areas and their residual ability to support processing of language stimuli. As we have seen, looking at basic resting state metabolism in language processing will not be very informative given the general hypometabolism observed in these areas in MCS patients. The implementation and adaptation of specific event-related functional neuroimaging and event-related potential paradigms could however be of particular interest. Based on single case and group studies, it has been shown that language-processing areas in the superior, middle, and inferior temporal lobes can be reliably activated in patients in a MCS. Using functional MRI or $H_2{}^{15}O$-PET, Laureys et al. (2000a, 2004b; Boly et al., 2004) presented to their patients auditory-verbal information such as the patient's own name, as opposed to noise, and observed extensive activation in the superior and middle temporal lobes specifically for the meaningful linguistic stimulus. Similar results have been observed by a different research team when presenting meaningful linguistic stimuli to a lower bound MCS patient (e.g., Owen et al., 2006). Even for patients in a VS, it has been shown that language stimuli activate language-processing areas in the temporal lobe, although this activation is restricted to the superior temporal lobe surrounding the primary auditory cortex and is disconnected from other temporal lobe regions (Laureys et al., 1999, 2000a, b). Other investigators have shed further light on the integrity of the underlying language network in patients with disorders of consciousness by contrasting fMRI responses to intelligible and unintelligible speech. Schiff et al. (2005) presented fully-comprehensible spoken narratives to a group of healthy volunteers and two patients who fulfilled the diagnostic criteria for MCS. In a second condition, the narratives were digitally reversed resulting in loss of speech content and prosody. Both the volunteers and patients showed robust activity in the superior and middle temporal gyri during exposure to the comprehensible narratives. However, unlike the volunteers, the MCS patients demonstrated marked reductions in activity during presentation of the reversed narratives. The investigators suggested that the MCS patients' inactivity in the reversed condition reflected an inability to drive language structures when exposed to effortful processing demands. This hypothesis was supported by post-scan interviews in which volunteers reported that they recognized the stimuli as potential speech stimuli and initially increased their attempts to understand it. Given these results, the possibility of receptive language processing deficits in MCS patients should be considered if a patient fails to show consistent activation in superior middle and inferior temporal lobes in response to the presentation of meaningful verbal stimuli in an fMRI paradigm, relative to other MCS patients and healthy controls.

It should be noted that although fMRI studies allow us to compare activation patterns in patients and control subjects, the existence of a similar activation profile in patients and control subjects does not automatically imply similar and accurate language processing in both populations, and hence language comprehension. For example, functional neuroimaging studies in healthy controls have shown that similar activation profiles are observed in superior, middle, and inferior temporal gyri when word (e.g., trailer) and nonword stimuli (e.g., traimer) are presented (Binder et al., 2000; Price et al., 1996), suggesting that even when verbal stimuli have no defined lexical and semantic content, and hence cannot be understood, lexical and semantic-processing areas in the temporal lobes are activated. This also means that a patient showing activation in these temporal areas following the presentation of a meaningful verbal stimulus might still be unable to comprehend the stimulus. More generally, fMRI activation provides information about the type of regions involved in a specific cognitive process, but does not necessarily provide information about the result and accuracy of the ongoing cognitive process. At the same time, negative findings in response to activation paradigms do not rule out the possibility that the capacity for language processing is retained. Many other factors may mask or suppress cortical activity associated with fMRI-based language tasks including disturbances in the blood-brain barrier, cerebrovascular and structural anomalies, impairments in subjects' level of arousal, attention and motivation, motion artifact and the field strength of the magnet (Brown, 2007).

Neurophysiological paradigms, using event-related potentials (ERP) measuring the electrical correlate of neural activity in response to specific stimuli, could provide further helpful information. Although this technology has a much lower spatial resolution, the temporal resolution is at the millisecond level, and, relative to fMRI which has a temporal resolution of 1000 ms at best, is much more suited to study the temporal succession of the different cognitive processes involved in online speech perception processes. In standard listening conditions, a spoken word is identified (i.e., its meaning is accessed) in less than 400 ms (Kotz et al., 2005; Marslen-Wilson and Welsh, 1978). In the speech perception literature, different paradigms have been developed allowing to capture the functioning of perceptual, lexical, and semantic processes. A very interesting ERP component is the negative amplitude occurring 100–200 ms after stimulus onset (mismatch negativity, MMN), and this particularly when a new stimulus occurs within a sequence of repetitive stimuli (e.g., da — da — da — ba). This component has been used very extensively to study acoustic and phonological processes (e.g., Hisagi et al., 2006; Näätänen, 1990; Ylinen et al., 2006). A further quality of the MMN is that it can be obtained in very passive conditions, where conscious awareness of the target stimulus is not necessary. In this paradigm, the participants are often exposed to a secondary task such as viewing a film, and the auditory stimuli of interest are presented via headphones to the participant, without the participant having to pay attention to the stimuli (Näätänen, 1990). The MMN is also used to reliably study speech perception processes in pre-conscious neonates and infants (e.g., Dehaene-Lambertz and Baillet, 1998). This renders the paradigm particularly interesting to identify speech perception problems in MCS, and possibly, also VS patients. This paradigm can be used to explore sensitivity to all phonetic contrasts existing in a given language at the consonant and vowel level (e.g., ba — ba — ba — pa or bi — bi — bi — bi — bu). If the patient fails to present an MMN response to deviant stimuli differing at the acoustic, phonetic or phonological level, this may suggest that linguistic information is not accurately processed at this level. Later potentials, such as the positive peak at 300 ms and the negative peak at 400 ms post-stimulus, have been used to study lexical and semantic processes. For example, in a lexical decision task, where word (e.g., house) and nonword stimuli (e.g., houme) are successively presented, an earlier P300 and an earlier N400 are observed if the target word stimulus is primed (preceded for a brief time period) by a semantically related word, indicating that the word and its semantic relationships have been identified (e.g., Hill et al., 2005). In a lexical decision task, the P300 to words shows a larger amplitude and a shorter latency when the words have been acquired early or are more frequent, indicating that the P300 indexes lexical recognition processes (Tainturier et al., 2005; Polich and Donchin, 1988). The P300 response is also larger for words as compared to nonwords (Pulvermüller et al., 2004). The later negativity at 400 ms (N400) has been extensively used to study higher level semantic processes, such as the detection of semantic plausibility of sentences, an N400 component being observed when a sentence ends with a semantically implausible word (e.g., the cat chased the door; Kutas and Hillyard, 1980). Hence, the observation of unexpected P300 and N400 patterns in response to word and sentence stimuli is likely to indicate abnormal lexical and/or semantic processes, consistent with findings of abnormal P300 and N400 in aphasic patients with lexico-semantic impairment (e.g., Hagoort et al., 1996; Pulvermüller et al., 2004).

Although the paradigms used for eliciting P300 and N400 components are attentionally more demanding paradigms (listening to words, pseudowords, or sentences) than the paradigms used to elicit MMN components, previous research in MCS patients has shown that reliable P300 components can be observed in MCS patients when hearing their own name as compared to an unfamiliar name (e.g., Laureys et al., 2004b; Perrin et al., 2006; Schnakers et al., 2008b). Even in some vegetative state (VS) patients, a P300 has been observed when comparing the patients' own names to unfamiliar names, however, these responses are less consistent for this patient group (Glass et al., 1998; Perrin et al., 2006). N400 components can also be reliably observed in MCS patients: Schoenle and Witzke (2004) showed that 67 MCS patients (from a total of 74 patients) showed N400 waves for semantically incongruent sentences, while this was only the case in 5 out of 46 VS patients (see also Kotchoubey et al., 2005, for related findings). On the other hand, early negative amplitudes involved in perceptual and phonological processes appear to be identifiable in the vast majority of VS patients (Perrin et al., 2006; Schnakers et al., 2008b).

Finally, at the behavioral level, and for patients in a MCS, the detection of possible signs for aphasia could also be attempted by using customized bedside aphasia screening batteries, varying the linguistic complexity (such as word frequency, age of acquisition, word length) of single word instructions and alternating the use of auditory-verbal, visual-verbal, and visual-nonverbal instructions. If a patient responds to simple instructions using short, high frequency words (“Raise your arm”; “Close your eyes”) but not to more complex instructions using longer and less frequent words (“Elevate your arm and lower your eyelids”), then this could be a possible indication of language-related, attentional or short-term memory difficulties. Evidence to support this contention is provided by a recent study by Nakase-Richardson et al. (2008). These authors found that patients who had emerged from MCS and were able to respond reliably to yes/no questions concerning situational orientation (e.g., “Am I pointing to the ceiling?”), showed a high rate of inconsistency (34% correct) when responding to questions of greater semantic complexity (e.g., “Will a stone sink in water?”).

The presentation modality of verbal information should also be varied and possible preserved capacities for processing written language should not be underestimated. If a patient responds consistently better to a written command than to the same command presented auditorily, then this is likely to indicate specific difficulties at the level of auditory-verbal input processing (assuming that audiometric testing, using auditory evoked potentials, has ruled out the existence of peripheral or central hearing disorders). It must be noted here that the processing of written and spoken language share the same semantic levels of representation, but that access to these semantic representations from written visual input uses a specific network involving the left posterior inferior temporal gyrus (fusiform gyrus) and the left supramarginal gyrus (e.g., Fiez and Petersen, 1998; McCandliss et al., 2003). Hence, in case of severe speech perception problems due to bilateral lesions at the level of the primary auditory cortex and superior temporal gyri, a patient might still be able to (partially) comprehend speech using the written input modality (Kirshner, 1995). Dissociations between written and auditory language processing have been very frequently reported in the aphasia literature (e.g., Caramazza and Hillis, 1990; Coppens et al., 1998; Majerus et al., 2001, 2004; Puel et al., 1982). Finally, visual-nonverbal communication capacities should also be assessed by providing the patient a visual or gestural description of the command he/she is requested to perform. If the patient is able to raise his/her hand after the examiner has performed the requested movement in front of the patient and the examiner has pointed to the patient to invite him/her to do the same, but if the patient does not perform the same movement upon auditory and written verbal request, then the existence of language-related disorders should be considered. This sort of dissociation in response accuracy to auditory and written verbal requests is illustrated in a case reported by one of the current authors (Smart et al., 2008). A 53-year-old male who developed locked-in syndrome following a pontine hemorrhage showed significantly poorer response consistency and accuracy when answering semantically complex questions presented verbally, but had little difficulty when the same questions were presented in written form. Although this pattern of findings was not indicative of language disturbance, auditory processing impairment was strongly suspected. Presentation of a passive fMRI speech paradigm failed to elicit the expected activity in primary and secondary auditory cortices. In contrast, exposure to passive visual stimuli revealed activation of the primary visual cortex with selective activation of the fusiform face and hippocampal place areas in response to faces and landscape scenes, respectively. Taken together with the bedside findings, these results were strongly suggestive of central deafness. Information gathered via this type of multimodal aphasia assessment will likely yield more clues regarding the probability of unrecognized language and auditory processing impairments in nonverbal and behaviorally unresponsive patients.

Implications for behavioral assessment of level of consciousness

Despite the different techniques discussed here, the detection of language disorders in the context of altered states of consciousness remains a very difficult enterprise. With respect to the assessment of levels of consciousness, the difficulty resides in the detection of behaviors consistent with minimal voluntary and conscious control, while ruling out the possibility that the non-observation of these behaviors is due to language difficulties preventing the patient from comprehending the task instruction and/or producing the required response. The aim of behavioral assessment should thus be to use the most appropriate presentation formats for items containing a verbal request and to avoid the situation where a response is entirely dependent upon the production of a verbal response. Although this general recommendation might conflict with the very precisely defined and standardized administration procedures guaranteeing the reliability of modern behavioral assessment scales such as the CRS-R (Giacino et al., 2004), the WHIM (Shiel et al., 2000), or the SMART (Gill-Thwaites and Munday, 2004), the sensitivity and validity of assessment might depend upon the possibility of adapting the administration modes of individual items to the patient's best receptive and productive abilities. In case of probable aphasic disorders, or simply in case of doubt, the following recommendations for behavioral assessment are proposed:

1. An item containing an auditory or a written verbal instruction should be presented repeatedly, and the best possible response should be scored.
2. If an item is designed to be administered through the auditory mode, and the patient fails to respond, a written prompt should be presented. Similarly, if there is no response to written presentation, an auditory prompt should be provided.
3. In any case, any failed verbal item should be readministered using a gestural or graphical presentation mode; for example, the experimenter performs the command in front of the participant, and the participant is asked (or requested via a gesture) to imitate the command. Aphasic patients should be able to imitate the gestural commands. However, examiners should be cautious in interpreting this type of performance as responses similar to the expected ones may be noted in patients who present with non-intentional imitation or utilization behavior arising from mesiobasal frontal lesions (Lhermitte et al., 1986).
4. Although the verbal instructions of most items are standardized, slight deviations should be allowed in order to allow for shorter formulations, to allow for reformulations using more frequent or familiar words.
5. When there is no explicit formulation associated with the item (such as "patient obeys to a verbal command," Item 15, WHIM), the shortest possible formulation should be used avoiding any unnecessary verbal additions (e.g., say "Raise your arm" or "Raise your arm, please", but do not say "May I ask you to raise your arm?" nor "Can you raise your arm?").

These recommendations are based upon the findings that aphasic symptoms are rarely global in the case of circumscribed cerebral lesions in the perisylvian area, and that elementary speech comprehension and production processes, as needed during the administration of behavioral assessment tools for altered states of consciousness, are still possible in the vast majority of aphasic patients. Cases of global aphasia leading to near complete loss of language comprehension and production abilities are possible, but they are typically associated with very extensive left-hemisphere lesions that can be easily identified based on structural CT or MRI scans.

Discussion

In this work, we proposed that a multimodal assessment protocol, combining specific fMRI, ERP and behavioral assessment protocols could allow to detect possible language impairment in patients with disorders of consciousness. However, the reader should keep in mind that results indicating possible language impairment obtained via these techniques will need to be considered with great care, and that some techniques and paradigms might be more informative than others.

First, with respect to functional neuroimaging results, the observation of resting state hypometabolism in language-processing areas is probably the most difficult-to-interpret situation. As we have shown, most MCS patients, irrespective of lesion location, will show hypometabolism in language-processing areas, relative to controls. However, this does not automatically imply that all MCS patients have language impairment. Hypometabolism in language-processing areas informs us about a decrease of the spontaneous level of activity in language-processing areas; this spontaneous decrease of activity could reflect the MCS patients' reduction of spontaneous verbal behavior and inner verbal thought rather than impaired language processing. In other words, language processing is reduced but not necessarily impaired. A number of studies have shown that resting state brain activity in healthy controls involves the active recruitment of language-processing areas and is related to the participants' engagement in "conceptual" processing (e.g., Binder et al., 1999). Hence the observation of hypometabolism in language-processing areas in MCS patients during passive, resting state conditions is probably not highly informative with respect to the detection of potential language impairment. On the other hand, fMRI paradigms trying to activate language-processing areas as a function of the controlled presentation of language stimuli may be a more powerful paradigm: if a patient activates semantic-processing areas following the presentation of word stimuli, then this indicates more clearly that language-processing areas can indeed be reliably activated. However, this does not yet inform us about the accuracy of language processes subserved by these regions. Furthermore, an absence of stimulus-related activation in language-processing areas could signal language impairment, but could also be due to sensory, anatomical, statistical, and technical factors described earlier. ERP techniques will probably present the highest informative value, as they measure online brain responses signaling the actual, successful identification of linguistic contrasts by the language system, and allow the exploration of a patient's speech perception abilities in a highly refined manner. Furthermore, as we have seen at least for perceptual and phonological factors, reliable ERP signals can be obtained even in patients with severely compromised consciousness levels such as VS patients. Finally, the power of structural imaging to highlight structural damage to language-processing areas should not be underestimated. In sum, ERP paradigms and structural imaging, in combination with adapted behavioral assessment protocols, might represent the fastest and most powerful techniques to explore the brain's potential to process language information in VS and MCS patients.

Conclusion and perspectives

Future research will be necessary to improve and refine multimodal assessment techniques for language impairment in VS and MCS patients. In order to reliably determine that a specific brain response or its absence signal potential language impairment, be it for fMRI or ERP paradigms, brain responses obtained in VS and MCS patients for stimulations contrasting phonological, lexical, and/or semantic information need to be directly compared with those of aphasic but conscious patients, and this as a function of phonological, lexical, and/or semantic language impairments that have been identified in these patients. A major challenge for conducting these across-patient group studies will be to select the appropriate baseline or control tasks (see also Crosson et al., 2007, for a review of additional methodological concerns for language-related fMRI in patient groups). For example, when identifying semantic processes, brain activation is often compared to a non-semantic linguistic condition such as distorted, meaningless speech stimuli. As we have seen, patients in MCS, whether language impaired or not, will present altered activation in language-processing areas during these baseline conditions or even rest; when contrasting the condition-of-interest to this type of baseline condition, abnormal brain activation patterns might in fact arise due to abnormal activation in the baseline condition, and not necessarily in the experimental condition. A possible solution is to use a nonlinguistic control condition, such as listening to simple environmental sounds and tone stimuli, for which we know that MCS patients present normal activation levels in at least a subset of language-processing areas (Laureys et al., 2000a), and to contrast activity of the language processing condition-of-interest with this nonlinguistic control condition.

With respect to the bedside aphasia assessment protocols we have proposed, their feasibility and sensitivity need to be validated via their administration to representative groups of MCS and aphasic patient groups in order to determine what type of language complexity (phonological, semantic, syntactic) affects verbal communication modes in MCS patients and whether language complexity affects communication in MCS and aphasic patients to the same extent. Similarly, with respect to the adaptations we have proposed for the administration of consciousness assessment scales, existing scales such as the WHIM, the

CRS-R, or the SMART should be screened for linguistic complexity of item formulations, as well as for the possibility to allow for repeated presentation and the use of alternative item presentation modalities (e.g., auditory vs. written item presentation). These scales should also be administered, following standard administration procedures, to fully conscious aphasic patients, in order to determine: (1) the extent to which the scoring of existing behavioral assessment scales is affected by concomitant language impairment, (2) what type of aphasic symptom is most detrimental for the assessment of levels of consciousness, and (3) what behavioral assessment scale is most affected by the patient's language impairment.

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