NEUROPSYCHOLOGICAL REHABILITATION
2005, 15 (3/4), 283–289

Psychology Press
Taylor & Francis Group

Cerebral processing of auditory and noxious stimuli in severely brain injured patients: Differences between VS and MCS

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We review cerebral processing of auditory and noxious stimuli in minimally conscious state (MCS) and vegetative state (VS) patients. In contrast with limited brain activation found in VS patients, MCS patients show activation similar to controls in response to auditory, emotional and noxious stimuli. Despite an apparent clinical similarity between MCS and VS patients, functional imaging data show striking differences in cortical segregation and integration between these two conditions. However, in the absence of a generally accepted neural correlate of consciousness as measured by functional neuroimaging, clinical assessment remains the gold standard for the evaluation and management of severely brain damaged patients.

Vegetative state (VS) is defined by the combination of recurring and prolonged periods of arousal and a lack of behavioural signs of awareness (ANA Committee on Ethical Affairs, 1993; Multi-Society Task Force on

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This research was supported by the Fonds National de la Recherche Scientifique, (FNRS), by the Reine Elisabeth Medical Foundation, by funds of the University of Liège and the Centre Hospitalier Universitaire Sart Tilman, Liège, Belgium, and by a Tom Slick Research Award on Consciousness of the Mind Science Foundation, TX. S. Laureys and P. Maquet are Research Associate and Research Director at the FNRS.

http://www.tandf.co.uk/journals/pp/09602011.html DOI:10.1080/09602010443000371

PVS, 1994). Minimally conscious state (MCS) patients show minimal but definite evidence of self or environment awareness but are unable to communicate (Giacino et al., 2002). Several studies underline the high frequency of misdiagnosis among VS and MCS patients (Andrews, Murphy, Munday, & Littlewood, 1996; Childs, Mercer, & Childs, 1993). Indeed, the bedside assessment of consciousness is intrinsically difficult since it can only rely on behavioural inferences. However, it is important to distinguish MCS from VS, because preliminary findings suggest there are meaningful differences in outcome (Giacino et al., 2002).

Although imaging studies cannot replace the bedside clinical assessment of these disorders of consciousness, they can help to objectively measure the cerebral activity of these patients and how it differs from normal controls. Moreover, it adds to the scientific search for the neural correlates of consciousness. Several functional imaging studies have been performed to investigate cerebral activation in response to external stimulation in VS patients (Menon et al., 1998; Owen et al., 2002; Plum, Schiff, Ribary, & Llinas, 1998; Schiff, Ribary, Plum, & Llinas, 1999; Schiff et al., 2002), yet only a few were performed in minimally conscious state patients (Bekinschtein et al., 2004; Hirsch et al., 2001). We present here recent data comparing brain activation induced by auditory and noxious stimuli in both patient populations.

AUDITORY PROCESSING

Using the $H_2^{15}O$-PET (positron emission tomography) technique, we measured changes in regional cerebral blood flow (rCBF) induced by simple auditory stimuli (clicks) in 5 MCS patients, 15 unsedated VS patients, and 15 controls (Boly et al., 2004). Controls were aged 40 ± 9 years (mean $\pm$ SD; 8 males). VS patients were aged 48 ± 17 years (12 males) and MCS patients 37 ± 12 years (3 males). They were diagnosed according to established criteria (ANA Committee on Ethical Affairs, 1993; Multi-Society Task Force on PVS, 1994, for VS and Giacino et al., 2002, for MCS), and following repetitive neurological examinations and careful anamnesis of family members and medical caregivers. Patients with uncertain diagnoses were excluded. The aetiologies of VS were: cardiorespiratory arrest ($n = 5$), diffuse axonal injury ($n = 3$), drug overdose ($n = 2$), prolonged respiratory insufficiency ($n = 2$), encephalitis with diffuse white matter injury ($n = 2$), and carbon monoxide intoxication ($n = 1$). The aetiologies of MCS were: respiratory arrest ($n = 1$), trauma ($n = 1$), encephalitis ($n = 1$), hypertensive encephalopathy ($n = 1$), and diffuse axonal injury ($n = 1$). All patients had preserved pupillary, corneal and vestibulo-ocular reflexes. Mean Glasgow Coma Scores (GCS); (Teasdale & Jennett, 1974)

on admission were 4.9 $\pm$ 2.5 (range 3–13) for the VS and 5.8 $\pm$ 4.8 (range 3–14) for the MCS patients. Patients were scanned 33 $\pm$ 11 (MCS) and 36 $\pm$ 9 (VS) days after admission, while in awake periods as demonstrated by simultaneous polygraphic recordings.

During the PET data acquisition, scans were performed during rest, (left then right) auditory stimulation, and (left then right) noxious stimulation (results of the latter are described below). Each condition was repeated three times and the order of presentation was pseudorandomised. Scans obtained during left-sided stimulation were flipped. Hence, results should be interpreted as contra- and ipsilateral to the side of stimulation and not as left- or right-sided. PET data were analysed using voxel-based statistical parametrical mapping (SPM, www.fil.ion.ucl.ac.uk/spm). Data from each subject were realigned, normalised into standard stereotaxic space, and smoothed (Friston, 1997). A random-effect analysis was performed, using a two-steps procedure (Holmes & Friston, 1998). The random-effect analysis is a conservative analysis that takes into account intersubject variability, and gives results representative at the population level. A first-level analysis took into account within-subject variances related to the experimental conditions, estimated according to the general linear model at each voxel. Proportional scaling performed global flow normalisation. Primary contrasts estimated the effect of auditory stimulation versus rest in each subject. The "contrast images" obtained were then entered into a second-level analysis, separating the data into three groups (controls, MCS, VS). We then performed two conjunction analyses looking for activation (1) common to controls and VS and (2) common to controls and MCS. We also looked for the groups (MCS–VS) $\times$ condition (stimulation–rest) interaction, searching for areas less activated in VS than in MCS patients. Given our expected activation in superior temporal areas (Laureys et al., 2000), results were thresholded at small-volume-corrected $p < .05$ (20 mm diameter sphere centred on peak voxels).

A functional connectivity analysis (Friston et al., 1997; Laureys et al., 2000) was also performed, to identify areas in which activity was modulated by secondary auditory cortex (Brodmann area 42, peak activation in controls) differently in MCS versus VS patients, using a fixed-effect approach. Such a psychophysiological interaction analysis explains the activity in one cortical area in terms of an interaction between the influence of another area and a given experimental context (i.e., being a vegetative or a minimally conscious patient). A psychophysiological interaction means that the contribution (i.e., regression slope) of one area to another changes significantly with the experimental context assessed with the general linear model as employed by statistical parametric mapping (Friston, 1997). Put simply, our statistical analysis identifies brain regions that show condition-dependent differences in modulation with another (chosen) region (i.e., area 42). As we expected

a large diversity of areas and no a priori areas could be suggested, p values were corrected for multiple comparisons at the cluster- or voxel-level, and results were thresholded at corrected p values $<.05$.

In normal subjects, stimulation increased rCBF bilaterally in areas involved in auditory processing: transverse temporal (Brodmann area 41) and superior temporal gyri (areas 42 and 22) (Figure 1a). VS patients activated bilateral area 41/42, but no significant activation was found in higher order associative area 22 (Figure 1c). The observed preservation of activation in VS patients could reflect a residual neural encoding of basic sound attributes, but with no further functional integration, as suggested in Laureys et al. (2000). In contrast, MCS patients activated similarly to controls (Figure 1b). Functional connectivity analysis showed that MCS, compared to VS, had higher interactions between auditory association area 42 and a wide cortical network known to be involved in normal auditory perception (including temporal and frontal association cortices). The activation of higher order associative cortices in MCS possibly corresponds to a more elaborate auditory processing, thought to be necessary for conscious perception (Baars, Ramsoy, & Laureys, 2003).

We recently also studied an MCS patient using complex auditory stimuli with and without emotional valence (Laureys et al., 2004). We used $H_2^{15}O$-PET imaging and SPM (fixed-effect analysis, results thresholded at uncorrected p-value $<.001$). Compared to meaningless noise, presentation of cries or the patient's own name produced a much more widespread activation, encompassing temporal, parietal and frontal associative areas. During the PET scanning, cognitive evoked potential recording also showed a P300 potential in response to the patient's own name and not to other names.

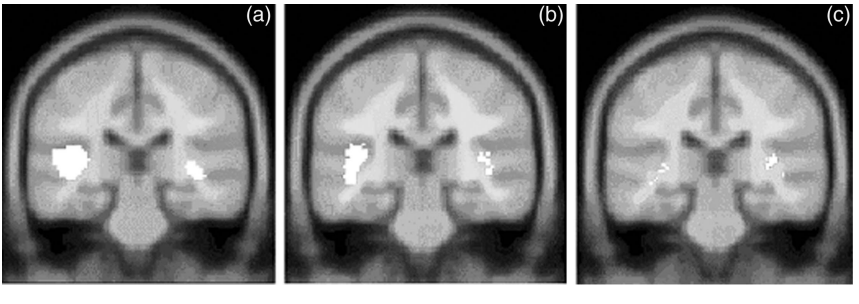

Figure 1. (a): brain areas showing an increase in regional cerebral blood flow during auditory stimulation in controls. (b) and (c): areas of increase of rCBF during auditory stimulation that are common to controls and respectively MCS patients (b) and VS patients (c). Results are projected on a coronal section of a normalised brain MRI template, 28 mm posterior to the anterior commissural line

These data suggest that MCS patients may be capable of extended cerebral processing of auditory stimuli, especially stimuli with emotional valence.

PAIN PROCESSING

Pain sensation is intrinsically a first person subjective experience and its third person evaluation is challenging in subjects that are non-communicative. Several authors have stressed the necessity of a better knowledge of brain activity in response to noxious stimuli in VS and MCS (Klein, 1997; McQuillen, 1991; Multi-Society Task Force on PVS, 1994). Noxious stimulation is also a routine clinical procedure in the bedside assessment of consciousness in brain-damaged patients. We investigated by means of $H_2^{15}O$-PET the cortical responses to noxious electrical stimulation of the median nerve at the wrist in 15 PVS patients compared to 15 controls (Laureys et al., 2002). Demographic data of controls and vegetative patients are reported above. PET data were pre-processed and analysed using SPM (random-effect analysis and functional connectivity analysis, as described above). For the random-effect analysis, three separate analyses were performed: one for the controls, one for VS patients and one interaction analysis looking at the differences of activation between VS patients and controls. Results were thresholded for the controls at whole-volume-corrected p value $<.05$, and for the patients at small-volume corrected p value $<.05$ (20 mm diameter sphere centred on peak voxels). The functional connectivity analysis looked for differences in modulation between primary somatosensory cortex and the rest of the brain in VS patients compared to controls. As we expected a large diversity of areas and no a priori areas could be suggested; results of the psychophysiological analysis were thresholded at $p < .05$ corrected for multiple comparisons.

In controls, painful stimuli activated a large set of areas known to be involved in pain processing: brainstem, thalamus, primary and secondary somatosensory cortex, insula, posterior parietal, superior temporal and anterior cingulate cortices. VS patients, despite their severe cerebral metabolic impairment, still activated brainstem, thalamus and primary somatosensory cortex. However, the functional connectivity analysis showed extended functional disconnections between primary somatosensory cortex and fronto-parietal association cortices in VS patients compared to controls. As previously described for auditory stimuli, the activation of primary somatosensory cortex in vegetative state patients was thus isolated and dissociated from higher-order associative cortices.

In sharp contrast to the VS, preliminary findings in an MCS patient show a close to normal neural activation in response to noxious stimulation. Most importantly, the MCS patient showed activation of the anterior cingulate

cortex. This region is well known to be involved in pain unpleasantness or affect (Rainville et al., 1997).

CONCLUSION

Despite an apparent clinical similarity between MCS and VS, functional imaging data show striking differences in cortical segregation and integration between these two conditions. The extent of activation found in MCS patients in response to both auditory and noxious stimulation likely allows them to reach a certain level of sensory and affective perception. However, it is important to stress that these PET results were obtained at the population level and some individual VS patients may show more elaborate cerebral activation, especially when complex and meaningful stimuli are used. Cognitive evoked potential studies have indeed shown that stimulation complexity influences cerebral responsiveness in VS and MCS patients (Kotchoubey et al., 2003). Finally, in the absence of a complete understanding of the neural correlate necessary and sufficient for conscious perception it remains difficult to interpret functional imaging data in brain damaged patients as proof or disproof of their consciousness.

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