EDITORIAL

Functional imaging to uncover willful brain behavior in noncommunicative patients

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Functional neuroimaging probes the regional distribution of neuronal activity, opening a window on brain dysfunction. This opportunity is particularly suited to the evaluation of disorders of consciousness (DOC), which are not reliably assessed by clinical observation and behavioral testing. The article by Monti et al.[1] in this issue of *Neurology*® illustrates this potential; it reports the application of fMRI to uncover signs of high-level cognitive processes in a sample of 28 patients. The authors employ a simple target detection task that requires both selective and sustained attention to be completed accurately in healthy participants (from whom subjective conscious reports can validate performance). Patients were instructed to count the number of times a target word was presented. The target words chosen were neutral (by standardized criteria for English language words), and individualized and randomized for each patient, eliminating any systematic influence of the word itself outside of a contingent relationship to the spoken instruction, "count." The counting condition was compared to a passive listening condition.

Remarkably, 3 out of 8 patients clinically judged as in a vegetative state (VS) demonstrated task responses; 6 out of 16 in a minimally conscious state (MCS) and 1 out of 4 emerged from MCS showed a task response. These findings reinforce 2 crucially important clinical implications for the practicing neurologist: (1) along with other recent studies,[2] the results demonstrate that clinical assessments of patients with severe brain injuries often cannot discriminate large differences in underlying integrative brain function; and (2) conversely, the findings highlight that sophisticated functional neuroimaging techniques can fail to identify the capacity to deploy high-level integrative brain functions in patients in whom this capacity appears indisputable on bedside examination.[3] As such, this work adds an important, cleanly constructed tool for the study of DOC and supports growing evidence of the generalizability of its results.[2]

This study takes an additional step toward underlying mechanistic differences in brain activity between patients showing positive task responses and those who did not by employing a statistical technique, psycho–physiologic interaction analysis (PPI). Using PPI, the investigators focused on the role of thalamocortical activation in producing the "top-down" cognitive control necessary to sustain the counting condition.[1] Patient responders demonstrated an increase in the functional connectivity between the anteriomedial thalamus (including the median dorsalis, anterior thalamic nucleus, and perforce rostral extensions of the intralaminar nuclei) and the prefrontal cortex compared to nonresponders.

Taken together with the wide variation in clinical diagnoses across the responder group, the connectivity findings pave the way for a better characterization of fundamental neurophysiologic processes underlying residual cognitive capacities in DOC (4–8). The preponderance of VS responders in this and other studies likely has a simple and intuitive explanation: as motor function is increasingly impaired, misdiagnosis of cognitive capacity is more likely. Accordingly, as the integrity of the corticothalamic system, particularly of the anterior forebrain mesocircuit,[4] becomes the focus of investigations, we should expect better clinical–physiologic correlations between neuronal activity and handling of cognitive demand, even for simple attentional tasks.[5]

A limitation impeding the widespread use of functional neuroimaging for DOC evaluation is the lack of external gold standard that would support the diagnostic value of neuroimaging for "signs of consciousness" detection. So, validation remains "internal"; the proof of responsiveness or consciousness comes from the findings themselves, generally through comparisons with healthy persons. Absence of external validation lessens the confidence in data interpretation of this kind, and in its clinical application. Therefore, there is a need for strict criteria to interpret neuroimaging data in terms of "demonstrating a state of consciousness," or uncovering "willful brain

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behavior" or "voluntary top-down process" (phrases from reference 1).

There is an obvious constraint with the present methodology: we cannot challenge an unresponsive patient without external stimulations. Despite efforts to reach similarity in the physical aspects of the stimulation, studies comparing cerebral reactions to various stimulations might involve "bottom-up" effects leading to differences in cerebral activity distribution. Therefore, it seems mandatory that differences detected in DOC patients are in line with the expected neuronal processes involved. This holds true even if plasticity and compensatory processes make brain activity vary according to the injury and the response to it. Also, the resting active network, the default mode network, is deactivated during tasks,[6] and there are disturbances in this network in DOC,[7] so it would be valuable to provide deactivation maps when comparing activity distribution of DOC patients studied in differing conditions.

Another limitation is the concern that studies carried out in specialty research centers may not truly reflect the wider DOC patient population, a fundamental issue in the era of evidence-based medicine. Most studies on functional imaging in DOC are carried out over years (2.5 years in reference 1), and enrolled patients are selected by health institutions referring patients to a specialized center where the neuroimaging study is conducted (3 large referring institutions in reference 1). Obviously, this mode of selection likely introduces biases that could affect outcomes. For instance, motivation for referring some patients and not others to the expert center might reflect underlying doubts about the actual status of the patient. When rigorous selection procedures are not adopted, it is hazardous to generalize the conclusions to the whole DOC population, as cautiously stated by Monti et al.[1] In particular, prevalence of residual consciousness in unresponsive patients remains to be estimated in well-designed studies.

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