OPEN

Functional Neuroimaging in Patients With Disorders of Consciousness: Caution Advised

Prognostication in patients with disorders of consciousness is a complex clinical problem, which can be impacted by multiple factors. The current approach to the assessment of patients with disorders of consciousness involves standardized behavioral examinations. Functional neuroimaging investigates evidence of neural responses in the absence of behavioral signs. In 2006, the earliest study reporting the use of neuroimaging in a patient with disordered consciousness used a functional magnetic resonance imaging (fMRI) mental imagery task to suggest the presence of residual cognitive capability in a patient diagnosed as being in a vegetative state, now referred to as unresponsive wakefulness state.[1] Since then, fMRI[2] and electroencephalography (EEG)[3] have been used to provide evidence of preserved cognitive processes in patients in varying states of consciousness. These and other studies have helped to define cognitive motor dissociation (evidence of command following during a motor imagery task)[4] and higher-order cortex motor dissociation (association cortex responses during language and music stimuli).[5]

Most recently, the optical neuroimaging technique functional near-infrared spectroscopy (fNIRS) has been used to investigate neural responses in patients with disorders of consciousness.[6] fNIRS measures the hemodynamic response to neural activity using a method similar to pulse oximetry. It uses multiple sources and detectors (optodes) to noninvasively measure the absorption of near-infrared light through the skull and produce maps of regional cerebral oxygenation. Like fMRI, fNIRS measures the dynamics of oxygen delivery resulting from localized neuronal activation.[7] Simultaneous EEG-fNIRS studies deliver the possibility of a direct bedside measure of neurovascular coupling,[8] and multimodal (although not necessarily simultaneous) imaging protocols are now being proposed for use in patients with disorders of consciousness. Kazazian et al[9] described a protocol, which will combine fMRI, EEG, and fNIRS studies across the first 10 days postinjury in 350 acutely brain-injured patients, with follow-up imaging at 12 months. The physiological signals measured by fMRI, EEG, and fNIRS as well as other factors relevant to the clinical use of these techniques are shown in Table 1.

It is clear that functional neuroimaging technologies are contributing new perspectives to the assessment of disorders of consciousness beyond those accessible through clinical behavioral assessments.[10] To date, studies have broadly been limited to clinical settings with the appropriate level of technical expertise and support infrastructure. However, continuing innovations in, and the availability of, low-cost wearable neuroimaging technologies (especially fNIRS) are likely to expand their use when studying patients in the acute and chronic phases of disordered consciousness. It is, therefore, timely to consider the array of context-specific challenges in data acquisition, analysis, and interpretation presented by the advent of this new horizon of functional neuroimaging, and to provide recommendations for addressing these challenges.

DATA ACQUISITION

The choice of imaging technique is informed by multiple factors including availability, cost, practical implementation in the required clinical setting, and the condition of the patient (Table 1). EEG and fNIRS are seen as more practical and cost-efficient alternatives to fMRI (also negating the need for transfer to a neuroimaging suite) with EEG providing a direct (rather than vascular-based) marker of neural activity. However, EEG measures can be impacted by electrically noisy environments, especially in the intensive care unit. The accuracy of fNIRS measurements can be influenced by intracranial blood, cerebral edema, blood contamination of the cerebrospinal fluid, and skull integrity, all of which alter the optical geometry of the head. Moreover, even with the improved engineering of wearable systems, head movement, jaw clenching, and changes to the coupling of EEG electrodes and fNIRS optodes with the skull surface will produce signal artifacts, which may be stimulus-related.

Study protocols for eliciting neuronal responses have necessarily been derived from those tested in small cohorts of healthy participants, so special consideration must be given to their translation into clinical studies of disorders of consciousness. To enable cross-study comparisons, protocols need to be standardized while also being linguistically, culturally, and clinically appropriate for individual patients (eg, those with dementia, deafness, aphasia, pain, and delirium).

Data Analyses

The analysis of functional neuroimaging data presents specific challenges even under the controlled environment of studies in healthy volunteers. Standardized and validated analysis pipelines are essential to deal with movement artifacts, stimulus-related changes in systemic physiology (eg, scalp blood flow and blood pressure, which impact fNIRS measures), and inadequate signal-to-noise. Determining statistically

The author has no conflicts of interest to declare.

Address correspondence to: Clare Elwell, PhD. E-mail: c.elwell@ucl.ac.uk.

DOI: 10.1097/ANA.0000000000000920

TABLE 1. Comparison of Three Functional Neuroimaging Techniques

	fMRI	EEG	fNIRS
Physiological signal measured	BOLD	Potential difference	ΔHbO_2 and ΔHHb
Penetration depth	Whole head	Brain cortex	Brain cortex
Spatial resolution (cm)	0.3 mm voxels	5-9	2-3
Temporal resolution (Hz)	1-3	> 1000	Up to 10
Limitations for use in clinical settings	Metal implants/pacemakers/transfer to imaging suite	Electrically noisy environments	Brain injury-related changes in optical geometry
Wearable	No	Yes	Yes
Cost	High	Low	Low

BOLD indicates blood oxygenation level-dependent; EEG, electrocorticography; fMRI, functional magnetic resonance imaging; fNIRS, functional near-infrared spectroscopy; HbO_2, oxyhemoglobin; HHb, deoxyhemoglobin.

significant findings at a group level in conscious volunteers and extrapolating these to an individual patient in a potentially dynamic state of arousal and consciousness are nontrivial. Advanced machine and deep learning techniques may aid the extraction of meaningful and reliable neuronal responses in patients with disorders of consciousness, but the scarcity of available data from these types of clinical studies impacts their usefulness in the short term.

Data Interpretation and Impact on Clinical Decision Making

The medical and ethical considerations of using functional imaging techniques for prognostication in patients with disorders of consciousness are wide-ranging.[11] The relationship between cognitive motor dissociation or higher order cortex motor dissociation with consciousness or potential for consciousness remains unclear, especially when ~25% of healthy participants do not demonstrate the expected functional neuroimaging responses when performing motor imagery tasks.[5] More recent studies have used functional neuroimaging data to suggest the reclassification of patients from the unresponsive wakefulness state to a minimally conscious state and/or the introduction of the classification of minimally conscious state* to denote a dissociation between behavioral diagnosis and neuroimaging findings.[12]

Of utmost importance is the impact of functional neuroimaging on the ongoing management of patients with disorders of consciousness and, specifically, the likelihood of functional neuroimaging being used to guide time-sensitive decisions regarding withdrawal of life-sustaining treatment or provision of neurorehabilitation services. The limited outcome data from current studies impedes the prognostic value of functional neuroimaging data in this context, especially when one study in a relatively large (n = 16) cohort of patients found no association between early fMRI and EEG responses and 6-month outcomes.[5] Evidence of neural responses on functional imaging may delay decisions to withdraw treatment and allow more time to assess recovery potential. In contrast, functional neuroimaging findings may make it more likely that life-sustaining treatment is continued even if the potential for a degree of recovery that would be acceptable to the patient (which will differ between individuals) has not changed. Moreover, in an environment of prognostic uncertainty, relatives can view the technological intervention of functional neuroimaging as a magic bullet of recovery prediction, so communication about the potential impact, or not, on the clinical management of their loved one must be handled carefully.

Opportunities for Future Research

As with all translation research, impactful clinical advances depend upon close collaboration and meaningful two-way communication between disciplines. In this case, physicists and engineers developing functional neuroimaging technologies and clinical specialists managing patients with disorders of consciousness must work together to ensure sufficient attention is paid to the clinical context and consequences of the functional neuroimaging measures, as well as to the methodological, implementation and data interpretation issues associated with the different technologies.

As innovations in the bioengineering of neuroimaging systems focus on democratizing how, when, and where the brain can be imaged, we should also acknowledge the need for systems to be optimized for specific clinical applications and for data analysis and interpretation methods to be aligned for specific patient groups. In addition, there is a clear need for appropriately funded multicentre outcome studies, which should focus on the relationship between evidence of covert consciousness and meaningful functional outcomes.

Much work is needed to understand the role of functional neuroimaging in the clinical management of patients with disorders of consciousness before these techniques can be used to reliably guide prognostication. Although functional neuroimaging has real potential in this area, caution is advised. The stakes for this new era of brain imaging and the patients it may serve are high.

Clare Elwell, PhD
Department of Medical Physics and Biomedical Engineering, University College London, UK

REFERENCES

1. Owen A, Coleman M, Boly M, et al. Detecting awareness in the vegetative state. *Science*. 2006;313:1401. doi:10.1126/science.1130197

2. Kazazian K, Norton L, Gofton T, et al. Cortical function in acute severe traumatic brain injury and at recovery: a longitudinal fMRI case study. *Brain*. 2020;10:604. doi:10.3390/brainsci10090604
3. Claassen J, Doyle K, Matory A, et al. Detection of brain activation in unresponsive patients with acute brain injury. *N Engl J Med*. 2019;380:2497–2505. doi:10.1056/NEJMoa1812757
4. Schiff N. Cognitive motor dissociation following severe brain injuries. *JAMA Neurol*. 2015;72:1413–1415. doi:10.1001/jamaneurol.2015.2899
5. Edlow B, Chatelle C, Spencer C, et al. Early detection of consciousness in patients with acute severe traumatic brain injury. *Brain*. 2017;140:2399–2414. doi:10.1093/brain/awx176
6. Chen H, Miao G, wang S, et al. Disturbed functional connectivity and topological properties of the frontal lobe in minimally conscious state based on resting-state fNIRS. *Front Neurosci*. 2023;17:1118395. doi:10.3389/fnins.2023.1118395
7. Pinti P, Tachtsidis I, Hamilton A, et al. The present and future of functional near-infrared spectroscopy (fNIRS) for cognitive neuroscience. *Ann NY Acad Sci*. 2020;1464:5–29. doi:10.1016/j.cobme.2017.09.011
8. Othman M, Bhattacharya M, Moller K, et al. Resting -state NIRS-EEG in unresponsive patients with acute brain injury: a proof-of-concept study. *Neurocrit Care*. 2021;34:31–44. doi:10.1007/s12028-020-00971-x
9. Kazazian K, Norton L, Laforge G, et al. Improving diagnosis and prognosis in acute severe brain injury: a multimodal imaging protocol. *Front Neurol*. 2023;12:757219. doi:10.3389/fneur.2021.757219
10. Alnagger N, Cardone P, Martial C, et al. The current and future contribution of neuroimaging to the understanding of disorders of consciousness. *Presse Med*. 2023;52:104163. doi:10.1016/j.lpm.2022.104163
11. Rohaut B, Eliseyev A, Claassen J. Uncovering consciousness in unresponsive ICU patients: technical, medical and ethical considerations. *Crit Care*. 2019;23:78. doi:10.1186/s13054-019-2370-4
12. Thibaut A, Panda R, Annen J, et al. Preservation of brain activity in unresponsive patients identifies MCS star. *Ann Neurol*. 2021;90: 89–100. doi:10.1002/ana.26095

Journal of Neurosurgical Anesthesiology Editorial Board

On behalf of the *Journal of Neurosurgical Anesthesiology* Editorial team, I would like to acknowledge the contributions of colleagues who have recently retired from the Editorial Board after many years of service to the journal: Drs Federico Bilotta, Ansgar Brambrink, Ian Herrick, Vesna Jevtovic-Todorovic, Masahiko Kawaguchi, and Irene Rozet. Their contributions have been pivotal to the development and governance of JNA, and I thank them for their service to the journal and to our specialty.

I also take this opportunity to welcome the following new members of the Editorial Board: Drs William Gross, Laura Hemmer, Amie Hoefnagel, Bhiken Naik, and Matt Whalin. I am grateful for their willingness to take on this important role among their many other commitments, and look forward to working with them over the next 3 years.

Martin Smith
Editor-in-Chief

The author has no conflicts of interest to disclose.
DOI: 10.1097/ANA.0000000000000924

