Unmasking Covert Language Processing in the Intensive Care Unit with Electroencephalography

For patients with severe brain injuries in the intensive care unit (ICU), consciousness can be present in the absence of purposeful responses on bedside examination.[1,2] If consciousness goes undetected, clinicians can render an inaccurate, pessimistic prognosis, increasing the risk that life-sustaining therapy is withdrawn for a patient who had the potential for neurological recovery. Withdrawal of life-sustaining therapy is a leading cause of death in ICU patients with severe traumatic brain injury and hypoxic–ischemic injury,[3,4] and early re-emergence of consciousness is a primary determinant of decisions regarding withdrawal of life-sustaining therapy.[5] Detection of consciousness in the ICU thus has time-sensitive, life-or-death consequences.

The prognostic relevance of early detection of consciousness in the ICU has been demonstrated primarily using behavioral examination.[6] The first signs of re-emergence of consciousness are typically visual fixation, gaze tracking, and pain localization,[7] but multiple confounders limit the behavioral examination, including pain, immobility from polytrauma, and disruption of central or peripheral motor pathways. Furthermore, patients may require continuous sedation or tolerate only brief, intermittent examinations owing to elevations in intracranial pressure, ventilator dyssynchrony, or bronchospasm. To circumvent these limitations, advanced electrophysiologic and neuroimaging tests have been developed to detect covert consciousness (ie, cognitive motor dissociation[8]), which is present in approximately 15% of patients[9] whose behavioral examination suggests a vegetative state (also known as unresponsive wakefulness syndrome). Task-based electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) protocols initially developed for patients with subacute-to-chronic disorders of consciousness (DoC)[10–13] are now being deployed in the ICU for patients with acute DoC.[1,2] The recent observation that early detection of covert consciousness using task-based EEG predicts 1-year functional recovery[2] suggests that covert consciousness has similar prognostic relevance to overt consciousness in the ICU.

Nonetheless, task-based EEG and fMRI protocols pose substantial cognitive demands on critically ill patients, as evidenced by high false-negative rates in patients who are able to follow commands on behavioral examination but not on task-based EEG or fMRI.[1] Even in healthy volunteers, the false-negative rate for task-based EEG and fMRI motor imagery protocols (ie, "imagine opening and closing your hand") is as high as 25%.[1,12] This high false-negative rate raises the possibility that consciousness might evade detection by behavioral examination and task-based EEG or fMRI protocols in some critically ill patients. Moreover, task-based EEG and fMRI require infrastructure and personnel that are currently unavailable at most hospitals, limiting their clinical utility and generalizability.

The cognitive demand, high false-negative rate, and limited generalizability of task-based protocols provide motivation for the ground-breaking study by Sokoliuk and colleagues[14] published in this issue of *Annals of Neurology*. The authors developed an EEG protocol that probes language function under passive stimulation, free of any task instruction. Specifically, the EEG protocol interrogates electrophysiologic responses to three levels of stimulus integration (single words, phrases, and whole sentences) according to frequency tagging in spectral EEG decomposition space. Crucially, all supra-single word information was removed from the stimuli (eg, there is no prosody effect related to phrase or sentence structure) to isolate the syntactico-semantic level of integration. This hierarchical language EEG protocol was performed in 28 critically ill patients with severe traumatic brain injury who were unresponsive on bedside examination. The key finding of the study is that EEG responses to language in the ICU were correlated with 3- and 6-month outcomes, as assessed by the Glasgow Outcome Scale-Extended. The EEG responses accounted for variance in outcomes beyond that accounted for by standard clinical predictors, such as the Glasgow Coma Scale score and head computed tomography scan. These results provide initial evidence that the response of a patient to a language stimulus in the ICU might predict long-term functional outcomes.

This elegant and promising study capitalizes on four previous findings. First, Tononi and colleagues[15] used frequency tagging in a binocular rivalry (ie, they used 1 time–frequency for each eye) while recording magnetoencephalography signals to probe cortical networks oscillating at the frequency of the consciously perceived stimulus. Second, fMRI and EEG studies conducted in healthy controls and in patients with DoC showed that hierarchical protocols can be used to investigate cortical networks engaged in processing linguistic structures, ranging from single words to phrases and sentences, in both the visual and auditory modalities.[16–19] Third, fMRI studies revealed that probing residual linguistic abilities can improve the accuracy of detecting and predicting recovery of consciousness in patients with DoC.[16] However, most of these studies, in particular those using EEG, were limited by the weakness of the reported effects.[18,19] Fourth, Ding and colleagues[20] combined frequency tagging and hierarchical linguistic structures to design the protocol used in the present study. The present results are also strengthened by a recent independent study that reported robust EEG results using a similar approach.[21]

From a neuroscientific perspective, the new findings by Sokoliuk and colleagues[14] raise important questions about the neural correlates of consciousness in the human brain.[22] Although the unmasking of cortical responses to integrated and complex linguistic stimuli clearly demonstrates the existence of high-level cognitive functions, it does not translate unequivocally in terms of conscious versus unconscious processing and state.[23,24] Activation of language networks for stimuli inaccessible to conscious self-report has been shown reliably in healthy conscious participants (eg, visual masking or attentional blink paradigms) and in patients with neurological conditions, such as left unilateral neglect.[25] More generally, the existence of cortical processing is a necessary but insufficient condition for consciousness. Cortically mediated behaviors and cognitions are not necessarily conscious, either in healthy conscious participants or in patients with DoC.[26] This is why a passive neuronal response is insufficient or equivocal, whereas active, volitional modulation of brain activity provides direct and unequivocal proof of consciousness. Indeed, the concept of covert consciousness (ie, cognitive motor dissociation) emerged from task-based fMRI and EEG studies that demonstrated active, willful modulation of brain activity.[10–13] In contrast, the passive response of the brain to a language stimulus in patients with DoC[1,16,27] or in healthy subjects undergoing anesthesia[17] has been interpreted historically as providing evidence of perception, but not necessarily of conscious comprehension.

From a clinical-translational perspective, the present findings raise the possibility that EEG-based tests for "covert cortical processing"[28] might have a role in ICU prognostication. Although the results of this single-center study will need to be replicated in larger, multi-center studies, the test proposed by Sokoliuk and colleagues[14] is safe, low cost, and feasible to perform at the bedside in the ICU. Even if test characteristics such as sensitivity and specificity for outcome prediction have yet to be elucidated fully, it is not too soon to consider the clinical and ethical implications of implementing this prognostic technique, in addition to similar EEG- and fMRI-based techniques, in the ICU.[5,29,30] The limitations of current prognostic models for individual patients with acute severe traumatic brain injury are well established,[28,31] because demographic, examination, and conventional neuroimaging data do not account for the large variance in outcomes. Given the time sensitivity and life-or-death stakes of early prognostication in the ICU, the potential clinical role of advanced prognostic techniques is being debated actively.[32]

Implementation of advanced electrophysiologic and neuroimaging techniques in the diagnostic classification of states of consciousness is rapidly gaining acceptance, culminating in the incorporation of these techniques into recently published clinical guidelines for patients with DoC.[33–35] In this context, the new study by Sokoliuk and colleagues[14] highlights the urgent need to create a new taxonomy for assessing states of consciousness in patients with DoC that combines expert behavioral examination with advanced measures of brain activity.

Acknowledgement

Dr Edlow is supported by grants from the National Institutes of Health (DP2HD101400, R21NS109627, and RF1NS115268), James S. McDonnell Foundation, and Tiny Blue Dot Foundation.

Author Contributions

The authors contributed equally to this work.

Potential Conflicts of Interest

Nothing to report.

Brian L. Edlow, MD

Center for Neurotechnology and Neurorecovery, Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA

Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA

Lionel Naccache, MD, PhD
PICNIC Lab Team, INSERM, U 1127, CNRS UMR 7225, Faculté de Médecine de Sorbonne Université, UMR S 1127, Institut du Cerveau et de la Moelle épinière, ICM, Hôpital Pitié-Salpêtrière, Paris, France
APHP, Departments of Neurology and of Clinical Neurophysiology, Hôpital de la Salpêtriere, Paris, France
Address correspondence to E-mail: bedlow@mgh.harvard.edu
[Correction added on 19 February, 2021, after first online publication: The copyright line was changed.]

References

1. Edlow BL, Chatelle C, Spencer CA, et al. Early detection of consciousness in patients with acute severe traumatic brain injury. Brain 2017;140:2399–2414.
2. 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.
3. Turgeon AF, Lauzier F, Simard JF, et al. Mortality associated with withdrawal of life-sustaining therapy for patients with severe traumatic brain injury: a Canadian multicentre cohort study. CMAJ 2011; 183:1581–1588.
4. Elmer J, Torres C, Aufderheide TP, et al. Association of early withdrawal of life-sustaining therapy for perceived neurological prognosis with mortality after cardiac arrest. Resuscitation 2016 May;102: 127–135.
5. Fins JJ. *Rights come to mind: brain injury, ethics, and the struggle for consciousness*. New York, NY: Cambridge University Press, 2015.
6. Giacino JT, Kalmar K. The vegetative and minimally conscious states: a comparison of clinical features and functional outcome. J Head Trauma Rehabil 1997;12:36–51.
7. Schnakers C, Vanhaudenhuyse A, Giacino J, et al. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. BMC Neurol 2009;9:35.
8. Schiff ND. Cognitive motor dissociation following severe brain injuries. JAMA Neurol 2015;72:1413–1415.
9. Kondziella D, Friberg CK, Frokjaer VG, et al. Preserved consciousness in vegetative and minimal conscious states: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2016;87:485–492.
10. Owen AM, Coleman MR, Boly M, et al. Detecting awareness in the vegetative state. Science 2006;313:1402.
11. Monti MM, Vanhaudenhuyse A, Coleman MR, et al. Willful modulation of brain activity in disorders of consciousness. N Engl J Med 2010;362:579–589.
12. Cruse D, Chennu S, Chatelle C, et al. Bedside detection of awareness in the vegetative state: a cohort study. Lancet 2011;378: 2088–2094.
13. Goldfine AM, Victor JD, Conte MM, et al. Determination of awareness in patients with severe brain injury using EEG power spectral analysis. Clin Neurophysiol 2011;122:2157–2168.
14. Sokoliuk R, Degano G, Banellis L, et al. Covert speech comprehension predicts recovery from acute unresponsive states. Ann Neurol. 2021.
15. Tononi G, Srinivasan R, Russell DP, Edelman GM. Investigating neural correlates of conscious perception by frequency-tagged neuromagnetic responses. Proc Natl Acad Sci U S A 1998;95: 3198–3203.
16. Coleman MR, Davis MH, Rodd JM, et al. Towards the routine use of brain imaging to aid the clinical diagnosis of disorders of consciousness. Brain 2009;132:2541–2552.
17. Davis MH, Coleman MR, Absalom AR, et al. Dissociating speech perception and comprehension at reduced levels of awareness. Proc Natl Acad Sci U S A 2007;104:16032–16037.
18. Rohaut B, Faugeras F, Chausson N, et al. Probing ERP correlates of verbal semantic processing in patients with impaired consciousness. Neuropsychologia 2015;66:279–292.
19. Cruse D, Beukema S, Chennu S, et al. The reliability of the N400 in single subjects: implications for patients with disorders of consciousness. Neuroimage Clin 2014;4:788–799.
20. Ding N, Melloni L, Zhang H, et al. Cortical tracking of hierarchical linguistic structures in connected speech. Nat Neurosci 2016;19: 158–164.
21. Gui P, Jiang Y, Zang D, et al. Assessing the depth of language processing in patients with disorders of consciousness. Nat Neurosci 2020;23:761–770.
22. Koch C, Massimini M, Boly M, Tononi G. Neural correlates of consciousness: progress and problems. Nat Rev Neurosci 2016;17: 307–321.
23. Naccache L. Why and how access consciousness can account for phenomenal consciousness. Philos Trans R Soc Lond B Biol Sci 2018; 373:20170357.
24. Cohen MA, Dennett DC. Consciousness cannot be separated from function. Trends Cogn Sci 2011;15:358–364.
25. Naccache L. Visual consciousness explained by its impairments. Curr Opin Neurol 2015;28:45–50.
26. Naccache L. Minimally conscious state or cortically mediated state? Brain 2018;141:949–960.
27. Braiman C, Fridman EA, Conte MM, et al. Cortical response to the natural speech envelope correlates with neuroimaging evidence of cognition in severe brain injury. Curr Biol 2018;28:3833–3839.
28. Edlow BL, Claassen J, Schiff ND, Greer DM. Recovery from disorders of consciousness: mechanisms, prognosis and emerging therapies. Nat Rev Neurol 2020. https://doi.org/10.1038/s41582-020-00428-x
29. Edlow BL, Fins JJ. Assessment of covert consciousness in the intensive care unit: clinical and ethical considerations. J Head Trauma Rehabil 2018;33:424–434.
30. Rohaut B, Eliseyev A, Claassen J. Uncovering consciousness in unresponsive ICU patients: technical, medical and ethical considerations. Crit Care 2019 Mar 9;23:78.
31. Dijkland SA, Retel Helmrich IRA, Nieboer D, et al. Outcome prediction after moderate and severe traumatic brain injury: external validation of two established prognostic models in 1742 European patients. J Neurotrauma 2020 Nov 9. https://doi.org/10.1089/neu.2020.7300
32. Provencio JJ, Hemphill JC, Claassen J, et al. The curing coma campaign: framing initial scientific challenges-proceedings of the first curing coma campaign scientific advisory council meeting. Neurocrit Care 2020 Aug;33:1–12.
33. Giacino JT, Katz DI, Schiff ND, et al. Practice guideline update recommendations summary: disorders of consciousness: report of the guideline development, dissemination, and implementation Subcommittee of the American Academy of neurology; the American congress of rehabilitation medicine; and the National Institute on Disability, Independent Living, and Rehabilitation Research. Neurology 2018 Sep 4;91:450–460.
34. Kondziella D, Bender A, et al. European academy of neurology guideline on the diagnosis of coma and other disorders of consciousness. Eur J Neurol 2020 May;27:741–756.
35. Comanducci A, Boly M, Claassen J, et al. Clinical and advanced neurophysiology in the prognostic and diagnostic evaluation of disorders of consciousness: review of an IFCN-endorsed expert group. Clin Neurophysiol 2020 Nov;131:2736–2765.