Measuring Consciousness in the Intensive Care Unit

Brian L. Edlow, MD[1,2], **Matteo Fecchio, PhD**[1], **Yelena G. Bodien, PhD**[1,3], **Angela Comanducci, MD**[4,5], **Mario Rosanova, MD, PhD**[6], **Silvia Casarotto, PhD**[4,6], **Michael J. Young, MD, MPhil**[1], **Jian Li, PhD**[1,2], **Darin D. Dougherty, MD, MSc**[2,7], **Christof Koch, PhD**[8,9], **Giulio Tononi, MD, PhD**[10], **Marcello Massimini, MD, PhD**[4,6], **Melanie Boly, MD, PhD**[11]

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

[2]Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Charlestown, MA, USA

[3]Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital and Harvard Medical School, Charlestown, MA, USA

[4]IRCCS, Fondazione Don Carlo Gnocchi Onlus, Milan, Italy

[5]Università Campus Bio-Medico di Roma, Rome, Italy

[6]Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy

[7]Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

[8]MindScope Program, Allen Institute, Seattle, WA, USA

[9]Tiny Blue Dot Foundation, Santa Monica, CA, USA

[10]Department of Psychiatry, University of Wisconsin-Madison, Madison, WI, USA

[11]Department of Neurology, University of Wisconsin-Madison, Madison, WI, USA

Abstract

Early reemergence of consciousness predicts long-term functional recovery for patients with severe brain injuries. However, tools to reliably detect consciousness in the intensive care unit (ICU) are lacking. Transcranial magnetic stimulation-electroencephalography has the potential

Corresponding author: B.L. Edlow, bedlow@mgh.harvard.edu.

to detect consciousness in the ICU, predict recovery, and prevent premature withdrawal of life-sustaining therapy.

Introduction

In intensive care units (ICUs) around the world, patients with severe brain injuries lie in bed, unresponsive, connected to life-sustaining ventilators and brain monitors. Within days of injury, clinicians assess each patient's chances for long-term recovery and provide families with a prognosis upon which decisions about life-sustaining therapy are made. Early recovery of consciousness is a key milestone that predicts long-term functional recovery [1–4]. However, because consciousness (in the sense of having an experience) is inherently subjective [5], it can be difficult to measure operationally and may go unrecognized in some patients [6]. Of the millions of people globally who experience a severe brain injury each year [7, 8], 15–20% may be covertly conscious, with higher levels of consciousness than their bedside behavioral assessment suggests [3, 6]. Either due to pain, sedation, or injury to central and peripheral motor pathways, a conscious individual's capacity for self-expression may be compromised. In this setting, it is essential that tools are developed to detect signs of consciousness (diagnosis) and provide families with an accurate picture of their loved ones' chances of functional recovery (prognosis).

To address this challenge, multiple advanced neurotechnologies have been developed over the past two decades, shedding new light on the physiology of consciousness and coma recovery. Yet reliable assessment of consciousness in the ICU remains elusive. Resting-state functional MRI studies reveal brain networks necessary for consciousness [5], but no single network is sufficient [9]. EEG studies demonstrate that coherence and entropy correlate with consciousness [10], but consciousness can emerge across a broad range of EEG spectral patterns [11]. Task-based functional MRI (fMRI) and EEG detect volitional brain activity [3, 4, 6] but suffer from high false-negative rates (i.e., failing to detect command-following in a conscious individual) [6, 12] and are challenging to implement in the ICU.

It is against this historical backdrop that transcranial magnetic stimulation (TMS)-EEG measurement of brain complexity becomes relevant for clinical translation in the ICU (Figure 1). Inspired by theoretical principles [13–15], TMS-EEG gauges, as a proxy for consciousness, the ability of distributed and differentiated groups of neurons to interact as a whole to produce complex dynamics. Growing evidence supports the notion that brain complexity – defined as the coexistence of differentiation and integration in the thalamocortical network – is a reliable marker of consciousness [16, 17]. Repeated administration of a brief TMS pulse to the cerebral cortex triggers a long-lasting (~300 milliseconds) brain-wide response whose complexity can be measured by EEG and quantified as the perturbational complexity index (PCI) [18]. The PCI value is normalized,

with 0 corresponding to the absence of statistically significant EEG response, and 1 being maximally complex.

Over the past 10 years, PCI values above an empirically derived threshold (PCI > 0.31) have identified consciousness with 100% specificity and 100% sensitivity in a validation dataset of 48 conscious brain-injured patients and 102 healthy subjects across a broad range of behavioral states, including resting wakefulness, anesthesia, slow-wave sleep and REM sleep [18, 19]. That is, whenever PCI ≤ 0.31, the subject is either in a deep sleep or anesthetized, while PCI > 0.31 corresponds to full consciousness, REM sleep with report of dreams, or a dissociative state with preserved self-awareness (i.e., ketamine). Furthermore, TMS-EEG measurements of PCI detect high complexity in > 90% of severely brain-injured patients who have recovered behaviorally to a minimally conscious state [19], as compared to a ~60% detection rate with task-based fMRI and EEG motor imagery paradigms [6]. This unparalleled performance motivates the translation of TMS-EEG to the ICU as a tool to measure consciousness – a first, albeit primitive, consciousness-detector [20].

Detecting Signs of Consciousness

TMS-EEG provides four diagnostic advantages over resting-state and task-based methods to assess consciousness. First, TMS-EEG applies a perturbational rather than an observational approach. Unlike resting-state EEG [10, 21], which probes correlational network properties, TMS-EEG measures neuronal interactions from a causal perspective, providing a more reliable (i.e., higher signal-to-noise ratio) and comprehensive assessment of brain dynamics [17]. For example, TMS-EEG may uncover complexity in the presence of diffuse slowing of the resting-state EEG background.

Second, TMS-EEG bypasses sensory systems, which can be impaired in patients with traumatic, hypoxic, and other forms of brain injury. Rather than relying on vision, touch, hearing, or smell, TMS-EEG directly accesses the primary sensory and association regions of the cerebral cortex, reducing confounders and increasing the reliability of the physiological measurements.

Third, TMS-EEG bypasses motor systems and is thus not dependent on a behavioral output. Focal lesions in the brain, spinal cord or peripheral nerves may disrupt central or peripheral motor pathways, preventing self-expression. In addition, diffuse weakness from myopathy or polyneuropathy may prevent self-expression due to quadriplegia or prolonged mechanical ventilation [22]. Patients with extensive trauma may also have pain or orthopedic injuries that prohibit movement, even if neural motor pathways are intact.

Fourth, no cognitive effort is required for TMS-EEG, an advantage that is particularly relevant to patients with orbitofrontal and basal forebrain lesions, which deplete attentional and working memory resources. Patients with frontal-forebrain disconnection syndromes may be unable to sustain attention on simple tasks, leading to delayed or absent responses during task-based paradigms despite preserved consciousness [23].

For these four reasons, TMS-EEG measurements provide unprecedented sensitivity and specificity of the state of consciousness in severely brain-injured patients [18, 19]. While

other advanced methods for detecting signs of consciousness, such as task-based EEG and fMRI, are currently more feasible and more likely to be reimbursed by insurers [8, 24], the methodological advantages of TMS-EEG provide a rationale for its potential utility in the ICU, as well as its cost-effectiveness. We advocate for multimodal studies [25] that compare the performance characteristics of TMS-EEG, task-based EEG [3, 4, 6], task-based fMRI [6, 26], and behavioral assessments in critically ill patients with DoC [27–30]. A key unanswered question in the ICU, where patients may not tolerate cessation of sedation for longer than a few minutes, is whether TMS-EEG provides greater diagnostic yield for detecting signs of consciousness than repeated behavioral assessments.

Clinical Utility and Ethical Imperative

The most compelling clinical application of TMS-EEG to the ICU is as a prognostic tool. Because early emergence of consciousness in the ICU predicts long-term outcomes, the unparalleled diagnostic characteristics of TMS-EEG can improve prognostic accuracy. Indeed, emerging evidence from patients in the subacute-to-chronic stage of brain injury suggests that TMS-EEG measurements of PCI can stratify behaviorally unresponsive patients into subgroups with high, moderate, and low chances of recovering behavioral signs of consciousness [19].

The ethical rationale for clinical translation of TMS-EEG into the ICU setting is its potential to improve goal-concordant care and prevent premature withdrawal of life-sustaining therapy (WLST). Currently, WLST is the most common cause of death (~80%) in patients with acute disorders of consciousness (DoC) due to anoxic [31] or traumatic [32] causes. However, families and caregivers often make life-or-death decisions in the ICU without a clear understanding of their loved one's state of consciousness or potential for recovery. Given that impressions of a patient's level of consciousness and likelihood of recovery are primary determinants of family decisions about WLST [33], early detection of consciousness in the ICU may have life-or-death consequences.

Ethical principles guiding WLST decisions include autonomy – the importance of respecting and promoting a patient's personal values and goals – and non-maleficence – the idea that clinicians should not do harm by prolonging life for a patient whose current and future quality-of-life is unacceptable to them [34]. However, there is often insufficient evidence available to determine whether a behaviorally unresponsive patient is conscious or not [35] and to determine their likelihood of recovering consciousness [9, 31]. Obtaining more accurate indicators of consciousness and predictors of recovery is essential for ensuring that ethical, goal-concordant decisions are made in clinical care [36]. To promote patient autonomy and avoid undue harm, decisions about WLST, pain control, and neurorehabilitation should be informed by a patient's level of consciousness and capacity for recovery – a goal that TMS-EEG, with its unprecedented sensitivity, is ideally poised to accomplish in the ICU.

Importantly, recovery of consciousness is not inextricably linked to recovery of functional independence. Although evidence of consciousness (behavioral or covert) in the ICU predicts long-term functional recovery at the group level [1–4], individual patients with

covert consciousness may die after discharge from the ICU or experience long-term functional disability [4]. For example, sensorimotor deficits that impair self-expression in the ICU may persist, leading to chronic functional disability and a compromised quality of life despite preserved consciousness [37]. Future studies will thus have a higher likelihood of impacting clinical practice if they select endpoints that measure recovery of both consciousness and functional independence [38, 39]. In parallel, there is an ethical imperative to elucidate clinician and family perspectives on how advanced neurotechnologies like TMS-EEG should be responsibly integrated into clinical practice [35, 40–42].

Endorsement Without Implementation

In 2018, twelve years after the first report of covert consciousness [43], academic institutions began to endorse the clinical implementation of advanced neurotechnologies for detection of covert consciousness. The American Academy of Neurology, American Congress of Rehabilitation Medicine and the United States National Institute of Disability, Independent Living and Rehabilitation Research endorsed these techniques for the clinical evaluation of patients with DoC in the subacute-to-chronic stages of recovery [44]. In 2020, the European Academy of Neurology similarly recommended task-based fMRI and EEG. They expanded this clinical recommendation to include TMS-EEG and extended the time course to the acute setting [45]. That same year, the International Federation of Clinical Neurophysiology proposed a stepwise clinical evaluation of consciousness [46], endorsing TMS-EEG to identify unresponsive patients who may benefit from rehabilitation.

Yet despite the endorsement of advanced neurotechnologies for clinical use, implementation has stalled. An international survey conducted by the Curing Coma Campaign found that less than 10% of clinicians caring for patients with DoC have access to these tools [8]. The slow pace of clinical implementation may be partly attributable to debates about the suitability of advanced neurotechnologies for clinical use in the ICU [47], given that guideline recommendations are based mostly on subacute-to-chronic data. Moreover, the strength of the evidence is poor due to the limited number of studies and their small sample sizes. Nevertheless, international support is growing for clinical implementation of advanced neurotechnologies [48], consistent with these guidelines. Accordingly, we argue here that the primary barriers to clinical translation are methodological and logistical, and therefore capable of being overcome by a sustained, international effort.

Barriers to Clinical Translation of TMS-EEG

Clinical implementation of TMS-EEG has been limited by multiple methodological hurdles [49, 50]. A 2022 consensus statement identified three inter-connected challenges preventing clinical translation of TMS-EEG: 1) the logistical complexity of its application; 2) the technical difficulty of obtaining high-quality EEG signals; and 3) insufficient validation of analytic pipelines [51]. We advocate for a comprehensive framework to overcome each of these challenges.

From a logistical standpoint, clinical translation of TMS-EEG to the ICU setting will require a portable tool. TMS equipment is comprised of a TMS stimulator and coil, a cooling unit to prevent overheating of the system, a navigation system with a stereotactic camera to guide precise cortical targeting [52], and a computer display with a three-dimensional brain map for real-time monitoring (Figure 1). While several companies have reduced the dimensions of the TMS unit, few have created a compact, portable TMS device that can feasibly be used in an ICU patient's room.

To maximize feasibility and deployability, a portable TMS-EEG device will need to support a variety of inputs to its neuroimaging-guided navigation system. At hospitals with access to advanced MRI data (e.g., resting-state fMRI for functional connectivity or diffusion MRI for structural connectivity), a TMS-EEG technologist may upload connectivity maps to the TMS-EEG console and view connectivity data interactively (Figure). At hospitals without access to advanced MRI data, the technologist may use standard neuroimaging guidance with computed tomography or T1-weighted MRI scans [18, 19, 53]. Of note, recent advances in machine learning enable synthesis of T1-weighted MRI scans at 1 mm isotropic resolution from low-resolution MRI scans, or even from CT scans [54, 55]. These advances have potential to support international dissemination of imaging-guided TMS-EEG at hospitals in academic and community settings.

From a technical standpoint, optimizing EEG signal-to-noise properties is essential to obtain reliable PCI measurements and reduce the duration of the TMS-EEG session. Real-time read-outs are needed to minimize muscle artifacts and auditory-evoked potentials, while maximizing cortical signals [56, 57]. TMS-EEG data acquisition protocols that have been developed on high-density, 64-electrode EEG systems will need to be simplified to allow for robust PCI measurement using standard, 19-electrode clinical EEG systems [58].

Given that only one TMS-evoked potential is needed to assess a patient's capacity for consciousness, another future goal is development of neuroimaging priors to guide TMS targeting (Figure 1A). Currently, comprehensive cortical mapping finds the optimal 'entry point' that generates the highest PCI value. Multiple cortical sites are tested, requiring approximately 200 stimulations at each site (~ 8 minutes per site). By targeting cortical regions with high levels of structural or functional connectivity, as identified by diffusion MRI and resting-state fMRI, respectively, the chances of obtaining optimal complexity measures are likely to rise, reducing acquisition time to that of other bedside diagnostic tests performed in the ICU that range from 30–60 minutes in duration.

Finally, there is an urgent need to validate a standardized analytic pipeline for TMS-EEG data that will provide clinicians and families with reliable brain complexity information in real-time. TMS-EEG has the potential to be deployed at the bedside for serial assessment of brain complexity, similar to the daily assessments of cerebral blood flow velocity performed with transcranial doppler ultrasound for patients with aneurysmal subarachnoid hemorrhage. Serial measurement of brain complexity is crucial for patients with DoC because of frequent fluctuations in their level of consciousness [59].

Safety Considerations

The safety of TMS-EEG is well-established, especially when TMS pulses are delivered at low frequency (<1 Hz), as they are for calculating brain complexity. Minor side effects, such as scalp discomfort or headache, have been reported [60]. These side effects can be mitigated by modifying the TMS stimulation target if muscle twitching is observed. A survey involving 174 labs and 318,560 TMS sessions showed that the risk of inducing seizures, the most serious potential side effect, is below 1 in 10,000 when TMS is used within the safety guidelines and in low-frequency mode, even in patients at high risk of seizures [9, 61]. Further studies are needed to determine whether the incidence of seizures in patients with acute severe brain injuries is similarly low [19, 53, 62–64].

The Clinical Trial Horizon

Prior studies have applied TMS-EEG in the subacute and chronic care settings [18, 19, 65]. Attention should now turn to optimizing TMS-EEG for use in the acute ICU setting and performing an international, multi-center trial to validate its diagnostic and prognostic utility. To achieve this goal, partnerships between the neuroscience and clinical communities will need to be strengthened, along with ties to engineers developing faster, more compact TMS-EEG devices. The design of such technologies will allow validation of standardized data acquisition and analysis procedures that yield reliable PCI measurements across sites. There is also a need for common data elements (CDEs) to facilitate standardized reporting of TMS-EEG results, a goal that is now being pursued by the Curing Coma Campaign [66]. Additional applications in future clinical trials include the use of TMS-EEG to predict individualized responses to therapies [67], and to measure subclinical therapeutic responses [68]. It may also be possible for TMS-EEG to predict a patient's risk of delirium [69, 70], a common ICU complication.

Conclusions

In the decades-long search for a "consciousness-detector", TMS-EEG provides performance characteristics that surpass those of other advanced neurotechnologies. International guidelines have begun to endorse the clinical application of TMS-EEG to patients with DoC. Yet logistical and methodological barriers currently prevent clinical implementation of TMS-EEG in the ICU. Translation of TMS-EEG to the ICU has the potential to provide clinicians and families with a reliable index of consciousness – one that could substantially impact decisions about the continuation of life-sustaining therapy. We advocate for multicenter trials to test the reliability of TMS-EEG measures of PCI in critically ill patients with severe brain injuries to meet these clinical and ethical imperatives.

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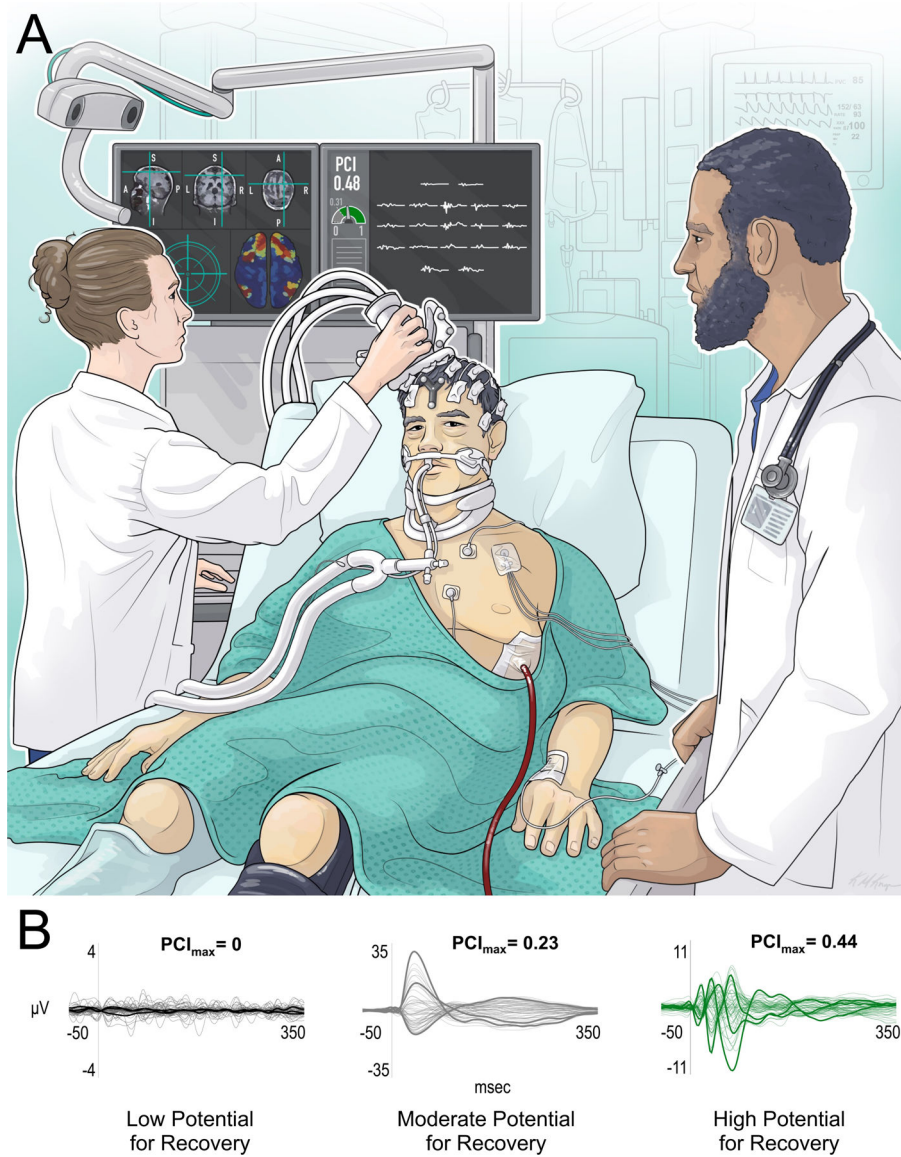
Figure. 1. Stimulating the brain to determine its capacity for consciousness.
(**A**) A technologist (left) with expertise in transcranial magnetic stimulation-electroencephalography (TMS-EEG) measures the perturbational complexity index (PCI) in a patient with a severe traumatic brain injury (center), while a physician observes (right). The technician stimulates the right premotor cortex based on precise anatomic guidance provided by the T1-weighted magnetic resonance imaging (MRI) scan on the top of the left screen. A functional MRI connectivity map is used to identify cortical sites to be targeted (e.g., highly connected regions shown in red are likely to have higher PCI values). The turquoise aiming device on the bottom left of the screen provides real-time feedback about the precision of target stimulation. On the right screen, the technologist visually assesses for artifacts and determines the reliability of TMS-evoked potentials recorded by 19 EEG electrodes. In this illustrative patient, the PCI value of 0.48 is above the empirically derived cut-off of 0.31, indicating that the patient's brain has the same complexity as that

of conscious subjects. (**B**) TMS-evoked EEG waveforms that indicate low (black), moderate (gray), and high (green) potential for recovery of behavioral signs of consciousness. These waveforms are adapted from Casarotto et al. 2016 [19], where low potential for recovery was observed with PCI = 0, moderate potential for recovery with 0 < PCI   0.31, and high potential for recovery with PCI > 0.31. Abbreviations: A = anterior; I = inferior; L = left; P = posterior; R = right; S = superior.