NEUROSCIENCE

Making Waves in Consciousness Research

Nicholas D. Schiff

A new strategy for quantifying consciousness in human brains may have broad applications in the clinic and in neurobiology research labs (Casali *et al.*, this issue).

Recent discoveries highlight the critical need for surrogate measures of wakeful conscious brain activity to assess patients with severe brain injuries. Although some patients harbor considerable cognitive reserve undisclosed by bedside examination (*1, 2*), detection of even the earliest recovery of consciousness reflected in the minimally conscious state (MCS) has important implications for prognosis and treatment (*3, 4*). In their pioneering study, Casali and colleagues (*5*) introduce a theoretically based measurement of resting brain state that combines pulses of transcranial magnetic stimulation (TMS), high-density electroencephalographic recordings, and an analytic framework based on the algorithmic complexity of data elements derived from the measured electrical activity after the TMS pulse.

In their study, Casali *et al.* use electroencephalography (EEG) to measure the electrocortical responses of the brain induced by the TMS pulses. EEG records the time-varying voltages recorded from dense electrode-sensor arrays placed on the scalp. In prior studies, the investigators demonstrated that time-averaging of the EEG signal after repetitive TMS pulses generate reproducible wave patterns of activity that show reliable sensitivity to the level of consciousness (Fig. 1). Brain states that correlate with unconsciousness—including non–rapid eye movement (NREM) sleep, pharmacologically induced coma, and vegetative state (VS) after structural brain injuries—show either very locally generated TMS responses or more widespread brain activations with stereotypical, simple dynamics; in contrast, the TMS response from healthy controls in the wakeful conscious state and during dreaming (REM) sleep or brain-injured subjects with varying levels of conscious behaviors generally show complex, longer-lasting EEG responses. In the present report, Casali *et al.* (*5*) advance a new empirical measure, the perturbational complexity index (PCI), to quantify the TMS EEG response and test its potential as a unified measurement scale to grade level of consciousness.

PCI is based on a theoretical framework that considers wakeful consciousness as a state that requires integration of information across multiple brain regions with a high degree of differentiation of the activity localized within separate regions. To calculate PCI, many short segments of EEG traces taken after each TMS pulse are averaged, and the underlying sources of the resulting EEG pattern are modeled with the use of source-localization methods. This process produces a matrix of binary values summarizing the significant activation of different modeled sources at each point in time. Algorithmic-complexity measures are then used to estimate the compressibility of the strings of binary values (similar to zipping an electronic file) represented in the data matrix. The PCI index is a normalized measure that depends primarily on the number of different patterns of such binary values extracted from the EEG data within a given time sample contained in the matrix, and not on the overall amount of significant activity. (For example, many significant time points arising on multiple sources in similar patterns will not increase PCI.) High PCI values are obtained only if the initial TMS perturbation alters activity in a large set of integrated brain regions that each then react differently over time. As such, PCI captures and quantifies the concept that wakeful conscious brain states are characterized by both functional integration and differentiation, and that unconscious brain states are not.

PCI values from 32 healthy individuals who were studied while awake, under different types of general anesthesia and in different stages of sleep, showed that conscious brain states consistently demonstrated significantly higher PCI values than those of unconscious brain states. Critically, PCI measurements within single subjects obtained across different states demonstrated the same correlation of higher values with more conscious brain states. Most compelling, when TMS responses were measured in 20 brain-injured subjects sampled across varying levels of function—from VS to MCS to confusional state to locked-in state (Fig. 1)—the investigators observed a graded increase in PCI values, which is consistent with the level of consciousness estimated in each of these states.

CLINICAL IMPLICATIONS

A major strength of the PCI is that assessment of conciousness does not depend on the integrity of specific sensory pathways or motor efferent systems. In addition, the PCI results obtained in healthy controls were insensitive to placement of the TMS pulse across several cortical sites, supporting the flexible use of this approach in most patients with structural brain injuries. The ability to index the likelihood that a conscious brain state is present in a patient without concomitant behavioral evidence is of great value in the clinic, as misdiagnosis rates are high when behavioral evidence of consciousness is limited (*6*).

Recent large-population studies of patients with disorders of consciousness (*3, 4*) provide evidence that the recovery process after severe traumatic brain injuries continues for months to years across all levels of functional outcome. Within the first year of recovery, a majority of patients who remain in MCS for months after traumatic injury will recover consciousness (68%), and a substantial fraction recover to an independence in activities of daily living (21%); in addition, further recovery has been detected at 1, 2, and 5 years after severe traumatic brain injury (*3*). Surrogate measures that can reliably distinguish VS from MCS are crucial and will have an impact on clinical practice because similar long-term improvements have not been documented for VS patients.

An important limitation, however, is that PCI is specific to the patient's state at the time of measurement, and if this state fluctuates dramatically within the day or across days, as often happens in patients with disorders of consciousness, PCI will not disclose the potential for a measurement made at a different time to reveal greater potentiality. Nonetheless, the greatest utility of such measures may be to provide adjunctive assessment of patients in

Feil Family Brain Mind Institute, Weill Cornell Medical College, New York, NY 10065, USA.

Corresponding author. E-mail: nds2001@med.cornell.edu

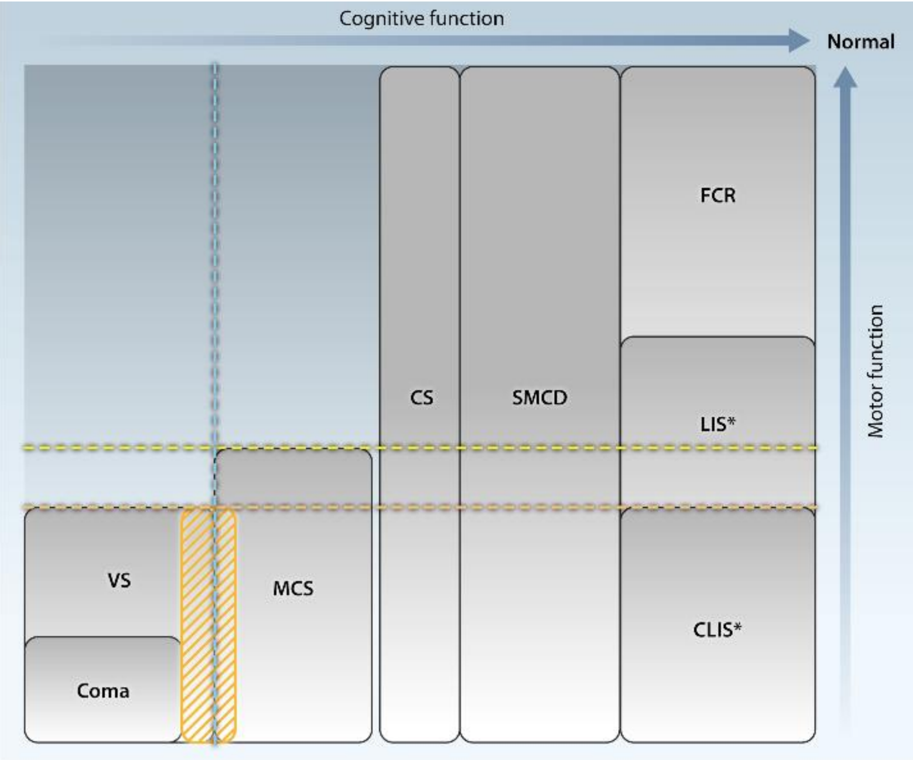

Fig. 1. Consciousness, cognition, and behavior. The distinctions among clinical disorders of consciousness can be best captured on a two-dimensional axis by comparing the degree of impaired cognitive function against the degree of motor function. At the bottom left, the functional equivalence of coma and vegetative state (VS) as unconscious brain states in which there is no behavioral evidence of consciousness (VS differs from coma by intermittent eye open periods) is indicated by their placement to the left of the blue vertical dotted line, which indicates total loss of cognitive function. The hatched orange rectangle between Coma/VS and minimally conscious state (MCS) indicates a transition zone in which fragments of behavior not tied to sensory stimuli may be observed before the unequivocal but potentially intermittent behavioral evidence of consciousness demonstrated by MCS patients. After emergence from MCS, recovery patterns include the confusional state (CS), in which patients cannot be formally tested by using standard neuropsychometric measures, and a range of cognitive functions that can be observed with standard measures, from severe to moderate cognitive disability (SMCD) to the normal range (FCR, full cognitive recovery). Locked-in state (LIS) designates normal conscious awareness but severe motor impairment, limiting communication channels typically to only eye movements; the asterisk indicates that LIS is not a disorder of consciousness, and that LIS patients retain normal cognitive function by definition (*9*). The horizontal dotted orange line indicates the total loss of functional movements; without surrogate measures, it is not possible to independently judge level of consciousness across the range of VS to the complete locked-in state (CLIS) in patients without any behavioral response. The gap between this line and the dotted horizontal yellow line indicates the presence of inconsistent functional movements and a restricted range of uncertainty in establishing cognitive level from MCS to LIS. Casali *et al*. introduce a measurement, PCI, based on time-averaging of EEG responses after TMS pulses. In NREM sleep, a small number of derived EEG generators are identified with limited temporal evolution; wakeful states show a larger number of EEG generators with complex spatiotemporal evolution over longer time durations. PCI indices show a sharp separation between Coma/VS and MCS/CS/LIS patient populations; MCS/CS/LIS patients exhibit a range of PCI values similar to those of healthy controls in wakeful states, whereas Coma/VS patients show values comparable to NREM sleep or healthy controls under anesthesia.

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intensive care units (ICUs), where patients often have only brief periods of sedation reduction to allow for assessments needed to manage their medical care. It would be a major clinical advance if the EEG-TMS-PCI method could provide prognostic information about brain function in the ICU setting. The present report does not show that this approach will be beneficial when tested in large patient samples or in other clinical settings such as the ICU, but the findings clearly offer promising leads to follow.

SCIENCE OF CONCIOUSNESS

Beyond its potential future clinical utility, the EEG-TMS-PCI approach taken by the investigators (*5*) has important conceptual implications for the study of consciousness. The results support a research focus on further tracking of complex spatiotemporal dynamics in EEG data and exploration of their relationship to the conscious state. A wide range of EEG dynamics must separate patients across the spectrum from MCS to full consciousness that nonetheless exhibit overlapping ranges of PCI values. Variations on the approach taken in this study may be more sensitive to such differences and provide insights into the differences in brain activity, particularly approaches that assess responses to structured sensory stimuli (*7*).

Other theoretically derived measures exist that can quantify the complex spatiotemporal dynamics of spontaneous brain activity (*8*). If further accumulated evidence supports the use of PCI as a graded measure of consciousness, it will become an important tool with which to evaluate these other measures to determine whether they offer complementary mechanistic insights into conscious states that fall within the various ranges of wakeful PCI values. The present findings invite further investigation of the functional integration of different brain systems and the differential activities within the specific networks that show graded behavioral differences across stages of consciousness recovery beyond the MCS and in other forms of altered consciousness.

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