

Ripples of consciousness

Jacobo D. Sitt^{1,2,3}, Jean-Rémi King^{1,2,3}, Lionel Naccache^{3,4,5}, and Stanislas Dehaene^{1,2,6,7}

¹ Cognitive Neuroimaging Unit, Institut National de la Santé et de la Recherche Médicale, U992, F-91191 Gif/Yvette, France

² NeuroSpin Center, Institute of Biomedicine Commissariat à l'Énergie Atomique, F-91191 Gif/Yvette, France

³ Institut du Cerveau et de la Moelle Épineuse Research Center, Institut National de la Santé et de la Recherche Médicale, U975 Paris, France

⁴ AP-HP, Groupe hospitalier Pitié-Salpêtrière, Department of Neurophysiology, Paris, France

⁵ Faculté de Médecine Pitié-Salpêtrière, Université Paris 6, Paris, France

⁶ Université Paris 11, Orsay, France

⁷ Collège de France, F-75005 Paris, France

Casali *et al.* recently showed that the complexity of the electrophysiological brain response to a transcranial magnetic stimulation pulse distinguishes conscious from unconscious humans in a variety of conditions. In addition to its theoretical implications, this novel method paves the way to a quantitative assessment of the states of consciousness.

Every minute, millions of people lose (and recover) consciousness, because of the natural sleep-wake cycle, but also because of abnormal conditions, such as coma, vegetative state, complex epileptic seizures, or general anesthesia. Yet, the precise neuronal mechanisms responsible for consciousness are poorly understood, and detecting whether a person is conscious therefore remains a major challenge.

In an exciting recent paper, Casali *et al.* [1] introduced a quantitative assay of the state of consciousness. Their work capitalizes on the electroencephalography (EEG) response evoked by a cortical transcranial magnetic stimulation (TMS) pulse. Previous research by the same group [2] demonstrated that, in conscious subjects, TMS pulses systematically elicit a complex spatiotemporal pattern of activation, whereas when the subjects are anesthetized, asleep, or in a vegetative state, TMS induces only a short and undifferentiated response (Figure 1). In their new work [1], the authors quantify the complexity of this EEG response. They first reconstruct its cortical sources and then use algorithmic information theory tools to estimate the complexity of its spatiotemporal dynamics. They term the outcome Perturbational Complexity Index (PCI), a number that ranges between 0 (no complexity) and 1 (maximal complexity).

Casali *et al.* applied this method to a large panel of subjects (n=32), obtaining recordings during wakefulness, light deep and REM sleep, and anesthesia with midazolam, xenon, or propofol. Whereas all awake subjects presented a PCI above 0.44, all unconscious sleeping and anesthetized patients systematically showed values below 0.31. Thus, remarkably, the proposed index was distributed bimodally and separated all conscious from all unconscious individu-

als. Furthermore, the authors tested this method in twelve patients with disorders of consciousness (DOC) and eight conscious brain-injured subjects. Vegetative state patients (n=6) had PCIs similar to the anesthesia and sleeping groups, yet patients in a minimally conscious state (n=6) or emerging from it (n=6) had significantly higher PCIs (although they remained smaller than those of awake subjects). Finally, conscious but paralyzed patients ('locked-in syndrome', n=2), whose behavior may be confounded with a vegetative state, presented PCIs similar to healthy awake controls. These findings represent a major advance in the search for an empirical quantitative metric for consciousness, with important theoretical and clinical implications.

Theoretical implications

Casali *et al.* argue that the PCI was designed to detect 'integration' and 'differentiation', two central properties of the information integration theory of consciousness (IIT) [3]. According to the authors, integration can, in practice, be assessed by the global spread of cortical activation evoked by focal TMS, whereas differentiation relates to the fact that distinct regions are successively activated, without temporal redundancy. It should be noted, however, that EEG does not have the spatial resolution needed to evaluate the micro-differentiation of cell assemblies postulated in IIT and that the PCI is not directly related to Tononi's Phi measure (a formal quantification of the integrated information in a given network) proposed by IIT as a marker of consciousness. Although the technique was inspired by IIT ideas, the results so far merely show that TMS elicits a complex series of ripples across different brain areas only in conscious subjects. As such, they remain compatible with other models that associate consciousness with a preserved functional thalamocortical system able to 'broadcast' local activation to many distant cortical sites or to entertain long-lasting reverberating states [4,5].

A remarkable finding is that the PCI is quantitatively identical regardless of the initial site of TMS application [1]. This finding fits with IIT's hypothesis that only information integration matters for the measurement of consciousness, whereas the specific anatomical areas involved can be disregarded. Nonetheless, this aspect of the

Corresponding author: Sitt, J.D. (jdsitt@gmail.com); Dehaene, S. (stanislas.dehaene@gmail.com).

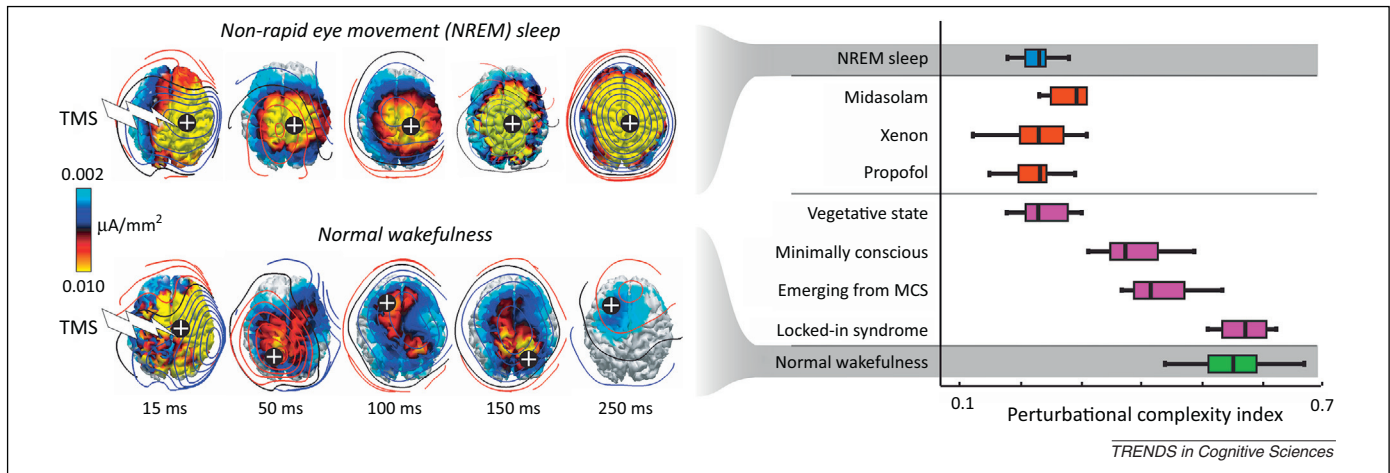


Figure 1. Cortical activation evoked by a TMS pulse and perturbational complexity index. The left panel (adapted from [2]) presents the current densities elicited by a TMS pulse over the somatosensory cortex. The moving cross marks the location of maximum current at each time point. Whereas the TMS pulse elicits only a local response in NREM sleep (top), in wakefulness it triggers a spatiotemporal sequence of maximal activations in different cortical locations (bottom). In the right panel (adapted from [1]), the perturbational complexity index (PCI) discriminates well these two patterns of responses, as well as those obtained in pharmacological and pathological unconscious conditions (red and purple).

research limits the interpretation of the precise neural mechanisms at work during conscious states. It would be important to know whether prefrontal, cingular, or precuneus cortices, as well as thalamocortical loops are systematically involved, as predicted by previous studies [4].

One important methodological aspect is the length of the time window used for PCI computation. In [1], the analysis was performed on a 300 ms window following TMS. Although this choice may have been optimal, it seems arbitrary, as IIT theory does not specify the time scale at which information integration should take place. Conscious processing might well be significantly slower in patients with diffuse white-matter lesions, demyelinating diseases, or during development. Indeed, a recent study showed that human infants present the same electrophysiological signatures of visual conscious perception as adults, but at much slower time scale [6]. It will be important to verify whether the PCI is robust to such temporal changes.

Clinical implications

Although Casali *et al.*'s patient sample remains small, their approach holds great promise for the diagnosis of vegetative state patients and the monitoring of anesthesia. TMS stimulation has the clear advantage of directly perturbing the cortex with a strong stimulus, thus generating large EEG signals without requiring the integrity of a particular sensory pathway. Furthermore, unlike other paradigms previously tested to detect consciousness (see [7], for a review), this passive method does not depend on attention, task instructions, or language comprehension. Nevertheless, because TMS-compatible EEG is not available in most clinics, it would be valuable to investigate if the TMS pulse is necessary or if it could be replaced by another sensory stimulus. Supp *et al.* [8] showed that the sequence of EEG responses to median nerve stimulation decreases dramatically under propofol anesthesia.

Similarly, the late long-lasting event-related potentials evoked by an auditory oddball provide a tentative marker of consciousness in DOC patients [9]. Perhaps one might even dispense with the stimulus altogether and simply evaluate the presence of distributed and durable activation patterns in ongoing EEG. In recent work, King *et al.* show that a new EEG marker of the sharing of information across long cortical distances provides a sensitive index of consciousness in a large cohort of DOC patients ($n=167$) [10].

Finally, hundreds of TMS pulses are needed to compute a single PCI value. This limitation may become relevant for minimally conscious patients in whom consciousness fluctuates over time or for the real-time monitoring of anesthesia. Could future research provide higher temporal resolution, faster acquisition and computation times, and ultimately a single-trial index of consciousness? Casali *et al.*'s research demonstrates that the dream of such a quantitative 'consciousness-o-meter' may not be out of reach.

References

- 1 Casali, A.G. *et al.* (2013) A theoretically based index of consciousness independent of sensory processing and behavior. *Sci. Transl. Med.* 5, 198ra105
- 2 Massimini, M. *et al.* (2007) Triggering sleep slow waves by transcranial magnetic stimulation. *Proc. Natl. Acad. Sci. U.S.A.* 104, 8496–8501
- 3 Tononi, G. (2004) An information integration theory of consciousness. *BMC Neurosci.* 5, 42
- 4 Dehaene, S. and Changeux, J-P. (2011) Experimental and theoretical approaches to conscious processing. *Neuron* 70, 200–227
- 5 Lamme, V.A.F. and Roelfsema, P.R. (2000) The distinct modes of vision offered by feedforward and recurrent processing. *Trends Neurosci.* 23, 571–579
- 6 Kouider, S. *et al.* (2013) A neural marker of perceptual consciousness in infants. *Science* 340, 376–380
- 7 Harrison, A.H. and Connolly, J.F. (2013) Finding a way in: a review and practical evaluation of fMRI and EEG for detection and assessment in disorders of consciousness. *Neurosci. Biobehav. Rev.* <http://dx.doi.org/10.1016/j.neubiorev.2013.05.004>

- 8 Supp, G.G. *et al.* (2011) Cortical hypersynchrony predicts breakdown of sensory processing during loss of consciousness. *Curr. Biol.* 21, 1988–1993
- 9 King, J.R. *et al.* (2013) Single-trial decoding of auditory novelty responses facilitates the detection of residual consciousness. *Neuroimage* 83C, 726–738

- 10 King, J.R. *et al.* (2013) Information sharing in the brain indexes consciousness in noncommunicative patients. *Curr. Biol.* <http://dx.doi.org/10.1016/j.cub.2013.07.075>

1364-6613/\$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
<http://dx.doi.org/10.1016/j.tics.2013.09.003> Trends in Cognitive
 Sciences, November 2013, Vol. 17, No. 11



Early signs of brain asymmetry

Michael C. Corballis

School of Psychology, University of Auckland, Private Bag 92019, Auckland, New Zealand

A new study shows a leftward asymmetry of the choroid plexus in two-thirds of first-trimester human fetuses. This is the earliest brain asymmetry so far identified and may be a precursor to other asymmetries, including that of the temporal planum, which is evident from the 31st week of gestation.

The body plan of most animals, including humans, is to all outward appearances bilaterally symmetrical, so that functional asymmetries of brain and behaviour have long been sources of fascination. The near universal human preference for using the right hand has given rise to superstition, symbolism and prejudice as far back as the historical record takes us, and the discoveries from the late 19th century of a predominantly left-hemispheric specialization for speech and language, along with complementary right-hemispheric specializations, has led to notions of a fundamental duality pervading human affairs, whether in art, politics, religion, or even business. Until quite recently, asymmetry of function has also been considered a special feature of the human brain, perhaps even a defining one, but comparable asymmetries are now widely documented in a wide range of species [1].

More recently, too, discoveries of anatomical asymmetries have suggested potential physical bases for behavioural and functional ones. These asymmetries include a counterclockwise ‘torque’, in which the right frontal pole protrudes beyond the left and the left occipital pole protrudes beyond the right, as well as enlargements of Broca’s area, the arcuate fasciculus, and the temporal planum on the left relative to the right [2]. Chimpanzees, too, show leftward asymmetries of the temporal planum and the homolog of Broca’s area, as well as a population-level preference for the right hand, although the incidence of right-handedness is only approximately 65–70 percent, well below the incidence of approximately 90 percent in humans.

Little is known of the genetic bases of these asymmetries, but at least some of them are inborn and measurable well before birth. The earliest sign of anatomical asymmetry so far identified comes from a new study that shows the choroid plexus to be larger on the left than on the right in approximately two-thirds of human fetuses in the 11th to 13th week of gestation – the first trimester of

life [3]. The choroid plexus is a structure in the ventricles of the brain that produces cerebrospinal fluid. It is present in the third and fourth ventricles, and fills the lateral ventricles in the first trimester. The shape of the choroid plexus, the so-called ‘butterfly sign’, in the lateral ventricles has proven to be one of the most sensitive first-trimester sign of brain abnormalities [4], and it is in this region that the asymmetry was apparent [Figure 1].

There is reason to conjecture that this asymmetry underlies the asymmetry of the temporal planum, which is detectable in approximately two-thirds of human fetuses from the 31st week of gestation [5]. The cerebrospinal fluid has long been considered a ‘sink’ for the clearance of brain metabolites, but evidence increasingly shows that it plays a role in brain development, synthesizing a large number of peptides, growth factors and cytokines. The choroid plexus grows smaller with advancing age, and in the first trimester its large size creates relatively short distances for bioactive substance to reach target neural tissue. It is therefore ideally situated to exert a strong influence early in fetal development. Due to the asymmetry, that influence is likely to be stronger on the left than on the right.



Figure 1. Ultrasound image of choroid plexus at first trimester, showing enlargement on the left. Reproduced with permission from the American Institute of Ultrasound in Medicine.