

**Title:** Listening for the rhythm of a conscious brain

**Authors:** Rodika Sokoliuk ([r.sokoliuk@bham.ac.uk](mailto:r.sokoliuk@bham.ac.uk)) and Damian Cruse ([d.cruse@bham.ac.uk](mailto:d.cruse@bham.ac.uk))

**Affiliations:** School of Psychology, University of Birmingham, Edgbaston, England, B15 2TT; Centre for Human Brain Health, University of Birmingham, Edgbaston, England, B15 2TT.

The question of whether someone is conscious of themselves and their environment may initially appear to be a philosophical thought experiment. However, for many families and clinicians throughout the world, it is a challenge with profound implications for decision-making after severe brain injury. The current standard approach to answering the question of consciousness in the clinic is to observe the patient's behaviour for evidence of purposeful action, such as tracking a moving object. However, due to inequalities in healthcare provision both across and within countries, many patients never receive standardised behavioural assessment. Consequently, misdiagnoses of so-called prolonged disorders of consciousness (PDOC) occur at alarmingly high rates: ~40% when standardised assessment is not available and ~30% when a standardised assessment is not conducted longitudinally (Wannez *et al.*, 2017). With the recent confirmation from the UK's Supreme Court that withdrawal of clinically assisted nutrition and hydration from individuals with PDOC may occur without the involvement of the courts (UK Supreme Court, 2018), access to accurate diagnostic tools is all the more imperative. In this issue of *Brain*, a trans-European collaboration provides hope for accurate, accessible, and objective diagnoses of consciousness in this challenging patient group.

Over the last decade, researchers have identified an array of markers within the electroencephalogram (EEG) of patients with PDOC that differ between those who are conscious (i.e. the minimally conscious state) and those who are entirely unconscious (i.e. the vegetative state, also known as unresponsive wakefulness syndrome [UWS]). These markers may be *task-based* changes in the EEG that occur in response to stimuli, such as sounds or verbal instructions, or *task-free* features of the patient's EEG at rest. Engemann *et al* (2018), in this issue of *Brain*, apply advances in machine learning to the largest ever dataset of PDOC brain data and demonstrate that a combination of theoretically- and empirically-motivated EEG markers can accurately diagnose patients' levels of consciousness.

To test the efficacy of a machine learning method, researchers first require a set of *training* data for which they and their algorithm know the 'truth' - i.e. which data correspond to patients who are conscious by standardised assessment, and which belong to those who are not conscious. The researchers then apply the trained model to previously unseen *test* data from one patient in order to estimate their 'true' diagnosis. Crucially, the model described by Engemann *et al* accurately diagnoses patients even when the training and test data were recorded in different countries, with different EEG equipment, and different EEG protocols. The success of this model, therefore, creates the real possibility for an objective online tool that families and clinicians across the world could use with locally recorded EEG data, and consequently improve the accuracy of diagnosis and subsequent decision-making. Indeed, through a range of stress-tests, the authors demonstrate that their model performs well with only a few minutes of data recorded from 16 electrodes; fewer than the 19-channel EEG montage typically available in clinical EEG protocols.

While the diagnostic accuracy of the model is impressive, there is nevertheless potential for the model to misdiagnose patients due to fluctuations in levels of consciousness over time. Indeed, clinicians must conduct multiple behavioural assessments of consciousness before they can achieve a stable and accurate diagnosis (Wannez *et al.*, 2017). Equally, the level of consciousness that is evident in a patient's EEG is likely to fluctuate both within and across days, and may therefore require multiple EEG sessions before a stable diagnosis can be reached. Importantly, as the diagnostic model described by Engemann *et al* is robust with brief EEG recordings from a range of EEG systems and protocols, these necessarily longitudinal assessments of EEG may be more tractable now than ever before.

Interestingly, the authors report that power in the alpha band of the EEG (8-12Hz) was consistently the most informative feature used by the models for accurate diagnosis. Alpha oscillations are the most prominent rhythm in the healthy brain and have long been associated with neuronal idling, such that high alpha power was thought to reflect a state of underlying cortical inactivity. While the alpha rhythm can be seen with the naked eye in the EEG of healthy individuals, it is considerably reduced in PDOC (see Figure 1). Resting state alpha oscillations in the healthy brain are thought to be generated within thalamus and its connections with cortex (Roux *et al.*, 2013). Thalamic damage is perhaps the most consistent structural impairment observed across PDOC, and differentiates minimally conscious state from unresponsive wakefulness syndrome (Fernandez-Espejo *et al.*, 2010). Therefore, EEG alpha power may be the most

informative marker in this diagnostic model precisely because it reflects the relative level of damage to brain structures that are known to underlie a patient's *level* of consciousness.

A complementary interpretation is that EEG alpha power also reflects an important aspect of the capacity for *contents* of consciousness in PDOC. Indeed, recent evidence suggests that alpha oscillations play a functional role in both cognition and perception. For example, visual perception relies on alpha oscillations to segment incoming visual information into bite-sized snapshots of ~100ms for visual cortex to process (VanRullen, 2016). When we pay attention to one side of our visual field, alpha power decreases over contralateral visual cortex and increases over ipsilateral visual cortex. The active inhibition hypothesis of alpha oscillations (Jensen and Mazaheri, 2010) proposes that increases in alpha power reflect inhibition of processing in task-irrelevant brain regions, while decreases in alpha power provide a boost to neural processing in task-relevant regions. Furthermore, in support of a functional role of alpha oscillations, the extent to which alpha becomes lateralised during spatial attention correlates with detection accuracy of visual targets (see Jensen and Mazaheri, 2010, for a review). Therefore, without a functional alpha rhythm to orchestrate the activity of relevant cortical regions, PDOC cortex becomes incapable of functional perception and cognition. Patients would not perceive the world in discrete perceptual cycles and would be unable to selectively attend to sensory stimuli, such as a relative's voice or the instructions of a rehabilitation specialist. While the alpha power markers used in the diagnostic model described by Engemann *et al* were summarised across the whole head, recent evidence of multiple, functionally dissociable neural sources of alpha oscillations (Sokoliuk *et al.*, 2018) suggests that a more fine-grained picture of the relative preservation of both levels and contents of consciousness in PDOC may be possible.

The importance of resting alpha power in this diagnostic model also raises the question of whether it is futile to pursue task-based, or 'active', methods for detecting consciousness. Perhaps the most well-known task-based paradigm involves asking patients to imagine that they are playing tennis and looking for activity in task-appropriate regions of their brain in order to infer that they obeyed the instruction, and are therefore conscious (Owen *et al.*, 2006). Evidence of consciousness from such 'active' methods is certainly compelling and appeals to our willingness to consider that someone is conscious only if they can show us with their (physical or mental) behaviour. However, a recent large-scale study of positron emission tomography and functional magnetic resonance imaging data showed that active paradigms were less useful for diagnosis than simple task-free measures (Stender *et al.*, 2014). Furthermore, in the study described in this issue of *Brain*, task-based markers of consciousness contributed little to the accuracy of diagnoses compared with task-free, passive, markers. Nevertheless, in our opinion, both task-free and task-based data are vital for solving the clinical challenges posed by PDOC. While task-free data may provide evidence for the preservation of a set of brain functions and structures that are minimally-required for demonstrating consciousness through overt or covert behaviour, they cannot answer a host of important questions about the patient's cognitive abilities. For example, can the patient understand what is being said to them by their families? Can the patient maintain attention for a sufficiently long time for rehabilitation efforts to succeed? Can the patient form or retrieve memories of important events? The answers to these questions may arguably assist families more in their decision-making than abstract questions of whether someone is 'conscious'. It may be that, in future, the method described in the current issue of *Brain* will allow accurate diagnosis of the global state of consciousness of a given patient, while subsequent task-based examinations can outline the cognitive profile of the patient to help guide decision-making and rehabilitation efforts.

Finally, the study by Engemann *et al* is a landmark in open-source big data in the field of PDOC. Indeed, the authors performed all analyses in the study with the open-source programming language of Python, and made the machine-learning 'recipe' publically available online alongside the scripts for EEG feature extraction. For non-behavioural measures of consciousness to achieve a true impact on clinical practise, the field must continue to generate and share larger and larger open-access datasets, thus developing more accurate methods to assist families and clinicians with their most difficult decisions.

## Glossary

***Prolonged disorder of consciousness:*** A state after severe brain injury in which an individual appears to be awake but exhibits minimal or no evidence of awareness of themselves and their environment. This category includes those who exhibit only minimal but reproducible evidence of consciousness (minimally conscious state) and those who are considered to be entirely unconscious (vegetative state, or unresponsive wakefulness syndrome).

**Machine learning:** Computer algorithms that independently learn to differentiate between two or more classes of things (in this case, patient groups) by observing features of those things (in this case, EEG activity).

**Alpha oscillations:** The most prominent rhythm in the healthy brain, found in the frequency range of 8-12Hz, they appear to function as an active inhibition mechanism in support of cognition, selectively shutting down task-irrelevant brain regions while boosting sensory processing in others. Human visual perception rhythmically fluctuates with the ongoing phase of alpha oscillations.

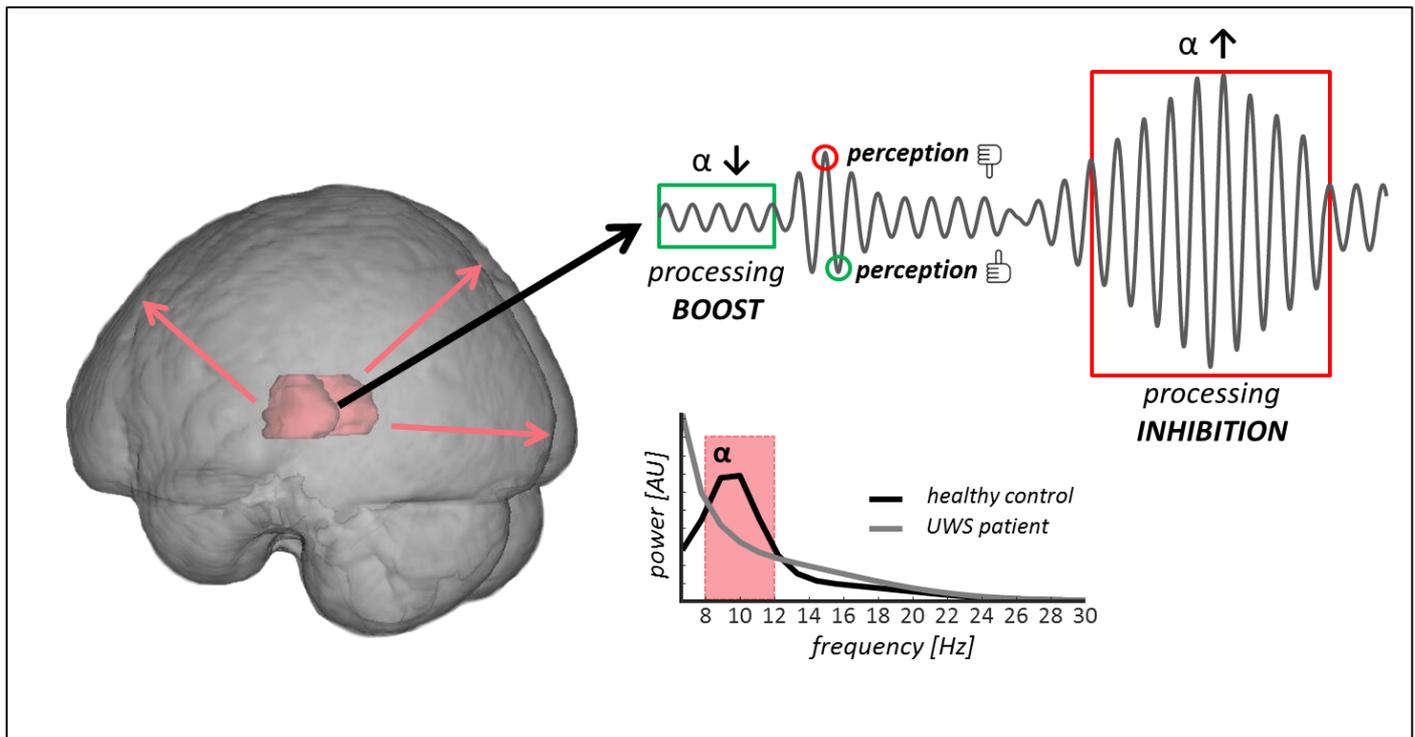


Figure 1 The thalamus (highlighted in pink within the transparent brain [left]) is highly connected to cortex and is implicated in generating alpha oscillations through thalamo-cortical loops. A schematic alpha oscillation [top right] demonstrates the proposed active inhibition mechanism of boosting (green rectangle) or inhibiting (red rectangle) sensory processing by means of power changes, and the perceptual boost observed at specific phases of the alpha oscillation. The power spectrum [lower centre] of a healthy individual (black line) shows a clear peak in the alpha band (at 10Hz), which is entirely absent from a typical patient with a diagnosis of UWS (grey line; data taken from doi:10.1016/j.nicl.2016.08.003).

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