

Given the intrinsic challenges of addressing this research question in a small cohort, the statistical analyses were designed to rule out, as far as possible, analytical biases, including oversampling bias. For the sake of stringency, the authors had to restrict their quantitative EEG analyses to some of the most accepted and established parameters, thus omitting others; these will hopefully be tested in future studies. Similarly, they did not explore other modalities for measuring connectivity, such as functional MRI or fluoro-deoxyglucose PET. These, however, are much less amenable to routine clinical use and are often too resource intensive, especially in the context of intensive care.

Rubin *et al.* should be congratulated on their extensive efforts to investigate the anaesthetic weaning process in such an under-studied patient cohort. Their findings have the potential to improve outcomes by proposing criteria to minimize the duration of pharmacologically induced coma to treat refractory status epilepticus. While the routine implementation of such sophisticated quantitative EEG analyses may still be challenging for many institutions, ever increasing computational power will facilitate its introduction. Machine learning algorithms applied to ‘big EEG data’ are likely to identify further reliable predictors that can be used to guide the

management of patients with refractory status epilepticus in years to come.

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Improving diagnosis and prognosis in disorders of consciousness

This scientific commentary refers to ‘Prognosis for patients with cognitive motor dissociation identified by brain-computer interface’, by Pan *et al.* (doi: 10.1093/brain/awaa026).

Over the past 25 years, considerable progress has been made in our understanding of so-called ‘disorders of consciousness’; coma, the minimally conscious state and the vegetative state

(now often referred to as ‘unresponsive wakefulness syndrome’ or UWS). All have been investigated using advanced neuroimaging techniques, including structural and functional MRI, evoked potentials acquired using EEG and functional near-infrared spectroscopy. A pivotal finding in this literature was the discovery that some patients who fulfil all of the clinical criteria for the vegetative state (VS)

remain aware, despite the complete absence of any behavioural signs such as command-following (Owen *et al.*, 2006). Moreover, this form of ‘covert consciousness’ can be detected, either using functional MRI (Owen *et al.*, 2006; Monti *et al.*, 2010), or at the bedside, using EEG (Cruse *et al.*, 2011). A recent review of >1000 patients with disorders of consciousness, tested across many independent

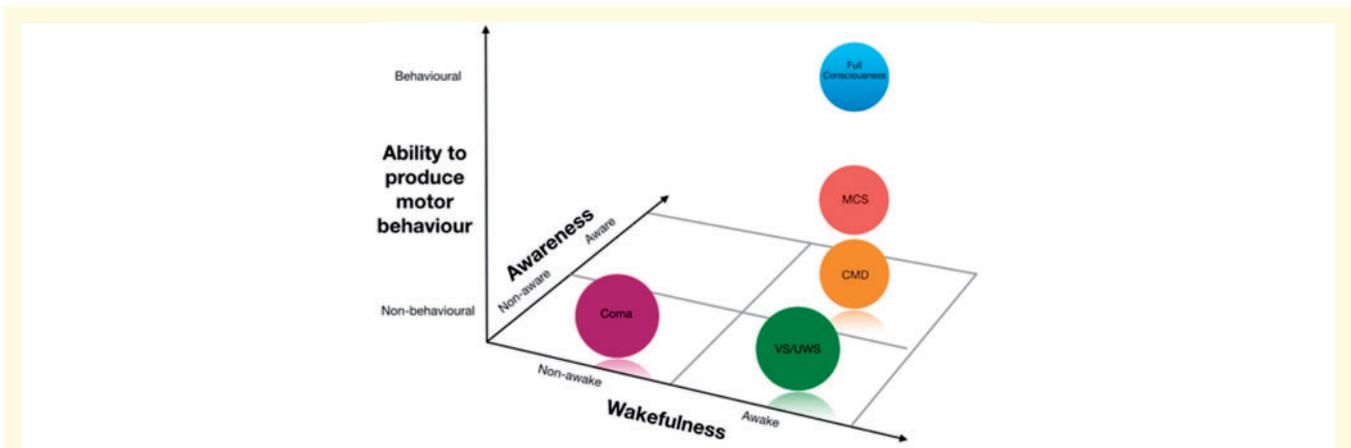


Figure 1 Disorders of consciousness: three dimensions. Disorders of consciousness can be characterized along three dimensions; wakefulness (x-axis), awareness (z-axis) and the ability to produce voluntary motor behaviour (e.g. command-following; y-axis). Coma patients lack wakefulness and command-following ability and are thought to lack any awareness. Minimally conscious patients (MCS) exhibit wakefulness and show intermittent signs of (some) awareness and behavioural responsiveness. Recent evidence (Owen *et al.*, 2006) has shown that the vegetative state/unresponsive wakefulness syndrome actually comprises two distinct conditions; those who are awake, behaviourally non-responsive and show no signs of awareness even when advanced neuroimaging techniques are used (labelled VS/UWS), and those who exhibit ‘cognitive-motor dissociation’ (CMD) and are awake and behaviourally non-responsive, yet show clear signs of awareness (e.g. neural command-following) when assessed with functional MRI or EEG. In the study by Pan and colleagues, 40% of patients who were awake, behaviourally non-responsive, but thought to be entirely unaware (i.e. with a clinical diagnosis of VS/UWS), were shown to be able to follow commands using EEG and were therefore reclassified as CMD. Of these, 83% subsequently progressed to a minimally conscious state. In contrast, of those patients who showed no signs of covert consciousness when assessed using the EEG task, only 18% showed any signs of consciousness on reassessment at 3 months.

centres using different neuroimaging techniques, confirmed that ~20% are, in fact, covertly aware and able to follow commands by modifying their brain activity (Kondziella *et al.*, 2016). Indeed, in some cases, patients previously assumed to be vegetative for many years have been able to communicate their thoughts and wishes using these advanced neuro-imaging methods (Monti *et al.*, 2010; Fernández-Espejo and Owen, 2013). Based on these and other findings, formal clinical bodies in the UK and the USA have recently recommended that functional MRI and EEG now be used in the management of vegetative and minimally conscious patients (Giacino *et al.*, 2018).

While exact numbers are difficult to determine, these discoveries suggest that some tens of thousands of patients worldwide have been erroneously assumed to be ‘awake but unaware’, sometimes for decades at a time, when in fact they have remained conscious throughout; aware of who they are, where they are, and the predicament they are in. To be clear, this issue is not one of clinical misdiagnosis

(although that is certainly an extant problem in this most challenging population of patients); rather, for the most part, these patients have not been identified simply because the technology did not exist to bring their real situation to light.

Nevertheless, one important question that remains is how this phenomenon, which has been termed ‘cognitive motor dissociation’ or CMD (Schiff, 2015) relates to prognosis; that is, are such patients more likely to show signs of recovery than patients who are truly VS/UWS, despite their indistinguishable behavioural signs and similar clinical profiles? In this issue of *Brain*, Pan and co-workers have made some progress in answering this question by following a relatively large group of CMD patients who were identified using a novel (evoked) EEG command-following task, and then comparing their clinical outcomes to those of patients who showed no signs of covert awareness (Pan *et al.*, 2020). Seventy-eight patients, clinically diagnosed as VS/UWS or minimally conscious, were asked to focus their attention on one of two stimuli presented on a computer

screen (e.g. a familiar or an unfamiliar face), while a machine learning classifier attempted to decode their EEG response to determine whether or not they were attending to the stimulus as requested. Evidence that they were consistently attending to the appropriate stimulus was taken as confirmation that they were ‘command-following’; not in the traditional way (e.g. by moving a finger or blinking an eye), but by modulating their focus of attention according to a specific instruction to do so (and thus, changing their pattern of brain activity in a manner that could be detected by the classifier). Similar logic has been used successfully in the past to identify covert consciousness in patients who clinically appear to be VS/UWS (Owen *et al.*, 2006; Cruse *et al.*, 2011), and to turn these neural responses into a rudimentary form of (‘yes/no’) communication between the patient and the outside world (Monti *et al.*, 2010). Of 45 patients diagnosed as VS/UWS, Pan and colleagues showed that 18 (40%) were able to perform their neural command-following task, suggesting that they were aware, despite their clinical profile. While this is somewhat higher

than the percentage of VS/UWS patients who have previously been shown to be covertly aware through either functional MRI (Monti *et al.*, 2010) or EEG (Cruse *et al.*, 2011; for a review, see Kondziella *et al.*, 2016), exact inclusion criteria (e.g. time since injury) and sample sizes vary from study to study, which likely accounts for this variability. Nevertheless, the fact remains that in the latest investigation by Pan and colleagues, 40% of patients thought to be entirely unaware with a clinical diagnosis of VS/UWS were able to follow commands consistently enough to be classified as aware by a novel machine learning algorithm. Moreover, when followed-up 3 months later using the Coma Recovery Scale-Revised, 15 of these 18 patients (83%) had progressed to a minimally conscious state, showing behavioural signs of consciousness that were absent, or undetected, at the time of the EEG evaluation. In stark contrast, of the 27 VS/UWS patients who showed no signs of covert consciousness when assessed using the EEG task, only five (18%) showed any signs of consciousness on reassessment at 3 months. These results argue, rather compellingly, that when residual awareness is detected using an EEG-based command-following procedure, some improvement is more likely than when early signs of covert awareness are not detected. Of course, at some level, this result is entirely intuitive; presumably, if some consciousness remains, then a patient is likely less severely brain damaged than when no consciousness remains, and with less severe brain damage the prognosis is likely to be better. Nevertheless, this is a brave new world where preserved ‘consciousness’ is being inferred solely based on a predicted neural response to a specific stimulus (rather than, say, via verbal report), and in this light the result is potentially transformative.

The pattern was similar among the slightly smaller group of patients who were diagnosed as being in a minimally conscious state (i.e. exhibiting inconsistent, but reproducible signs of awareness through behavioural responses) at the time of the EEG evaluation. That is to say, of 16 minimally

conscious patients who were able to perform the EEG command-following task successfully, 14 (87%) showed improved Coma Recovery Scale scores 3 months later, compared to only 4 of the 17 (23%) who had not been able to perform the EEG task. Thus, as was the case with the VS/UWS group, in the majority of minimally conscious patients who showed inconsistent behavioural signs of conscious awareness, being deemed capable of ‘neural command-following’ by a machine learning classifier predicted that they would experience some improvement over the next 3 months.

The Pan *et al.* (2020) study makes two crucial contributions to the existing literature. First, it suggests that EEG-based neural command-following tasks may improve diagnostic accuracy in patients with disorders of consciousness. Thus, overall, 44% of patients who appeared not to be able to follow commands behaviourally could do so using the EEG system, confirming that their actual state of awareness was rather different to that suggested by their formal clinical diagnosis (either completely unaware in the case of VS/UWS, or showing inconsistent signs of awareness in the case of minimally conscious state). EEG is more cost-effective than functional MRI (arguably the gold standard for identifying covert consciousness in behaviourally non-responsive patients) and, more importantly, it is portable, meaning that it can be deployed at the bedside and/or is suitable for patients who may have contraindications for functional MRI. Second, this study introduces a new tool for improving prognosis in patients with disorders of consciousness. Thus, overall, 85% of patients who could perform the EEG neural command-following task showed some signs of clinical improvement 3 months later. Although other studies with smaller sample sizes have investigated outcomes in patients with disorders of consciousness (Curley *et al.*, 2018), this is the first to show a statistically significant relationship between clinical improvement and the presence of covert command-following abilities.

On a final cautionary note, when discussing prognosis after severe brain injury, it is important not to conflate improvement with recovery. In the study by Pan *et al.*, clinical improvement among the CMD group was, for the most part, modest (Supplementary Table 1 in Pan *et al.*, 2020). Meaningful recovery (e.g. to resume normal activities of daily living), in patients with disorders of consciousness is rare and, where it occurs, is usually accompanied by significant and permanent disabilities. Nevertheless, by providing a tool that improves both diagnostic accuracy and predicts clinical improvement (however modest), the work of Pan and colleagues will, hopefully, drive further efforts to develop interventions to facilitate recovery and to improve the quality of life of these patients.

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Atrophy network mapping of transdiagnostic cognitive and neuropsychiatric symptoms

This scientific commentary refers to ‘Network localization of clinical, cognitive, and neuropsychiatric symptoms in Alzheimer’s disease’, by Tetreault *et al.* (doi:10.1093/brain/awaa058).

One of the most significant challenges in diagnosis and monitoring of Alzheimer’s disease, as well as biomarker and treatment development, is the considerable heterogeneity in clinical presentation and pathology observed across individuals. In this issue of *Brain*, Tetreault and co-workers introduce a new technique aimed at finding underlying patterns within this heterogeneity by mapping clinical, cognitive and neuropsychiatric symptoms to large-scale brain networks (Tetreault *et al.*, 2020).

A decade ago, Seeley *et al.*’s (2009) landmark paper provided evidence of meaningful patterns of syndrome-specific atrophy across five neurodegenerative dementias, including behavioural variant frontotemporal dementia and corticobasal syndrome. The peak region of cortical atrophy across groups with the same clinical syndrome was used as a seed in functional connectivity analysis in cognitively normal individuals. Healthy functional connectomes closely resembled the patterns of atrophy

observed in the clinical syndromes, being both distinct from each other and reflecting known, domain-specific, functional networks that mirrored the principal deficit in each syndrome. For example, Alzheimer’s disease was associated with episodic memory deficits and atrophy within medial temporal and posterior cingulate regions, while patients with semantic dementia had word finding and object naming difficulties associated with prominent left temporal pole atrophy. Later, Zhou *et al.* (2012) clarified the mechanisms by which atrophy may spread through functional networks, namely via the transneuronal spread of pathology in high use, high vulnerability network nodes. While a critical step in formalizing the importance of large-scale distributed brain networks underlying dementia syndromes, these studies stopped short of identifying brain networks associated with specific symptoms. This is important for two reasons. First, within clinical syndromes, there is significant heterogeneity in the symptoms presented by individual patients. Symptoms include both cognitive deficits, such as memory impairment, and neuropsychiatric problems such as hallucinations or delusions. Second, the same symptom may occur across clinical syndromes, suggesting the underlying

molecular pathology alone cannot account for the clinical phenotype (Pievani *et al.*, 2014; Husain, 2017).

The technique of lesion network mapping was developed in an effort to understand one of the most heterogeneous clinical populations, ischaemic stroke patients. Stroke patients present a complex challenge to cognitive neurology, and our understanding of brain-behaviour mapping, because patients with the same symptom can have damage in different, even non-overlapping regions (Fox, 2018). Lesion network mapping sought to reconcile this heterogeneity, positing that a given symptom arises because damage has occurred somewhere within a distributed, large-scale, symptom-specific network (Fox, 2018). This approach has been successfully applied to the identification of functional networks underlying symptoms ranging from memory deficits to delusions, auditory hallucinations and disorders of volition, familiarity and agency (Fox, 2018).

Tetreault *et al.* now introduce a new method, atrophy network mapping, that applies the logic of lesion network mapping to a clinical syndrome associated with more diffuse brain damage, namely Alzheimer’s disease. This