Functional 'unlocking': bedside detection of covert awareness after severe brain damage

This scientific commentary refers to 'Characterization of EEG signals revealing covert cognition in the injured brain', by Curley *et al.* (doi:10.1093/brain/awy070).

Severe acute brain damage, most often caused by trauma, anoxia or stroke, can result in coma—a transient state characterized by complete absence of wakefulness and of signs of awareness. The recovery of wakefulness without signs of awareness heralds a transition to vegetative state/unresponsive wakefulness syndrome (VS/UWS). Patients in a minimally conscious state (MCS) show reproducible purposeful behaviours but remain unable to communicate. MCS can be divided into MCS+ and MCS− depending on the presence or absence of inconsistent language functions. Emergence of MCS (EMCS) is diagnosed when patients regain functional communication. Finally, patients with locked-in syndrome can be misdiagnosed with these disorders of consciousness because of complete paralysis of voluntary muscles, except for eye-coded communication (Gosseries *et al.*, 2014). Prevalence rates of VS/UWS and MCS are difficult to evaluate because of a lack of systematic surveillance. In the USA, prevalence estimates range from 25 000 to 420 000 for VS/UWS and from 112 000 to 280 000 for MCS (Hirschberg and Giacino, 2011). In this issue of *Brain*, Curley and coworkers address the difficult problem of detecting covert awareness in non-communicative patients with severe brain damage (Curley *et al.*, 2018).

The detection of covert awareness in patients with disorders of consciousness after coma has important consequences for diagnosis, prognosis and therapy, including pain management, rehabilitation and end-of-life decisions. However, high rates of misdiagnosis (up to ~40%) have repeatedly been reported between VS/UWS and MCS. At least five repeated behavioural assessments with a validated standardized scale, the Coma Recovery Scale-Revised (CRS-R), are required to make an accurate clinical diagnosis (Wannez *et al.*, 2017). Yet even after exhaustive behavioural assessments are performed, signs of covert awareness can be detected in ~20% of patients in a behavioural VS/UWS with functional MRI and EEG command-following paradigms (e.g. Monti *et al.*, 2010; Cruse *et al.*, 2011) or with transcranial magnetic stimulation combined with high-density EEG (TMS-EEG) (Casarotto *et al.*, 2016). These findings have recently led to the definition of a new clinical entity, referred to as MCS*, functional locked-in syndrome or cognitive motor dissociation syndrome (CMD), where patients are behaviourally unresponsive but show evidence of covert awareness with neuroimaging. While the pathophysiology of CMD remains unclear, the majority of patients diagnosed so far had sustained a traumatic brain injury. The recognition of a high prevalence of CMD after severe brain damage creates an urgent need to improve routine diagnosis of covert awareness and to find means to re-establish communication with these behaviourally unresponsive but conscious individuals. Despite constituting a significant advance, functional MRI command-following paradigms are challenging to use in routine clinical practice because of their lack of portability. Curley *et al.* describe a new approach to detect covert awareness in patients with severe brain damage at the bedside, using repetitive testing with EEG command-following paradigms. The New York team led by Nicholas Schiff used a variety of tasks, aiming to assess within-subject reliability of responses while taking into account between-subject variability in brain physiology after brain damage. They also performed a systematic comparison between EEG, behavioural data and functional MRI command-following paradigms.

The new study included 28 patients with severe acquired brain damage and 15 controls. Among these 28 patients, 17 met behavioural criteria for MCS (one of whom also had an assessment while behaviourally in VS/UWS), eight for EMCS (two of whom also had an assessment while behaviourally in MCS) and three for VS/UWS. The authors performed assessments using a 37-electrode EEG system in most subjects (two patients were recorded with 23 and 29 electrodes). Mental imagery tasks consisted of imagining playing tennis, spatial navigation, swimming, and/or finger tapping. Data analysis quantified changes in EEG power during 10–14 s silent periods following task instructions compared to 10–14 s silent periods following instructions to rest. Criteria for a positive response to command required two outcomes: first, results had to show significance in at least one run and a trend towards significance in at least one other run for a difference between task and rest in a given channel for at least two contiguous frequency bins, after a two-group resampling test. Second, results also had to be significant after correction for multiple comparisons across channels using the false discovery rate for a two-group test applied to concatenated data from all runs of a given task. These conservative criteria led to an estimation of false positives of 8% in shuffled data from the 'tennis' paradigm.

Evidence of EEG command-following was found in 21/28 patients studied (2/3 VS/UWS, 11/17 MCS and all eight EMCS)—and all 15 controls. Evidence of functional MRI response to command was found in 9/23 patients (five EEG command-follower patients could not undergo MRI). This is in contrast with previous studies (Monti *et al.*, 2010; Cruse *et al.*,

2011), which documented ~20% responders in VS/UWS and no evidence of functional MRI command-following in MCS. Curley *et al.*'s high response rate using both EEG and functional MRI could be related to differences in task design: shorter blocks of 10–14 s could be more sensitive to detecting patient responders with fluctuating arousal. A higher sensitivity of EEG for detecting covert command-following in MCS is also in line with results of a previous EEG study assessing increases in P300 amplitude after patients were instructed to voluntarily attend to their own name (Schnakers *et al.*, 2008). As Curley *et al.* mention, their higher rate of responders may also be partly explained by selection bias: included patients were able to undergo repetitive good quality assessments, and all except one had EEG backgrounds that were only mildly to moderately abnormal.

Command-following with EEG or functional MRI is suggestive of preserved communication abilities, as such paradigms have previously been used by VS/UWS patients to accurately answer questions with yes/no choices (Monti *et al.*, 2010). Importantly, among the 21 EEG command-followers in Curley *et al.* (2018), only 40% showed communication abilities according to the CRS-R. Assessments of EEG command-following abilities may provide added value to detect patients who may be candidates for EEG-based brain-computer interfaces, allowing them to consciously control and interact with their environment.

For most patients, EEG responses to command were only achieved for one of the tasks. These findings are in line with the need for repeated behavioural assessments to sensitively detect consciousness at the bedside (Wannez *et al.*, 2017). Five MCS patients who were at first categorized as non-responders in some tasks were found to have positive responses after rejecting trials with low vigilance at EEG baseline. All of these patients were found to have positive responses in other tasks. Future studies may restrict testing conditions to periods with sustained EEG arousal, perhaps optimized through EEG vigilance monitoring coupled to arousal facilitation procedures.

EEG responses to command in healthy volunteers showed a consistent attenuation of alpha-beta power over central channels. Patients with brain damage showed variable but reproducible spatiotemporal patterns of EEG responses, with either increased or decreased power in delta to beta frequencies. These differences in EEG patterns may be partially explained by deafferentation, with local activation reflected by decreased sleep-like oscillations rather than by a normal dampening of thalamocortical idle rhythms. The authors also reported the observation of a patient tested twice during recovery, whose response at first took the form of an increase, then a decrease in alpha power. This finding raises important questions about neural processes transcending particular brain oscillations that may sustain consciousness and cognition.

Although more sensitive than previous functional MRI designs, the sensitivity of Curley *et al.*'s approach was not perfect: six MCS subjects did not respond to EEG tasks, one of whom had shown intentional communication abilities behaviourally. These findings emphasize the complementarity of clinical and neuroimaging approaches, with clear added value of EEG compared to functional MRI. In a more general sense, clinical or motor-independent command-following paradigms may also miss conscious patients with aphasia, abulia or sensory impairment that would prevent their participation in tasks (Boly *et al.*, 2007). Therefore, assessments of 'resting state' spontaneous brain activity using metabolic PET imaging, functional MRI or EEG provide useful complementary information (Gosseries *et al.*, 2014). Objective markers of consciousness derived from theoretical approaches—such as TMS-EEG with the perturbational complexity index (PCI) (Casarotto *et al.*, 2016)—also constitute promising indices shown to be highly sensitive and specific for detecting consciousness in motor-unresponsive subjects.

Perhaps the most important contributions of Curley *et al.* (2018) are to pave the way for large-scale investigations on the prevalence of covert awareness after severe brain damage, and to show that many patients behaviourally in MCS may in reality be in a state closer to a functional locked-in syndrome rather than in a sedated state. As the ability to communicate is the strongest predictor of good quality of life in chronic locked-in syndrome (with an odds ratio of 20) (Bruno *et al.*, 2011), ethical principles of both beneficence and respect for autonomy should prompt us to continue efforts to re-establish communication with CMD subjects. Novel technologies such as those reported here by Curley *et al.* will eventually lead to a revised nosology of post-coma states, based on objective brain measures of residual cognition, unbiased by motor incapacity. Ultimately, this will enable these vulnerable patients to demand their right to better rehabilitation care, self-determination and quality of life.

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Is longitudinal tau PET ready for use in Alzheimer's disease clinical trials?

This scientific commentary refers to 'Longitudinal tau PET in ageing and Alzheimer's disease', by Jack, Jr *et al.* (doi:10.1093/brain/awy059).

Tau PET imaging, using radiotracers like ^{18}F-flortaucipir, has been shown to reliably detect the tau-containing paired helical filaments typical of Alzheimer's disease dementia *in vitro* and *in vivo* (Smith *et al.*, 2016). ^{18}F-flortaucipir may also bind to tau aggregates in other tauopathies, including corticobasal degeneration and progressive supranuclear palsy, albeit to a much lesser extent compared to Alzheimer's disease (Smith *et al.*, 2017). Given the central role that accumulation of tau pathology is thought to play in the progression and clinical manifestation of Alzheimer's disease, the ability to measure this pathology *in vivo* represents a major step forward and provides opportunities for early diagnosis and assessment of target engagement in clinical trials. As tau PET is a novel technology, longitudinal studies determining the change over time in the regional uptake of ^{18}F-flortaucipir have not been available to date. In this issue of *Brain*, Jack and co-workers evaluate the change over 1 year in tau PET signal in a relatively large group of clinically unimpaired individuals with differing amyloid-β status (59 amyloid-β-negative and 37 amyloid-β-positive), as well as 30 amyloid-β-positive individuals with mild cognitive impairment or Alzheimer's disease dementia (Jack *et al.*, 2018).

The results reveal significant tau accumulation in the amyloid-β-positive clinically unimpaired group, in a pattern that is not restricted to the medial temporal lobe but also encompasses medial parietal areas, including the posterior cingulate cortex. This suggests that the initial accumulation of tau aggregates in Alzheimer's disease may not be restricted to the medial temporal lobes as much as implied by Braak staging. Instead, Jack *et al.* demonstrate that early longitudinal tau aggregation coincides with regions showing accumulation of amyloid-β fibrils during the earliest stages of preclinical Alzheimer's disease (Palmqvist *et al.*, 2017). Although there was no significant change at the group level among the amyloid-β-negative unimpaired group, previous cross-sectional studies have revealed mild associations between older age and increased retention of ^{18}F-flortaucipir in the medial temporal lobe (Lowe *et al.*, 2018). This might be congruent with a very slow and subtle accumulation of tau aggregates in these regions over decades in amyloid-β-negative individuals. However, the observation that amyloid-β positivity was the strongest predictor of tau accumulation among unimpaired individuals reiterates that accumulation of amyloid-β fibrils is an important driver for the build-up of tau aggregates during preclinical Alzheimer's disease (Price and Morris, 1999), at least to reach the levels detectable with tau PET imaging.

It is possible that PET imaging with tracers like ^{18}F-flortaucipir or ^{18}F-florbetapir may not be able to detect the earliest accumulation of either tau or amyloid-β, as these tracers reveal only certain aspects of the pathology that occur later in the disease process (Fig. 1). Specifically, the amyloid tracers (^{11}C-PiB and the ^{18}F ligands) were developed from Thioflavin-T, and measure predominantly amyloid-β fibrils in cored/neuritic plaques, and more variably diffuse plaques. Thus, amyloid PET imaging techniques likely do not measure intraneuronal accumulation of amyloid-β in endosomes/multivesicular bodies, or the intracellular as well as extracellular amyloid-β oligomers, which probably precede the