Severe brain injury from cardiac arrest, trauma, stroke, and other causes can result in a disorder of consciousness (DOC). DOC includes vegetative state (VS) and minimally conscious state (MCS), which are defined, respectively, as no and minimal interaction with the environment. Key to this definition is that these diagnoses are based solely on observed behavior and not on the underlying brain pathology. This reliance on behavior implies that patients can be falsely diagnosed due to damage to motor systems out of proportion to brain systems responsible for conscious awareness; in other words, if a patient can’t move, there is no way to know that they are conscious.

One approach to improve diagnostic accuracy has been to bypass the motor system with direct readouts of brain activity to demonstrate that patients can follow commands. A groundbreaking report of this approach came in 2006 by Adrian Owen and colleagues, where they used functional MRI (fMRI) to show that a woman in VS after TBI could follow commands: imagining playing tennis and imagining walking around her house. The same group later published a case series of five more DOC patients who demonstrated fMRI evidence of command following, with one of them able to use the imagery tasks to answer five out of six autobiographical questions correctly.

While fMRI is a powerful tool, it requires patients be brought to it, so they might not be in an ideal state during that specific time, and it is impractical to establish consistent communication.

Another approach has been to use EEG to detect evidence of specific brain activities. Event-related potential analysis has been used as a marker of enhanced attention to specific words (e.g., asking a patient to attend to a specific name out of a stream of names). A more direct approach has been to read out cortical activity via changes in frequency content of the EEG (using power spectral analysis). We found that this approach can be successful.
in identifying motor imagery in healthy controls and two patients with severe traumatic brain injury (one in MCS and one in Locked-In-State).  

In 2011, Damian Cruse, Adrian Owen, and colleagues published in *The Lancet* a new technique using EEG to show evidence of command following (motor imagery). It garnered a great deal of news attention as the bedside technique found evidence for command following in three out of 16 VS patients. The authors used a newer approach called “machine learning,” whereby they used a computer algorithm to find differences in the EEG between hand and foot movement imagery in the subjects. This algorithm is akin to how email programs differentiate spam from regular email; the programs know nothing about spam, they simply get trained to distinguish features of emails that associate with spam (e.g., certain words or senders). This is different from standard analysis approaches where one looks for canonical signal changes in the power spectra (e.g., reductions in alpha-frequency power over motor cortex during hand movement imagery).

We were surprised by the findings, since there was a higher than expected rate of positive patients, and three out of 12 healthy controls showed no evidence for command following on the EEG. On review of the original data, we were further surprised, as all of the “positive” patient subjects showed slow monotonous EEGs consistent with severe cortical dysfunction. We next performed standard power spectral analysis and found no changes in cortical activity during the motor imagery tasks in any of the patients, though we did find evidence in all of the controls. We evaluated the machine learning methodology and found that it assumed that the EEG never changed except as due to task; this could have led to false positive findings, as the patients’ EEG had fluctuating amount of muscle artifact. This is akin to your spam filter failing because, by chance, all of your initial spam emails are short and non-spam are long, so the filter “learns” that all short emails are spam. The results of our reanalysis were also published in *The Lancet* and demonstrate the importance of data sharing to validate findings of key studies.

For a clinical neurologist, the above findings and related studies have some important implications. First, there is now repeated evidence that patients who are behaviorally in VS or MCS can have evidence of command following requiring language comprehension and motor imagery ability. On the one hand, this could be thought of as the “tip of the iceberg,” since there could be many others with retained higher-level abilities but not enough language or motor cortex to be recognized by these command following tasks. On the other hand, these patients are likely uncommon (note that the majority of published reports are based on chosen subjects, rather than an inclusive sample).

Second, our reanalysis of the Cruse, et al. 2011 paper, combined with our unpublished data, suggest that detailed neurological testing needs to play a major role in evaluation of level of consciousness. High quality behavioral exam, often requiring multiple attempts, is an essential first step to capture signs of consciousness that may be subtle and fluctuate. Clinical EEG can also be useful, as it is a marker of corticothalamic function and likely suggests which patients have residual conscious processing (though prospective studies are needed to confirm this). In regards to imaging, anatomical MRI showing location of brain injury has shown little correlation with cortical function, though FDG PET and quantitative blood flow MRI are promising tools. Regarding research tools, resting state EEG and combined TMS-EEG have also been shown to correlate with level of consciousness.

As for next steps, from a research standpoint, the functional brain imaging approaches mentioned above all need to be tested in larger, unselected cohorts who are followed prospectively to determine repeatability of the findings, and correlation with gold-standard clinical outcomes such as recovery of consciousness. From a clinical standpoint, the take-home message is that patients with disorders of consciousness can have a wide range of underlying brain functions and therefore require detailed expert exam to ensure accurate diagnosis. Without information about the true functioning of the brain, we are unable to make accurate prognoses and treatment recommendations to our patients’ families and caregivers.

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