

the incorporation of accurate and reliable 25-hydroxyvitamin D testing and that misclassification remains a challenge. That noted, whether even robust measurement of the 25-hydroxyvitamin D metabolite in serum accurately reflects whole-body vitamin D status in all individuals remains uncertain.

Stewart Pattman and colleagues suggest that fibromyalgia and chronic fatigue are appropriate conditions to request vitamin D measures. We cannot identify convincing evidence to support this assertion, and there is no evidence from large placebo-controlled randomised trials:<sup>1</sup> replete vitamin D status does not exclude these disorders, and there is no robust evidence that vitamin D supplementation improves symptoms. Further, people with fatigue and pain will probably spend less time outdoors, which leads to lower 25-hydroxyvitamin D (ie, reverse causality).

We agree that diagnosis of osteomalacia requires biochemical testing that could include 25-hydroxyvitamin D. We do not, however, believe that an increasing incidence of osteomalacia accounts for the increasing vitamin D requests. The National Institute for Health and Clinical Excellence guidelines for the secondary prevention of osteoporotic fragility fractures in postmenopausal women state that "vitamin D supplementation should be provided unless clinicians are confident that women who receive treatment for osteoporosis...are vitamin D replete".<sup>2</sup> Given that a significant majority of elderly women, particularly in northern latitudes, and particularly through the winter months, are likely to have insufficient 25-hydroxyvitamin D, the benefit of widespread testing is unclear, especially if supplements are to be prescribed irrespective of the result.

Our comments were intended as general guidance and clinical decisions are best made on a case-specific basis with specialist input as appropriate.

Furthermore, we respectfully suggest that asking clinicians to think through critically whether vitamin D testing is appropriate, particularly among asymptomatic people and particularly in conditions not linked to bone disease, is not to cast "unwarranted aspersions".

Alan Peiris and colleagues suggest that latitude and seasonality cannot predict vitamin D deficiency, citing data from an observational study of individuals who attended a vitamin D seminar and took supplements. Latitude and season are not investigated in that paper.<sup>3</sup> Peiris and colleagues suggest that widespread supplementation programmes could proceed without further evidence or trials of efficacy or safety. The Institute of Medicine does not seem to concur with this view.<sup>4</sup> We therefore reiterate the need to resist making causal inferences on the basis of observational evidence, which Peiris and colleagues seem to advocate.<sup>5</sup>

We declare that we have no conflicts of interest.

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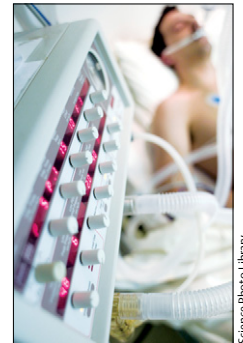
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## Bedside detection of awareness in the vegetative state

Damian Cruse and colleagues (Dec 17, p 2088)<sup>1</sup> report EEG evidence of command-following in three patients apparently in the vegetative state. However, the known alterations of brain function after severe injury associated with vegetative state and minimally conscious state, along with the relatively weak EEG signals seen in the study's healthy controls, raise concerns about the validity of the findings.

Previous studies that used EEG signals to identify motor imagery in paralysed conscious patients<sup>2,3</sup> or to indicate awareness in disorders of consciousness<sup>4</sup> used simple EEG features: systematic changes in voltage ("power") in alternating imagery and rest conditions. Cruse and colleagues instead use a classifier based on a combination of many EEG parameters. Neither raw EEG, nor individual parameter values, nor their weightings by the classifier are presented. Thus, it is difficult to assess the approach's biological underpinnings, and credibility hinges on rigorous statistical controls.

However, establishment of such controls is daunting: the EEG is statistically non-stationary and typically contains gradually changing contaminants such as electromyographic noise (including the known stimulus-linked startle in patients in the vegetative state<sup>5</sup>). In a block-design study, it is therefore difficult to separate selective task-driven responses from artifactual changes that happen to covary with task. Cruse and colleagues' use of 0.5 s of pre-tone brain activity is an insufficient control. In comparison with the 3 s analysed post-tone, the pre-tone control classifier is likely to be insensitive to the confounds that must be excluded.



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Since identification of command-following is so crucial for diagnosis and care of patients in vegetative and minimally conscious states, the importance of thoroughly vetted, transparent methods cannot be overstated.

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### Authors' reply

Andrew Goldfine and colleagues make three comments about our paper. First, they imply that we do not use “power” as features in our analyses. In the Methods section<sup>1</sup> we clearly stated that we used power values as features, in line with many published studies on motor imagery and the contemporary brain-computer interface.

Second, they argue that an unspecified factor could have covaried in time with our randomly varying task structure, leading to reliable, yet erroneous, classification. In fact, randomisation is used in task design specifically to preclude conditions under which such covariation could occur. Indeed, in our paper we report data from healthy controls who were asked simply to listen to the same task instructions and “mind-

wander”, rather than complete the imagery tasks. As we reported, no positive EEG outcomes occurred under these conditions. By contrast, 75% of these participants were able to return significantly classifiable EEG data when actually following the commands. In short, the data show that random EEG fluctuations (by any known or unknown variable) were not sufficient to return a single, significant classification.

Third, Goldfine and colleagues argue, reasonably, that a 500 ms baseline might be insufficient for comparison with an action period of 3 s. Accordingly, we have rerun our analyses, comparing the 500-ms-wide “baseline” time window before the tone (–500 ms to 0 ms) with an equal-sized time window beginning 1 s after the tone (ie, far beyond any possible “stimulus-linked startle”, of the sort described by Goldfine and colleagues<sup>2</sup>). That is to say, exactly the same number of band-power values are entered into the analyses at pre-tone and post-tone time-points. The results were unchanged; as we reported in the paper, the same three patients in the vegetative state returned significant classification values in the post-tone window, but non-significant classification values in the pre-tone window—confirming that they were, indeed, following commands.

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Disorders of consciousness are at a historic epistemological junction: those who think like Damian Cruse and colleagues<sup>1</sup> continue to search within the vegetative state for evidence of misdiagnosis. However, we believe that, when a pathological state presents itself, we must research its treatment and prognosis rather than striving to search for a different diagnosis. To try to disprove the diagnosis of the vegetative state is like appearing during a liver transplant with evidence that the diseased liver in reality still works, albeit only partly. Cruse and colleagues persist in the assertion that many diagnoses are wrong and that the incidence of vegetative state is overestimated compared with minimally conscious state. For us, this is the obvious natural consequence of the fact that differences between vegetative and minimally conscious states have not yet been categorised in many of the protocols for diagnosis and treatment used by health systems worldwide.

Finding unexpected signs of consciousness simply means changing the diagnosis from vegetative state to locked-in syndrome. It means that consciousness was not evident on clinical examination, but has come to light through paraclinical testing. In our view, the most sensible thing to do is to approach disorders of consciousness as neurologists rather than instrumentalists and to develop reliable prognostic methods, validated on cohorts of an ever-increasing number of patients.<sup>2</sup> We must also acknowledge the overlap between locked-in syndrome and vegetative state: a necessity which we have emphasised on many occasions.<sup>3,4</sup>

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