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Authors' reply

The primary suggestion put forward by Andrew Goldfine and colleagues is that a permutation test should have been used to infer command-following in our 2011 publication in *The Lancet*.[1] One obvious problem with this argument is that, if a permutation test were used for all of the patients, half of them would only produce 36 permutations that could contribute to the test. It is accepted statistical practice that at least 1000 permutations are required to draw valid conclusions.[2,3] As such, the outcome of their suggested approach would be statistically invalid for half the patients in our original study—ie, no one can know whether the answer generated by their approach is right or wrong because it is not an appropriate test to use given the data available.

One could argue that a task requiring more frequent switches between commands could be used to generate the requisite number of permutations. However, such a task would inevitably increase the cognitive load substantially and would probably be impossible for severely brain-injured patients to do. Indeed, the task that we chose for our study, with its blocked structure, has cognitive demands that are more similar to the mental imagery tasks that have previously been shown to detect awareness in a significant proportion of vegetative state patients using functional magnetic resonance imaging (fMRI).[4]

Moreover, Goldfine and colleagues' suggestion that our patient data violate the independence requirement of the binomial test is based on an assumption that the patient group should be treated as homogeneous. To make their point, they show that, across the patient group, there seems to be a violation of independence—ie, a U-shaped histogram of p values. Although this might be the case across the group as a whole, it is certainly not the case when the data are inspected on an individual patient basis. It is widely accepted, even by Goldfine and colleagues,[5–10] that a significant minority of patients (about 17%[4]) who are diagnosed as being in the vegetative state nevertheless retain some level of conscious awareness and are able to follow commands detected by fMRI. By extension then, this group is clearly not at all homogeneous—that is to say, some are likely to be truly vegetative, whereas others might appear to be vegetative behaviourally, but are in fact covertly aware. It makes little sense, therefore, to group all of our vegetative state patients together in the way suggested by Goldfine and colleagues, because the (known) majority of truly vegetative patients will water down the covertly aware subgroup, rendering the latter more difficult to detect using any statistical method. Indeed, when we applied the same test for independence used by Goldfine and colleagues to each patient dataset individually, rather than as a group (ie, using the standard working hypothesis that all patients are different), we found that all three of our positive patients pass the assumption of independence—ie, one-tailed histograms. By Goldfine and colleagues' own test, therefore, our use of the binomial method is validated in these positive individuals.

Although there are few known truths when attempting to detect covert awareness, the one thing we can assume to know is that when healthy volunteers are asked to do the imagery tasks described in our original paper, they are doing them. Equally, when asked to not do the imagery tasks, it is reasonable to assume that they are not doing them. It is reassuring then, that our task and analyses identified significant command-following in 75% of the healthy participants who contributed to the original *Lancet* article (and correctly detected the absence of command-following in 100% of cases). Although not perfect, this is, on balance, a reasonable approximation of the only known truth. By stark contrast, the method expounded by Goldfine and colleagues only detects command-following in 40% of the healthy participants they analysed. In short, because their method fails to detect command-following in 60% of healthy volunteers, it is equally likely to fail to detect command-following (where it exists) in most patients.

Goldfine and colleagues also point to differences in the spatial and spectral characteristics of the neural command-following response seen in our three positive patients, relative to healthy controls. We would certainly have to agree that there are differences (as one would expect after serious brain injury), but question their relevance here. Indeed, in their own recent EEG study, Goldfine and colleagues[8] highlight the "variability in healthy control results, along with the fact that those with severe brain injury have differences in neuroanatomy and connectivity due to injury and the recovery process", yet go on to accept as evidence of command-following a broad range of EEG responses that varied widely in terms of their spatial and spectral characteristics. They also state that "It is not possible to determine whether the reason for the difference in this patient's [EEG] spectral pattern [when compared with healthy controls] reflects variation in the way the task was performed, or an injury-induced reorganization in cerebral networks supporting the behavior".[8] Our interpretation of these spatial and spectral differences, therefore, concurs fully with their own and does nothing to undermine the key results reported in our *Lancet* paper.

These methodological concerns about Goldfine and colleagues' assumptions notwithstanding, their reanalysis only pushes two of our three positive patients to just beyond the widely accepted $p<0·05$ threshold for significance—ie, to $p=0·06$ and $p=0·09$, respectively. To dismiss the third patient, whose data remain significant, they state that the statistical threshold for accepting command-following should be adjusted to account for the number of patients who have been assessed (a so-called multiple comparisons correction). We know of no groups in this field who routinely use such a conservative correction with patient data, including Goldfine and colleagues.[6,8–10] In this particular case, the only reason for doing so would be if we had no a-priori hypothesis. In the Introduction to our *Lancet* paper, we reviewed several previous papers,[4,11] and concluded that "these findings confirm that a population of patients exist who meet all the behavioural criteria for the vegetative state, but nevertheless retain a level of covert awareness that cannot be detected by thorough behavioural assessment". Our a-priori hypothesis could hardly have been clearer.

Finally, it is reassuring to note that corroborative data using independent methods, including a previously validated fMRI test of command-following,[11] is available for two of our three positive patients. These data confirm that these patients were aware during the same week in which the EEG data in question was acquired.

In conclusion, Goldfine and colleagues make some interesting points about the choice of statistical model when seeking to identify covert command-following in severely brain-injured patients. Their unconventional cross-validation approach does suggest that the EEG responses of two of our three positive patients became less consistent across time, and argues for future iterations of the task structure to be altered to accommodate this. Indeed, our goal, like that of Goldfine and colleagues, is to develop increasingly sensitive tools to identify covert command-following and, in that spirit, we have recently published a method that more formally addresses many of their current concerns.[12] Clearly, it is only through the continuing improvement of our complementary approaches that we will converge on the optimum methods for accurately identifying covert awareness, where it exists, in every severely brain-injured patient.

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A: Please declare any conflicts of interest. If none state "We declare that we have no conflicts of interest."