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ORIGINAL ARTICLE

Lies, damned lies and diagnoses: Estimating the clinical utility of assessments of covert awareness in the vegetative state

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Abstract

Background: Functional neuroimaging of patients in the vegetative state has been shown to provide diagnostic and prognostic information beyond that which conventional behavioural assessments may allow. However, before these promising approaches may reach large numbers of patients through a standard clinical protocol, it is necessary to determine the utility of these assessments—i.e. the accuracy of their diagnoses.
Methods and results: This study demonstrated that, due to the nature of statistical testing and the absence of a 'ground truth' of consciousness, it is impossible to calculate the conventional measures of clinical utility—sensitivity and specificity—for diagnoses made on the basis of functional neuroimaging for command-following. Nevertheless, it is crucial for such measures to be determined in order for valuable clinical resources to be distributed wisely. Therefore, a number of alternative guidelines are offered for the estimation of clinical utility.
Conclusions: By evaluating new and existing functional neuroimaging methods against the proposed guidelines, this study argues that it may be possible to achieve dramatically and efficiently improved diagnostic and prognostic accuracy for all vegetative state patients.

Keywords

Awareness, minimally conscious state, sensitivity, specificity, vegetative state

History

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Introduction

In recent years it has become increasingly apparent that the absence of behavioural evidence for command following is not necessarily indicative of the true absence of awareness or of the absence of an ability to follow commands under appropriate conditions. When provided with an opportunity to follow commands covertly, such as by engaging in mental imagery, a sub-set of patients who have been diagnosed as entirely unaware—i.e. in the Vegetative State (VS; or Unresponsive Wakefulness Syndrome, UWS [1])—have produced patterns of neural activity that are formally indistinguishable from those produced by healthy aware individuals. This increasing body of evidence from functional magnetic resonance imaging (fMRI [2–5]) and electroencephalography (EEG [6–11]) has served to highlight the high rate of misdiagnosis associated with behavioural assessments of awareness [12–14]. The potential of neuroimaging-based assessments of covert awareness to increase diagnostic and prognostic accuracy in the VS/UWS has led some to argue for their inclusion in a standard clinical assessment protocol [15] (see Table I for a summary of some of the current techniques).

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However, a test that cannot detect covert awareness with a high level of accuracy would be an inappropriate use of valuable clinical resources. Therefore, the utility of these tests for detecting awareness in the VS/UWS must be determined before they can be incorporated into the clinical routine. When investigating the utility of a clinical test, the match or mismatch between the outcomes of the test and the 'truth' of the situation must be considered. Typically, this is summarized in a 2×2 contingency table (two outcomes vs. two truths; see Table II) in which all possible truths are described. Clearly, it is the goal of any clinical test to maximize the likelihood of a 'true' outcome and to minimize the likelihood of a 'false' one.

This article will argue that the clinical utility of tests for covert awareness cannot be evaluated in the same way as other clinical assessments. However, it recommends a number of approaches that allow for utility to be estimated and that it is hoped will ultimately allow for the informed inclusion of covert awareness assessments in the clinical routine. First, the challenges posed by each possible outcome of an assessment of covert awareness are considered.

True positives

When a test concludes that a condition is present when it is truly present, the test has returned a true positive, or a hit. In the clinical domain, the number of true-positives is used to

Table I. Summary of current functional neuroimaging techniques for detecting covert command-following in the vegetative state. True and false positive rate estimates are derived from the associated manuscripts and the estimation method employed in each study is described.

Article	Command(s) to follow	True positive estimate	True positive estimation method	False positive estimate	False positive estimation method
Owen et al. [2] (also Boly et al. [18])	Mental imagery (fMRI)	100% (36/36)	Healthy controls	0% (0/1)	Healthy control not instructed to follow commands
Schnakers et al. [9]	Count target words (ERP)	100% (12/12)	Healthy controls	Not estimated	–
Bekinschtein et al. [26]	Detect auditory irregularities (ERP)	100% (11/11)	Healthy controls	0% (0/21)	Healthy controls with diminished awareness of stimuli (distraction)
Goldfine et al. [8]	Mental imagery (EEG)	100% (5/5)	Healthy controls	Not estimated	–
Bardin et al. [4]	Mental imagery (fMRI)	100% (14/14)	Healthy controls	Not estimated	–
Cruse et al. [6, 7]	Mental imagery (EEG)	75% (9/12)	Healthy controls	0% (0/12)	Same controls instructed not to follow the commands
Cruse et al. [11]	Motor attempt (EEG)	100% (6/6)	Healthy controls	0% (0/6)	Same controls instructed not to follow the commands
Lulé et al. [10]	Count target words (ERP)	94% (15/16)	Healthy controls	Not estimated	–

fMRI, functional magnetic resonance imaging; ERP, event-related potentials; EEG, electroencephalography.

Table II. Test outcomes *vs.* the truth. Formulae for the calculation of sensitivity and specificity are also provided.

	The truth	
Test outcome	Awareness present	Awareness absent
Evidence present	True Positive (T+)	False Positive (F+)
Evidence absent	False Negative (F−)	True Negative (T−)
	Sensitivity = n(T+)/(n(T+) + n(F−))	Specificity = n(T−)/(n(T−) + n(F+))

describe the *sensitivity* of the test (or the number of true positives/number of true positives + number of false negatives). In the case of a test of covert awareness, the sensitivity would describe the likelihood of judging an individual to be aware when they are truly aware.

Clearly, the accuracy of a test outcome can only be determined through comparison with the 'truth'. In the majority of clinical fields, the truth can be derived from a gold standard laboratory assessment—e.g. a biopsy, or post-mortem investigation. However, when detecting covert awareness, what is the gold standard from which the 'truth' can be derived?

While behavioural assessment is the current clinical standard for detecting awareness, it certainly does not represent the ground 'truth' of awareness. For example, in cases of complete locked-in syndrome—that is, the inability to produce any volitional motor output whatsoever—a behavioural assessment of awareness would wrongly consider a fully conscious individual to be unconscious [16, 17]. Since there can be no biopsy or post-mortem result against which covert test outcomes may be compared, a common and practical solution to the absence of the 'absolute truth' has been to estimate the sensitivity of the test in healthy, awake individuals, since their awareness is presumably assured. For example, the mental imagery fMRI approach of Owen et al. [2] and Monti et al. [3] could detect command-following and, therefore, awareness, in all of 36 healthy controls [18] and so could be said to have an estimated sensitivity of 100%, while the motor imagery approach described by Cruse et al. [6, 7] had an estimated sensitivity of 75% (see also Guger et al. [19]).

One could argue that the sensitivity of a test in healthy individuals is not an appropriate estimate of its sensitivity in patients in the VS/UWS. For example, the specific pathology of a patient may make a covert marker of awareness less easy to detect, either through specific structural damages to the brain regions of interest or through secondary cognitive deficits. This may, therefore, lead to an over-estimation of sensitivity based on healthy individuals. Equally, one could argue that a covertly aware patient will be considerably more motivated to demonstrate their awareness than a typical healthy control participant whose awareness is not in question and so will be more likely to comply with task instructions. As a result, sensitivity may in fact be under-estimated in healthy individuals. Despite these challenges to the interpretation of healthy sensitivity, in the absence of a ground truth for patients, this form of estimation is preferable to no estimation at all. Indeed, a task that cannot detect awareness in individuals who are demonstrably aware is unlikely to do so in patients either.

One means of more accurately determining the truth of a positive outcome is to administer multiple complimentary assessments. When the evidence from a range of neuroimaging assessments or modalities converges on a positive outcome, then greater confidence can be had in both the outcome and the accuracy of the contributing tests (see Cruse et al. [20]; see False Positives below). Furthermore, an estimation of the prognostic value of a positive outcome is beneficial in this regard. Since it is known that overtly aware individuals have a considerably better prognosis than patients in the VS/UWS [21–23], if it is found that those patients who have been judged to be *covertly* aware are also subsequently more likely to recover, then confidence in the truth of the positive outcomes of that assessment will also be increased [24–28].

False positives

When a test considers a patient to be aware, when they are unaware, then the test has returned a false positive or a false alarm. Estimating the rate of false positives is crucial in order to determine the overall validity of an assessment. For example, consider a test that returns a positive outcome for all data with which it is presented—whether the 'truth' is positive or negative. Due to all of the true positives that will be returned, the test will have 100% sensitivity. However, it will also have a 100% false positive rate. On its own, the sensitivity measure suggests that the test is excellent, while simultaneous examination of the false positive rate makes it clear that this test is entirely useless, as it is heavily biased toward a positive outcome, regardless of the input. Indeed, in accordance with signal detection theory, the true ability of a test to discriminate between aware and unaware individuals can only be determined on the basis of the difference between the true positive and false positive rates [29] (see also Specificity below).

As with true positives, the rate of false positives can be estimated in healthy individuals. In tasks with specific command-following instructions, for example, one approach is to have healthy control participants complete the entire task twice—once when following the task instructions and once when listening to the same instructions but not following the commands [6, 11, 30, 31]. The false positive rate can, thereby, be estimated as the likelihood that a healthy individual will be judged to have followed command when they were in fact not following command. Another approach is to have healthy individuals complete the task under conditions of diminished awareness. For example, the absence of positive results from sedated healthy individuals—i.e. those who are demonstrably unaware—would indicate that the test has a 0% rate of false positives [25]. Similarly, distraction can be used to reduce or remove the explicit awareness of task stimuli in healthy individuals [26, 32]. Therefore, if an 'aware' outcome is returned by a test of a healthy individual who is not aware of the task stimuli or who is not complying with the task instructions, then that task can be said to have a non-zero false positive rate.

Evidently, an ideal test will return no false positives. However, it is the nature of statistical significance testing that a non-zero false positive rate will exist.

In all neuroimaging assessments, the patient's neural responses are evaluated against a particular statistical threshold. In simple terms, when an 'aware' response—i.e. activity in a brain-region of interest—is said to have been observed with a statistical significance of $p < 0.05$, there is an $\sim$5% chance that the effect does not truly exist—i.e. it is a false positive (see Christley [33] for an expansion of this point). Therefore, if 20 patients are tested independently, each with a false-positive threshold of 5%, it is likely that one of these patients will be determined to be 'aware' when they are not.

When multiple independent tests are performed in this way, it is best practice to reduce the group-level statistical threshold in order to reduce the likelihood of false positives—for example, the Bonferroni correction suggests dividing the threshold by the number of independent tests. In the example of 20 patients, this would result in a new threshold of 0.25% (5%/20) or a roughly one in 400 chance of a false positive. Indeed, it has been suggested that this type of approach should be applied to tests of covert awareness in VS/UWS patients [34]. However, as the likelihood of false positives is reduced, so too is the likelihood of a true positive since a larger effect is now required in order to pass the more conservative statistical test. While robust statistical methods are crucial, it is clear that this approach is entirely inappropriate as, in a clinical setting, a new adjustment to the significance threshold will occur with each new patient who is tested, thus diminishing the likelihoods of both true *and* false positives at an exponential rate. Within a relatively small number of independent assessments, the test will have no ability to discriminate between the unaware and the aware whatsoever.

A small false positive rate is, therefore, unavoidable in any statistical test with a non-zero true positive rate. In order to overcome this inherent difficulty, it is once again wise to scrutinize the results of multiple forms of assessment—e.g. both EEG and fMRI. If a positive result with one test has come about by chance—i.e. it is a false positive—then the likelihood that a false positive will also occur with another independent assessment is low. In this way, a battery of assessments using multiple modalities will allow for the disambiguation of true and false positives.

The rate of false positives also contributes to the estimation of the positive predictive value of a test, i.e. the probability that a patient is truly aware given that the test considers them to be aware. By Bayes' Theorem, the positive predictive value of a test of awareness is strongly influenced by the prevalence or base rate of covert awareness in the Vegetative State. However, as discussed above, the true prevalence of covert awareness cannot be determined due to the absence of a gold-standard assessment. As a result, the positive predictive value of a test must also be approximated with data from healthy control participants (as discussed below, the accompanying 'negative predictive value' metric is inappropriate when describing assessments of this sort).

True negatives

When a test returns a negative outcome and the truth is also negative, the test has returned a true negative. The rate of true negatives can be used to estimate the *specificity* of a test, i.e. the likelihood of the test to *not* detect awareness, given that the individual is not aware (or the number of true negatives/the number of true negatives + the number of false positives). Unlike other clinical tests, specificity can never truly be estimated for tests of covert awareness. Due to the nature of significance testing, the absence of statistically significant evidence for the presence of an effect does not provide any evidence for its absence. In other words, a result either has statistical support—i.e. it is statistically significant beyond a particular threshold of doubt—or it is inconclusive or 'null'. It cannot be negative [35]. Indeed, there is no reason to believe that an individual who has evidence for covert awareness at a statistical significance of $p = 0.06$ is any less aware than an individual for whom this statistical significance is $p = 0.04$. However, with a conventional threshold set at $p < 0.05$, only the latter patient would be considered to be aware. As a result, it is critical in the interpretation of the outcomes of covert awareness assessments that no conclusions regarding the patient's level of awareness may be drawn on the basis of null results.

False negatives

Despite the inability of covert awareness tests to return 'negative' findings, it is nevertheless necessary for these tests to minimize the likelihood of inconclusive (null) results. Indeed, a test that fails to detect awareness in healthy aware individuals is demonstrably a bad test, as their awareness is the only 'truth' available. Therefore, an approximation to the false negative rate can be described as simply 'one minus the true positive rate'. For example, Cruse et al. [6] (see also Guger et al. [19]) reported a 75% true positive rate and, therefore, a 25% false null rate in their healthy control participants following commands with a motor imagery EEG paradigm [4].

Due to the inextricable linkage between all cells of the contingency table (see Table I), employing less conservative thresholds for detection of awareness will not only reduce the rate of false negatives (nulls), but will also simultaneously increase the rate of false positives. Equally, employing more conservative thresholds for detection of awareness in order to reduce false positives will simultaneously reduce the rate of true positives. Clearly, in the development of new assessment techniques, a balance must be struck between an acceptable rate of false positives and false negatives.

However, in a clinical setting, which is preferable: a false positive or a false negative? Clearly this depends upon the consequences of the test outcome. For example, when a positive test outcome has only benign consequences, a false positive would be less injurious than when the consequences of that outcome are more permanent. In cases of detecting awareness via an ability to covertly follow commands, since a false negative is in fact a null and inconclusive result, it provides no new information regarding the patient's level of awareness and is, therefore, unlikely to lead to changes in their care. A false positive, on the other hand, may lead to inappropriate changes in patient care or caregiver expectations. From this perspective, it could, therefore, be argued that a false negative is preferable to a false positive. However, from the authors' experience, the families and caregivers of patients in the VS/UWS typically consider the patient to be aware to some degree, despite having a clear understanding of the meaning of the patient's clinical diagnosis. Indeed, it was found that 90% of a group of VS/UWS patients were considered to have some level of awareness by their family members [36, 37]. Therefore, the majority of caregivers already have what could be considered a 'false belief' regarding the patient's (externally observable) level of awareness. A 'false positive' from a test for awareness for these individuals may, therefore, not have a dramatic influence on their beliefs.

Is it preferable, therefore, to falsely reinforce a belief that is already held by a caregiver or to administer a test that is so conservative that it misses a large proportion of truly covertly aware individuals who may, thereby, be precluded from communicating for the first time since their injury? [3]. While discussion of these ethical challenges is beyond the scope of this manuscript, it is clear that the appropriate balance between false negatives and false positives can only be determined through clinical and ethical dialogue [38, 39]. Nevertheless, the development of novel techniques that maximize true conclusions and minimize false ones must remain the goal of the community.

Guidelines for the determination of clinical utility

It is evident from the above discussion that the clinical utility of tests of covert awareness cannot be determined by conventional means. However, it is crucial that utility be estimated due to the potential for these assessments to dramatically improve prognostic and diagnostic accuracy in this complex patient group. On the basis of the challenges outlined above, a number of questions are offered that should be considered when evaluating the clinical utility of all tests of covert awareness:

(1) What is the true positive rate in healthy controls?
    (a) Is the magnitude of this rate sufficient for the stakes of the test outcome in patients?
    (b) The choice of an acceptable true positive rate will likely vary alongside the relative permanence of the implications of the test outcome, e.g. will it contribute to lasting treatment decisions? [38].
(2) What is the false positive rate?
    (a) This should be estimated under conditions of reduced awareness (e.g. sedation, sleep or distraction) or non-compliance with task instructions.
    (b) This value should be minimized, but not at the expense of point 3.
    (c) A non-zero false positive rate is inevitable, but its impact can be minimized through consideration of points 4 and 5.
(3) What is the false negative rate?: Due to the absence of true negatives, this can be estimated as simply one minus the true positive rate.
(4) Are the outcomes of this test convergent with other tests of covert awareness?: When there is cross-test coherence of outcome, increased confidence in the truth of a positive result is warranted.
(5) Does the outcome of this test have prognostic value?: Individuals who produce overt signs of awareness have a more favourable prognosis than those who do not. If individuals identified as covertly aware by this test are also more likely to demonstrate a level of recovery than those who are not, then greater confidence can be had in the clinical utility of this test.

Conclusions

Rigorous statistical tests are vital for the development of a viable clinical tool. However, the outcomes of statistical tests are, by nature, merely estimations of the truth. Since there can be no means of determining beyond any doubt the 'true' level of awareness possessed by a given patient, it is not possible to calculate the standard clinical measures of utility, i.e. sensitivity and specificity. Nevertheless, it is both possible and necessary to approximate these values by investigating the predictive value of the test in healthy control participants (see guidelines above). Ultimately, the challenge of interpreting the outcome of any individual test will be mitigated by the convergence of the outcomes of other independent assessments (see points 4 and 5, above). It is, therefore, evident that any clinical protocol for the identification of covert awareness will involve not one assessment, but a battery of assessments. When all of these tests are scrutinized according to the above guidelines, greater confidence can be had in their outcomes.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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