

Diagnostic precision of PET imaging and functional MRI in disorders of consciousness: a clinical validation study



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Summary

Background Bedside clinical examinations can have high rates of misdiagnosis of unresponsive wakefulness syndrome (vegetative state) or minimally conscious state. The diagnostic and prognostic usefulness of neuroimaging-based approaches has not been established in a clinical setting. We did a validation study of two neuroimaging-based diagnostic methods: PET imaging and functional MRI (fMRI).

Methods For this clinical validation study, we included patients referred to the University Hospital of Liège, Belgium, between January, 2008, and June, 2012, who were diagnosed by our unit with unresponsive wakefulness syndrome, locked-in syndrome, or minimally conscious state with traumatic or non-traumatic causes. We did repeated standardised clinical assessments with the Coma Recovery Scale–Revised (CRS–R), cerebral ¹⁸F-fluorodeoxyglucose (FDG) PET, and fMRI during mental activation tasks. We calculated the diagnostic accuracy of both imaging methods with CRS–R diagnosis as reference. We assessed outcome after 12 months with the Glasgow Outcome Scale–Extended.

Findings We included 41 patients with unresponsive wakefulness syndrome, four with locked-in syndrome, and 81 in a minimally conscious state (48=traumatic, 78=non-traumatic; 110=chronic, 16=subacute). ¹⁸F-FDG PET had high sensitivity for identification of patients in a minimally conscious state (93%, 95% CI 85–98) and high congruence (85%, 77–90) with behavioural CRS–R scores. The active fMRI method was less sensitive at diagnosis of a minimally conscious state (45%, 30–61) and had lower overall congruence with behavioural scores (63%, 51–73) than PET imaging. ¹⁸F-FDG PET correctly predicted outcome in 75 of 102 patients (74%, 64–81), and fMRI in 36 of 65 patients (56%, 43–67). 13 of 42 (32%) of the behaviourally unresponsive patients (ie, diagnosed as unresponsive with CRS–R) showed brain activity compatible with (minimal) consciousness (ie, activity associated with consciousness, but diminished compared with fully conscious individuals) on at least one neuroimaging test; 69% of these (9 of 13) patients subsequently recovered consciousness.

Interpretation Cerebral ¹⁸F-FDG PET could be used to complement bedside examinations and predict long-term recovery of patients with unresponsive wakefulness syndrome. Active fMRI might also be useful for differential diagnosis, but seems to be less accurate.

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Introduction

Many studies have been done on the differential diagnosis of disorders of consciousness.¹ The term covers several pathological states, characterised by diminished consciousness and responsiveness. Among these, patients with unresponsive wakefulness syndrome, also known as a vegetative state,^{1,2} retain arousal but show no behavioural signs of awareness.^{3,4} Patients in a minimally conscious state show fluctuating awareness, and can respond appropriately to some stimuli.⁵ By convention, emergence from minimally conscious state arises when the patient regains a capacity for functional communication or object use.⁵ Because these states occupy a border zone between awareness and unconsciousness, the distinction between them has important ethical and therapeutic implications.³ For example, patients in minimally conscious states are more likely to have pain or suffer, and might benefit from analgesic treatment or other

interventions aimed to improve quality of life.^{6,7} Patients in a minimally conscious state are also more likely to recover higher levels of consciousness than are patients with unresponsive wakefulness syndrome.^{3,8} Several countries have established the legal right of physicians to withdraw artificial life support from patients with unresponsive wakefulness syndrome^{9–11} but not from patients in a minimally conscious state.¹²

The detection of unambiguous signs of consciousness in severely brain-damaged patients is challenging. The frequency of misdiagnoses of patients with unresponsive wakefulness syndrome by clinical consensus methods is up to 40%.^{13–15} This error rate can be attenuated by the use of standardised scoring systems, such as the Coma Recovery Scale–Revised (CRS–R).^{16–18} However, misdiagnosis can still arise even with rigorous behavioural testing.¹⁹ Neuroimaging methods are being developed to complement the bedside examinations to

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investigate whether a patient has cerebral activity compatible with consciousness. These tests can assess spontaneous brain activity in the so-called resting brain, or specific responses to mental tasks. For example, findings of recent neuroimaging studies^{19–21} show that some patients diagnosed with unresponsive wakefulness syndrome probably can modulate their thoughts voluntarily, which suggests at least minimal awareness. The existence of locked-in syndrome^{22–24} proves that even behaviourally unresponsive patients can be conscious. This knowledge of a patient otherwise perceived as unconscious fundamentally alters his or her ethical, legal, and possibly social and therapeutic standing.

Consciousness is supported by internally and externally related awareness networks encompassing the frontoparietal associative cortices, cingulate gyrus, precuneus, and thalamus.^{24–28} Neural activity in these areas can be examined by ¹⁸F-fluorodeoxyglucose (FDG) PET, which allows visualisation of glucose metabolism at a whole brain level. Generally, the rate of cerebral energy turnover is proportional to the rate of synaptic firing. Therefore, lowered glucose metabolic rates suggest dysfunctional or dormant brain areas.²⁹ Specific metabolic decreases of the frontoparietal associative cortices are seen in patients with unresponsive wakefulness syndrome and those in a minimally conscious state. Patients in a minimally conscious state maintain partial metabolism in the frontoparietal networks, whereas patients with unresponsive wakefulness syndrome show a broad bilateral frontoparietal dysfunction.^{24,30–32} Similar findings of extensive frontoparietal hypometabolism are seen in deep sleep³³ and general anaesthesia,²⁷ suggesting that this pattern is associated with unawareness.

Activity in neuronal populations also triggers fluctuations in capillary deoxyhaemoglobin concentrations. Such increases can be seen with functional MRI (fMRI), and form the basis of maps of the functional architecture of brain activity.³⁴ When asked to do mental tasks, such as motor or visuospatial imagery tasks, healthy patients generate reproducible and specific patterns of brain activation.³⁵ Some patients with unresponsive wakefulness syndrome or those in a minimally conscious state can do similar mental tasks on request.^{19–21} Assuming that such brain activations constitute mental parallels of outward communication, fMRI testing might enable detection of consciousness in cases in which severe paralysis or spasticity makes regular communication impossible.

On the basis of these studies, FDG PET and fMRI might, in theory, distinguish patients in a minimally conscious state from those with unresponsive wakefulness syndrome. Because patients in a minimally conscious state, compared with patients with unresponsive wakefulness syndrome, have better outcomes, neuroimaging tests could also provide prognostic predictions. However, the diagnostic utility of these tests needs validation in clinical practice.

We aimed to test the hypothesis that neuroimaging with ¹⁸F-FDG PET at rest and fMRI during mental tasks can complement bedside clinical detection of consciousness and prediction of recovery. Inclusion of patients with locked-in syndrome (ie, a brain-damaged yet conscious control group)²⁴ allows internal validity to be controlled by verifying the ability of the tests to detect awareness in fully conscious but physically incapacitated patients.

Methods

Study design and participants

For this clinical validation study, we included patients referred to the University Hospital of Liège, Belgium, from clinical centres across Europe between January, 2008, and June, 2012, who were diagnosed with CRS–R as having unresponsive wakefulness syndrome, having locked-in syndrome, or being in a minimally conscious state. These patients were assessed with at least one neuroimaging-based examination. The study was approved by the Ethics Committee of the University Hospital of Liège, and legal guardians of all participating patients gave written informed consent. We assessed patients with locked-in syndrome as a separate internal validation control group; ethics approval applied to these patients too.

Procedures

All patients were diagnosed with four different methods: before admission by their referring hospital, designated the clinical consensus diagnosis on referral; on basis of repeated CRS–R assessments; and from each neuroimaging method of ¹⁸F-FDG PET and mental imagery fMRI. Both neuroimaging methods were attempted in each patient, but if the patient moved too much to obtain a reliable scan, the procedure was omitted. Therefore, not all patients were assessed with each imaging modality. CRS–R is deemed the most validated and sensitive method for discrimination of very low awareness.^{13,16,18,36} The scale consists of six subscales: auditory function, visual function, motor function, oromotor and verbal functions, communication, and level of arousal. The 23 items are ordered by degree of complexity, ranging from reflexive to cognitively mediated behaviours (appendix). Trained experienced neuropsychologists did a CRS–R assessment at least once a day for 5 days and used the best response to establish the final diagnosis. In case of remaining ambiguity or disagreement between examiners, the patient was re-assessed until consensus was reached within the neuropsychological team.

For ¹⁸F-FDG PET, we used statistical parametric mapping (SPM version 8) to identify brain regions with significantly decreased or preserved activity, after we scaled intensity to a global mean. The appendix gives details on image acquisition and preprocessing. We contrasted each patient against 39 healthy controls (17 men; mean age 46, SD 18 years). We contrasted patients against 39 healthy, paid volunteers, with no history of

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neurological disorders. A diagnosis was made by visual examination of the SPM analysis of hypometabolic and preserved regions. Complete bilateral hypometabolism of the associative frontoparietal cortex with no voxels with preserved metabolism led to a diagnosis of unresponsive wakefulness syndrome, whereas incomplete hypometabolism and partial preservation of activity within these areas yielded a diagnosis of minimally conscious state (figure 1).^{24,30,31,37} The stringent requirements for this classification and a dichotomous diagnostic framework minimise the subjective element in the pattern analysis. Failure to detect hypometabolic areas because of conservative statistical thresholds could lead to optimistic assessments of brain activity. Therefore, we used a lenient threshold in all contrasts; voxelwise results were deemed significant at uncorrected *p* values of less than 0.05.

For mental imagery fMRI, patients were asked to do motor and visuospatial imagery tasks during the scanning session.^{19,35} In the motor imagery task patients were instructed to imagine playing tennis, and in the spatial navigation task to imagine walking into their house, sequentially visualising while traversing the rooms. We compared activity patterns during motor imagery, spatial imagery, and rest. Functional data were preprocessed and analysed by use of SPM-8 with a two-step procedure (random effect analysis).^{19,35} The appendix shows information about image acquisition and preprocessing. We created a design matrix with a block design for every individual patient incorporating different stimulations (rest vs active task) as regressors of interest, and movement parameters as supplementary regressors.

We computed contrast images and identified differences in brain activity in response to active task as compared with rest. Results were thresholded at family wise error small volume corrected sphere ($p < 0.05$), centred around coordinates of areas previously associated with active tasks.^{19,20,35} The patients' activation patterns were compared with average patterns obtained from healthy controls (16 paid volunteers, with no history of neurological disorders [9 males, mean age 24 years, SD 12]; figure 2). For diagnosis of minimally conscious states, task-related activation was needed in at least one of the relevant anatomical areas.

Imaging data were analysed by neuroscientists masked to the behavioural results, and provisional diagnoses were provided by modality.

12 months after the initial assessment, we assessed functional outcome with the Glasgow Outcome Scale–Extended (GOS-E),³⁸ which rates the patient's status into one of eight categories ranging from dead to upper good recovery (appendix). We obtained outcome assessment from the patient's medical reports in our institution (University Hospital of Liège). In case of incomplete data, the referent physician or legal guardian was contacted. Because we tested the ability of each method to predict recovery of consciousness, the outcomes were ultimately stratified into two groups, unconscious (GOS-E ≤ 2) or

conscious (GOS-E > 2). We hypothesise that imaging diagnosis of minimally conscious states is predictive of recovery of consciousness, whereas imaging diagnosis of unresponsive wakefulness syndrome is predictive of no recovery.

We measured the sensitivity and specificity (terms that generally describe detection rate of disease in a healthy population) in two mutually exclusive disorders. Hence, we adapted the terminology to suit the circumstances. Sensitivity to a minimally conscious state signified the chance to correctly identify a patient with a CRS–R diagnosis of a minimally conscious state, and thereby rule out unresponsive wakefulness syndrome. This sensitivity to the minimally conscious state corresponds to specificity to unresponsive wakefulness syndrome. Specificity to a minimally conscious state signified the chance to correctly identify a patient with a CRS–R diagnosis of unresponsive wakefulness syndrome, ruling out minimally conscious states.

Statistical analysis

We calculated the diagnostic accuracy of each examination method by use of the best repeated CRS–R diagnosis as reference, and established the practical feasibility as the ratio of successfully executed examinations to examinations that could not be done. For each diagnostic modality, we recorded the total number of examinations and the number of examinations yielding interpretable results. From the interpretable results, we calculated the sensitivity to detect (minimal) consciousness (ie, activity

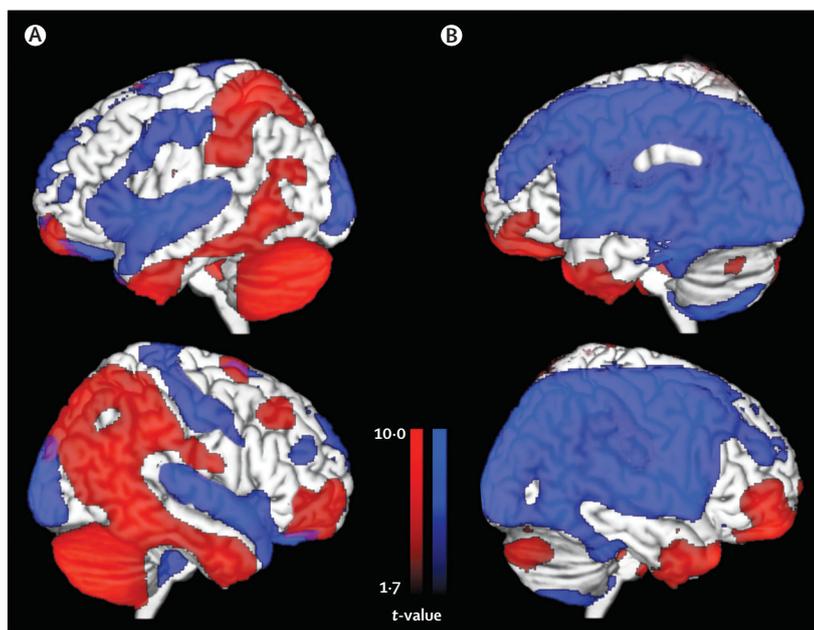


Figure 1: Statistical parametric mapping-analysis of fluorodeoxyglucose PET scans
(A) Minimally conscious state. (B) Unresponsive wakefulness syndrome. Areas where cerebral glucose metabolism is decreased and preserved in individual patients in a minimally conscious state and/or vegetative state (unresponsive wakefulness syndrome), compared with 39 healthy patients. Blue=areas with significantly lowered metabolism. Red=areas with preserved metabolism ($p < 0.05$).

associated with consciousness, but diminished compared with fully conscious individuals) as the ratio of patients who were in a minimally conscious state on the test to patients diagnosed as being in a minimally conscious state on the CRS–R. Because we treated the differential diagnosis as dichotomous, this number corresponds to the specificity to identify unresponsive wakefulness syndrome (appendix). Thus, the ratio of tests in agreement with CRS–R was calculated for minimally conscious states and unresponsive wakefulness syndrome. We counted the number of cases in which we detected signs of consciousness by neuroimaging but not behavioural methods.

We calculated correlations between diagnostic results with Pearson’s phi coefficient. To control for

confounders, we tested for correlation between diagnostic results by modality, time since injury (<1 month, <6 months, <1 year, and >1 year), and traumatic and non-traumatic causes. For all correlations, we used a two-tailed significance level of 5% after Bonferroni correction for six comparisons. For the clinical consensus diagnosis, we calculated sensitivity and relative congruence with CRS–R score only. We calculated the rate of correctly predicted outcomes by neuroimaging, and used the McNemar’s test to estimate the association between predicted and actual outcome. Differences in demographic and clinical characteristics (age, time since injury, cause, and diagnosis) between the cohort with outcome data and those lost to follow-up were assessed using Student’s *t* test. Likewise, for each imaging method, we tested clinical and demographic differences between patients who were examined and those who were not with Student’s *t* tests. Results were considered significant at $p < 0.05$, not corrected for multiple comparisons. Data were analysed with Stata (version 12).

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

130 people were eligible for the study but four were excluded because neuropsychologists could not reach a consensus diagnosis. The final patient population comprised 126 patients (mean age 41, SD 18 years, 75 men). At time of referral, 81 patients had been diagnosed as being in a minimally conscious state, 41 with unresponsive wakefulness syndrome, and four with locked-in syndrome (table 1).

All 126 patients who received a clinical consensus diagnosis before admission were included irrespective of the clinical difficulty of obtaining a diagnosis (table 2). However in 33 cases (27%), this diagnosis was ambiguous or not in accordance with commonly acknowledged clinical entities (eg, post-comatose state). When we excluded patients with an ambiguous clinical consensus diagnosis, CRS–R and the clinical consensus diagnosis scores agreed in 69 of 89 people (78%, 95% CI 68–85) of

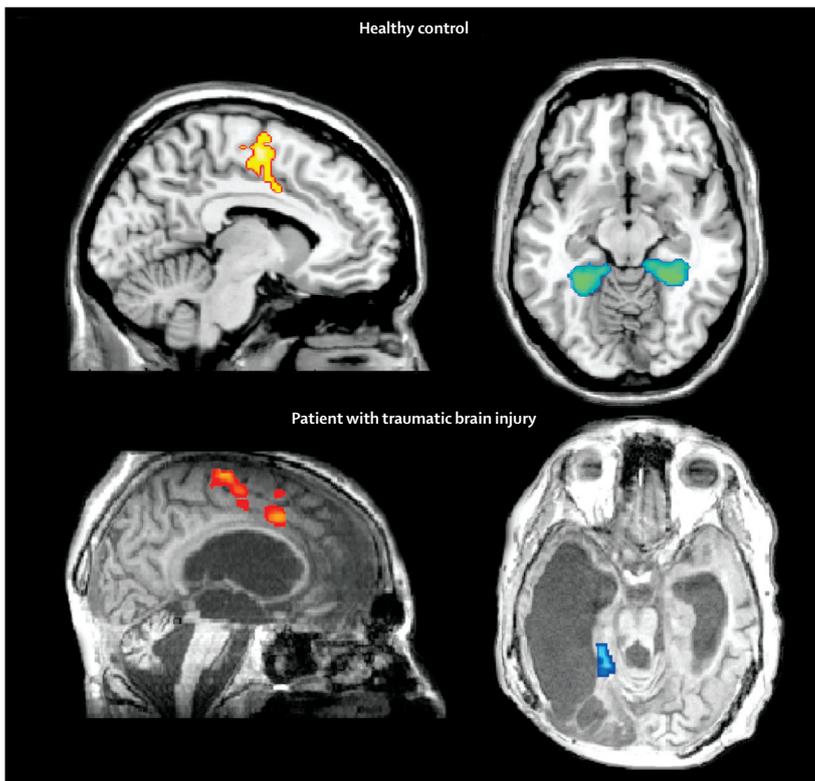


Figure 2: Functional MRI scans
Activations associated with the motor imagery compared with spatial imagery tasks (yellow and red) and the spatial imagery compared with motor imagery tasks (blue and green). These scans were obtained from a group of healthy controls and a patient with severe traumatic brain injury. Adapted from Monti and Vanhaudenhuyse and colleagues,³⁹ by permission of Massachusetts Medical Society.

	N	Mean age in years (SD)	Women (n)	Months since onset, mean (range)	<1 month since insult (n)	1–6 months since insult (n)	6–12 months since insult (n)	>1 year since insult (n)	Traumatic cause (n)
Minimally conscious state	81	39 (17)	29	39 (1 week to 24 years)	12	6	6	58	40
Unresponsive wakefulness syndrome (vegetative state)	41	43 (18)	18	27 (1 week to 21 years)	13	6	1	20	7
Locked-in syndrome	4	31 (16)	4	48 (9 months to 6 years)	0	1	0	3	1

Table 1: Population demographics and diagnosis by Coma Recovery Scale–Revised

cases (table 3). The sensitivity of clinical consensus diagnosis of minimally conscious state was 67% when compared against the diagnosis according to CRS-R (table 3).

We assessed 112 of 122 (92%) patients with ^{18}F -FDG PET (table 2). The remaining ten (8%) could not be scanned for technical or logistic reasons. All scans were of good quality. Demographic and clinical data did not differ significantly between the patients who were examined and those who were not (data not shown).

We recorded agreement between CRS-R and PET-imaging results in 95 of 112 (85%) cases. The sensitivity to identify behavioural minimally conscious state as defined by CRS-R was 93% (85–98; table 3). Time since injury did not correlate with diagnosis according to ^{18}F -FDG PET ($\phi=-0.123$, $p=0.99$). Traumatic cause correlated with a diagnosis of minimally conscious states ($\phi=0.324$, $p=0.01$). The appendix shows associations between imaging results and clinical consensus diagnosis.

We obtained outcome data for 102 of 112 (91%) patients. Demographic and clinical data were not significantly different between patients with outcome data and those lost to follow-up (data not shown) PET imaging correctly predicted 75 of 102 (74%) known outcomes. 51 of 76 (67%) of the patients diagnosed as being in a minimally conscious states by PET remained conscious on follow-up (24% had died). 24 of 26 (92%) diagnosed as unresponsive wakefulness syndrome by PET were unconscious (35%) or dead (56%) on follow-up (table 3). Imaging diagnosis correlated with outcome ($p<0.0001$).

We tested 72 of 122 (59% of the whole group) patients with mental imagery fMRI, leaving 50 patients (41%) who were not assessed, mainly because of spontaneous movement necessitating sedation before MRI (table 2) With fMRI, demographic and clinical data did not differ significantly between the patients who were examined and those who were not (data not shown).

70 of 72 (97%) remaining tests presented interpretable results, and two (3%) contained large motion artifacts, which made reliable analysis impossible. We recorded agreement between CRS-R and fMRI imaging results in 63% of the examinations. Agreement between CRS-R and fMRI was recorded in 44 of 70 (45%) cases (table 3). Two of the patients with unresponsive wakefulness syndrome had activity patterns compatible with (minimal) consciousness on ^{18}F -FDG PET, whereas the third was assessed only with fMRI. Assignment by time since injury ($\phi=-0.09$, $p=0.36$) or traumatic and non-traumatic cause ($\phi=0.07$, $p=0.55$) did not correlate with test results.

Outcome data were obtained for 65 of 70 (93%) patients. Demographic and clinical data were not significantly different between the group with outcome data and those lost in follow-up. Mental imagery fMRI predicted 56% of all known outcomes. 12 of 19 (63%) responders were conscious at follow-up (six of 19 [32%] had died). 24 of 46

(52%) non-responders were unconscious (nine of 46, 20%) or dead (15 of 46, 33%; table 3). Task response and outcome were significantly associated ($p=0.012$). Results from resting state ^{18}F -FDG PET and active fMRI showed significant correlation ($\phi=0.37$, $p=0.024$).

In summary, we detected brain activity deemed to suggest (minimal) consciousness with at least one neuroimaging modality in 13 of 41 (32%) patients diagnosed with unresponsive wakefulness syndrome (table 2). Of those, five were of traumatic cause (of seven patients with unresponsive wakefulness syndrome with a traumatic cause). Follow-up at 12 months after examination showed that nine of these 13 patients had progressed into minimally conscious states or a higher level of consciousness; three died from complications (eg, pneumonia) or withholding of treatment, and one remained unresponsive wakefulness syndrome (appendix). Aside from these nine, no patients diagnosed with unresponsive wakefulness recovered consciousness at

	Coma Recovery Scale-Revised results		
	UWS	MCS	Total
Clinical consensus diagnosis			
VS/UWS	33 (37%)	18 (20%)	51 (57%)
MCS	2 (2%)	36 (40%)	38 (43%)
Total	35 (39%)	54 (61%)	89 (100%)
^{18}F-FDG PET			
VS/UWS	24 (21%)	5 (4%)	29 (26%)
MCS	12 (11%)	71 (63%)	83 (74%)
Total	36 (32%)	76 (68%)	112 (100%)
Mental imagery fMRI			
VS/UWS	25 (36%)	23 (33%)	48 (69%)
MCS	3 (4%)	19 (27%)	22 (31%)
Total	28 (40%)	42 (60%)	70 (100%)

UWS=unresponsive wakefulness syndrome. MCS=minimally conscious state.

Table 2: Diagnostic results by modality

	Clinical consensus diagnosis	^{18}F -FDG PET	Mental imagery fMRI
Completed examinations (of 122)	122 (100%)	112 (91%)	72 (59%)
Number of interpretable examinations (of all completed)	89 (73%)	112 (100%)	70 (97%)
Overall congruence with Coma Recovery Scale-Revised (95% CI)	78% (68–85%)	85% (77–90%)	63% (51–73%)
Congruence with Coma Recovery Scale-Revised diagnoses of UWS (95% CI)	95% (82–99%)	67% (49–81%)	89% (71–98%)
Sensitivity to MCS (95% CI)	67% (52–79%)	93% (85–98%)	45% (30–61%)
Overall outcome prediction (95% CI)	..	74% (64–81%)	56% (43–67%)
Positive outcome prediction (95% CI)	..	67% (55–77%)	63% (41–81%)
Negative outcome prediction (95% CI)	..	92% (76–98%)	52% (38–66%)

FDG PET=fluorodeoxyglucose PET. UWS=unresponsive wakefulness syndrome. MCS=minimally conscious state. Outcome=conscious/unconscious, according to GOS-E at 12 months. Positive outcome=GOS-E >2, and negative outcome=GOS-E ≤2.

Table 3: Diagnostic characteristics by modality

1 year after examination. All four patients with locked-in syndrome were identified with CRS–R, ^{18}F -FDG PET, and fMRI as conscious on all applied examination modalities.

Discussion

As previously reported,¹³ we noted the clinical consensus diagnosis was imprecise. Even when we discounted the many unclear diagnoses, the clinical consensus diagnosis failed to correctly identify responsiveness in 33% of patients diagnosed as being in a minimally conscious state with CRS–R. This finding emphasises the need for standardised behavioural scoring systems in treatment facilities.

We recorded strong associations between results of clinical and functional neuroimaging tests. ^{18}F -FDG PET showed high sensitivity to identify minimally conscious states (93%), good overall congruence with repeated CRS–R scores (85%), furthermore, a high ratio of the examinations could be done (92%). We recorded a lower congruence for patients clinically diagnosed with unresponsive wakefulness syndrome (67%). This finding might be accounted for by the identification of patients in non-behavioural minimally conscious states by the imaging assessment. Cerebral FDG PET was reliable in both acute and chronic stages, and across all causes. The test provided a higher rate of positive results in patients with traumatic brain injury than non-traumatic causes. This result corresponds with previous findings that covert awareness is found mainly in patients with traumatic causes.^{21,39,40}

We found differential diagnosis with active mental imagery fMRI technically challenging. Only about half of the patients could be assessed, and we recorded low sensitivity to minimally conscious states (45% true positives) and overall congruence with CRS–R (63%). Absence of response led to a diagnosis of unresponsive wakefulness syndrome. Thus predictably, in view of the many false negatives, fMRI showed good agreement with CRS–R diagnoses of unresponsive wakefulness syndrome (89%). These data suggest that mental imagery functional MRI is less reliable for differential diagnostic purposes than is ^{18}F -FDG PET. Because mental imagery fMRI involves high-level cognition, its low sensitivity is unsurprising. However, this fMRI test might provide information about preserved cognitive capacity in a patient, and enable assisted communication. Therefore, although less sensitive, active fMRI might complement ^{18}F -FDG PET assessment.

We detected brain activity compatible with (minimal) consciousness in 32% of the patients with unresponsive wakefulness syndrome according to the CRS–R. However, without a true gold standard (ie, an exact and measurable neural correlate of consciousness), we cannot claim this as proof of awareness in these patients. The extensive discussion about awareness in unresponsive patients specifically addresses the validity of detection of consciousness by neuroimaging.^{1,19,20,35,41–43}

On this basis, neural signs of consciousness can be interpreted as evidence of phenomenal awareness. In support of this view, the tests correctly identified all patients with locked-in syndrome as conscious. At the 12 month follow-up, patients with unresponsive wakefulness syndrome with dissociation between behaviour and brain activity showed 23% mortality (three of 13) in agreement with previous reports.^{8,44} All deaths were from external factors, apparently unrelated to the individual level of brain functioning. Nine of the ten (90%) survivors had regained consciousness, and only one still had unresponsive wakefulness syndrome, consistent with the claim that the patients were already at the time of scanning in, or progressing towards, minimally conscious states. Because patients with unresponsive wakefulness syndrome with brain activity compatible with (minimal) consciousness represent a border zone between minimally conscious states and unresponsive wakefulness syndrome, the diagnosis of unresponsive wakefulness syndrome might not accurately describe their status. The term non-behavioural minimally conscious states could be used to characterise the clinical situation of these patients.^{45,46}

We hypothesised that neuroimaging diagnosis would predict prognosis. The results from assessments with ^{18}F -FDG PET, which correctly predicted long-term outcome (ie, presence of consciousness 1 year after examination) in 74% of patients, support this notion. Predictions of the absence of recovery of consciousness were more reliable than predictions of the presence of recovery of consciousness. Overall, the results correspond to expected prognoses of clinically diagnosed unresponsive wakefulness syndrome and minimally conscious states.³ fMRI was a less robust outcome predictor than ^{18}F -FDG PET. Our results could have been confounded negatively by high mortality, even in patients in minimally conscious states. PET correctly predicted all late recoveries from unresponsive wakefulness syndrome. Four of these patients had been unresponsive for more than 1 year at the time of assessment. This is interesting because the prognosis of patients with longstanding unresponsive wakefulness syndrome is poor.^{4,8,44} Our data suggest that recovery after unresponsive wakefulness syndrome might be associated with a status of non-behavioural minimally conscious states and functional neuroimaging seems to be able to detect these rare cases.

Findings of several studies have shown the limitations of behavioural diagnostic methods in disorders of consciousness, and mandated validation of neuroimaging-based methods.^{13,19–21} The ability of these diagnostic tests to detect brain activity compatible with awareness is crucial. However, definition of criteria for this validation is at risk of logical circularity.

Correct assessment of diagnostic accuracy needs a reliable standard to test against. The only broadly accepted test for phenomenal awareness is behavioural

responsiveness.⁴⁷ However, the reliability of the behavioural reference is a key issue. The diagnostic inter-rater agreement of one CRS–R assessment ranges between 89% and 100%,^{16–18} and inter-rater reliability on two subsequent days is roughly 95%.^{17,18} Thus, CRS–R is a robust method, even for one assessment. Serial CRS–R assessments by several experienced raters ensured a highly reliable clinical diagnosis. Because no gold standard exists for absence of consciousness, sensitivity to unresponsive wakefulness syndrome or specificity to minimally conscious states seem like meaningless measures. Therefore, we used the overall congruence with CRS–R to measure the examination accuracy. Inclusion of patients in a non-behavioural minimally conscious state might have negatively confounded this assessment. Even if both behavioural and neuroimaging outcomes are correct, a patient in a non-behavioural minimally conscious state will count as a diagnostic error, and weigh towards a pessimistic assessment of the test accuracy. Long-term outcome provides a complementary diagnostic reference, which might be less susceptible to this problem. Therefore, by use of CRS–R diagnosis and long-term outcome, we were able to verify the imaging diagnosis in both responsive and unresponsive patients.

Because our tertiary expert unit is specifically focused towards diagnostic neuroimaging of disorders of consciousness, we deem this study to be a test of the efficacy of the diagnostic methods, under optimum conditions, which might not be easily achieved in less specialised units. The clinical consensus diagnosis here provided a measure of the effectiveness of clinical diagnosis under imperfect real-world conditions. The population characteristics correspond to those seen in recent demographic studies^{48–50} (appendix).

Functional neuroimaging has important limitations. The image acquisition is expensive and logistically complicated. Additionally, the statistical analysis is complex, and contains a risk of false outcomes. The methods we used rely on blinded visual pattern analysis of PET^{24,30,31} and fMRI^{19,20,35} data, which despite standardised preprocessing and statistical analyses steps with published methods, introduced a subjective element to the diagnosis. We applied stringent criteria for the masked classification, but the risk of examiner bias cannot be completely eliminated.

We were unable to assess the rate of false positive detection of awareness in patients in unresponsive wakefulness syndrome. The agreement between imaging results from both modalities and the outcome data suggest that the rate is low. False negatives seem more prevalent. We recorded a globally hypometabolic cortex in patients in a behavioural minimally conscious state, which leads to a neuroimaging diagnosis as unresponsive wakefulness syndrome. Thus, even an FDG-PET reading suggestive of unresponsive wakefulness syndrome does not formally rule out consciousness, although this finding only affects a

Panel: Research in context

Systematic review

We searched Medline for reports published between Jan 1, 2000, and Dec 31, 2013, with variations on the terms “minimally conscious state”, “vegetative state”, “neuroimaging”, “MRI”, “PET”, “EEG”, “diagnosis” and “outcome”. We reviewed relevant original and review articles, and their reference lists and found no studies of the clinical accuracy of neuroimaging-based differential diagnosis between the disorders of consciousness. We found many neuroimaging studies describing differences in neural function and structure between the two disorders.¹ We assessed whether the findings provided grounds for a dichotomous distinction between the disorders on the basis of standardised behavioural assessment, and whether the methods were practically implementable in a clinical setting. We used two complementary and well-documented methods, resting state fluorodeoxyglucose (FDG) PET and functional MRI (fMRI) during mental imagery tasks.

Interpretation

We noted active paradigm fMRI was insufficiently sensitive to serve as primary diagnostic method, whereas ¹⁸F-FDG PET reliably differentiated the two disorders. Our results show that neuroimaging might substantially complement behavioural assessments in disorders of consciousness.

Our study is, to the best of our knowledge, the first clinical investigation of the diagnostic accuracy of multimodal neuroimaging methods in disorders of consciousness. Our data suggest that clinical consensus diagnosis is imprecise in the diagnosis of patients with disorders of consciousness compared with the Coma Recovery Scale-Revised (CRS–R). Further, we noted agreement between neuroimaging and CRS–R diagnoses, and that neuroimaging might predict absence of recovery of consciousness. We confirm that a substantial proportion of behaviourally unresponsive patients retain brain activity compatible with awareness. These results emphasise the need for continued development of diagnostic methods for disorders of consciousness, and show the practical usefulness of functional neuroimaging in these disorders.

few patients. Additionally, this shows that relative regional hypometabolism is not an indicator of amount of consciousness, but rather a practical marker to differentiate minimally conscious states from unresponsive wakefulness syndrome.

The false negative rate was high with fMRI, which might be because patients in minimally conscious state did not understand the task or did not have the drive to participate. This result highlights important limitations of cognitively evoked tests in disorders of consciousness. Overall, as behavioural diagnosis should take precedence; false negative neuroimaging tests pose minor problems for patients in minimally conscious states. However, the present imaging tests are not infallible, and further development remains necessary.

Therefore, neuroimaging diagnosis should not stand alone, but complement standardised behavioural assessments. By definition, neuroimaging cannot challenge a certain clinical diagnosis of minimally conscious states. Therefore, we propose that behavioural assessments and neuroimaging could be combined to screen for non-behavioural minimally conscious states, and identify cases with potential for long-term recovery of consciousness.

Our study has several potential limitations. The population was small, and collected at one tertiary expert

centre. However, patients were referred from several centres across Europe, precluding a local demographic bias. Additionally, the patient population seemed to correspond with other demographic studies with respect to characteristics and cause. Missing data from unsuccessful examinations constitute a potential source of exclusion bias. However, the neuroimaging methods were applied solely on the basis of their technical feasibility; spontaneous motion of the patient was the main challenge. Because minimally conscious patients tend to move more than those in an unresponsive wakefulness state,⁵¹ this might bias the examinations towards a pessimistic assessment of test sensitivity. We cannot rule out confounding factors in patients who were lost to follow-up, although they did not show any differences in terms of clinical characteristics.

In conclusion, repeated testing with the CRS–R complemented with a cerebral ¹⁸F-FDG PET examination provides a simple and reliable diagnostic programme with high sensitivity towards unresponsive but aware patients. fMRI during mental tasks might complement the assessment with information about preserved cognitive capability, but should not be the main imaging-based differential diagnostic method. Future work should aim to validate other promising neuroimaging-based differential diagnostic markers, such as quantified metabolic markers, resting state fMRI, or electroencephalography with transcranial magnetic stimulation.

Contributors

JS and SL conceived the study. M-AB, VC-V, AV, CC, AT, OG, MT, and MB did imaging data preprocessing and statistical analysis. OG, M-AB, VC-V, AV, AD, CC, AT, LH, MT, and CS did patient assessments. JS did the statistical analysis for the report. JS, OG, AG and SL wrote the report. All authors contributed to the subsequent drafts and approved the final version.

Declaration of interests

We declare that we have no competing interests.

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