Implementing novel imaging methods for improved diagnosis of disorder of consciousness patients

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The clinical evaluation of consciousness in disorder of consciousness (DOC) patients based on their exhibited behavior is difficult and remains erroneous in many cases. Recent studies demonstrated different levels of stimulus processing as well as evidence of some level of awareness in sub-groups of these patients. The aim of the current study was to examine the plausibility and challenges of implementing a clinical service for evaluation of consciousness level in DOC patients.

Eleven Patients (ages 11–67) diagnosed as being in vegetative or minimal conscious states were included. Functional MRI evaluations included auditory, language, voice familiarity, imagery, and visual tests.

In 9 patients auditory-related activation was found, however only in 5 of the subjects was differential activation found for language. Six patients exhibited differential response to their own name. In three patients a response to visual stimuli was identified. In one patient the auditory and linguistic systems were clearly activated in a hierarchical pattern, and moreover willful modulation of brain activity was identified in the imagery test.

We discuss the importance of using a wide battery of tests, the difference between our clinical cohort and previous publications, as well as the challenges of clinically implementing this method. Translating novel imaging methods into the clinical evaluation of DOC patients is essential for better diagnosis and may encourage treatment development.

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1. Introduction

In recent years, improvements in intensive care have led to an increase in the number of patients who survive severe brain injury. Although some of these patients recover, others awaken from the acute comatose state but do not show any signs of awareness. If repeated examinations yield no evidence of a sustained, reproducible, purposeful, or voluntary behavioral response to visual, auditory, tactile, or noxious stimuli, the patient is diagnosed as being in a vegetative state [1]. It should be noted that diagnosis is based on the ability to perform motor activity, and the lack of motor abilities does not necessarily indicate lack of awareness. Moreover, this approach focusing on awareness totally ignores higher cognitive and emotional processes.

Unlike the common practice in medicine, the diagnosis of disorders of consciousness is based solely on negative findings. While the classical clinical assessment is based on identifying exhibited behavior, in the consciousness disorders spectrum, the lack of response defines the disease. Furthermore, the absence of a clear anatomical or metabolic biomarker requires the physician to depend on subjective measurements. Often different opinions exist among different staff and family members and it is hard to untangle wishful thinking from the realistic situation. Therefore, there is a great need for objective measures for consciousness assessment [2].

A breakthrough in understanding consciousness disorders was achieved in a series of innovative studies showing the ability to use fMRI as a window to the internal processes in disorders of consciousness (DOC) patients. Functional imaging creates new possibilities of diagnosis since it enables the identifying of neural activity even in the absence of overt reaction. Coleman et al. [3] examined different levels of hierarchical auditory processing in patients suffering from disorders of consciousness. Surprisingly, they identified responses to sounds (60%), to language (46%), and even to semantic content of sentences (10%). Patients’ recovery was found to correlate with their level of response. In a seminal consequent study, Monti et al. [4] challenged the patients to perform an imagery task and demonstrated their ability not only to understand language passively but also to perform willful modulation of their brain activity [4]. Out of 54 patients tested, 5 performed volitional activity. Moreover, this method was used to communicate with one of these patients. A different approach evaluated “affective consciousness” — a response to pain cries of other people [5], and found responses in several vegetative patients that could not preform the imagery tasks.

The level of consciousness of patients was shown to be correlated to resting state fMRI parameters. Studies published recently suggest that the connectivity in the default network is correlated to level of consciousness [6–8], and that other connectivity measures such as...
inter-hemispheric connectivity [9], thalamocortical functional connectivity [10] and global connectivity [11] are related to the level of consciousness as well. However the meaning of these correlations requires additional research. Furthermore, it should be noted that resting state is especially vulnerable to motion artifacts and an improvement in controlling and correcting these artifacts is required before implementing these methods in the clinical set (for review and discussion see: [12,13]).

These ground-breaking results caused great interest and excitement in both the medical and scientific communities and inspired philosophical discussions regarding the meaning of human awareness. How is awareness defined and what kind of brain activation is required to describe a patient as “aware”? Brain responses to primary sensory stimuli and even high level language processing [14], contribute to the evaluation and diagnosis of the patient but are not sufficient to imply awareness. However the ability to perform volitional activity (as demonstrated by [4]) is usually related to awareness.

Beyond the scientific and ethical questions, the option to acquire knowledge regarding inner processes of patients, raised hope in the family members and there was a demand for a clinical service. Herein we report and discuss our attempt to implement fMRI methods as a clinical tool to evaluate residual functionality and consciousness in DOC patients.

2. Methods

2.1. Patients

Eleven patients diagnosed as being in vegetative (6) or minimal conscious state (5) were scanned. Patients (aged 11–67) suffered from traumatic brain injury (7) or anoxic brain damage (4) and their characteristics are detailed in Table 1. In all cases the initiative was taken by the patient’s family who believed that the patient is responsive and approached the fMRI unit in Hadassah, requesting better understanding of the condition of the patient. The Helsinki committee of Hadassah medical center has approved publishing these results.

<table>
<thead>
<tr>
<th>Patient</th>
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<th>Sex</th>
<th>Etiology</th>
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<td>MCS</td>
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</table>

2.2. Clinical management

Unlike other papers regarding functional imaging of unconscious patients, this paper describes a clinical evaluation performed by the initiative of the patients’ family rather than a structured research. In all cases families believed that the patient can hear and understand them, but nevertheless asked for reassurance. Family members were questioned as to the signs they identify for responsiveness and for signs of auditory and visual processing. The previous medical information of the patients were evaluated.

Family members were questioned regarding the patient’s habits prior to ictus in order to optimize tasks to patient and instructed how to prepare the patient for performing the tasks.

The meaning of negative results and the possibility of false-negative results were carefully explained to the family members before deciding on the procedure. We emphasized that results must be taken with care, especially in view of the novelty of the technology and the fluctuating states of the patients. Positive results were also given in a very cautious way, in order not to nurture false hopes. In each case, a very detailed answer was given, mentioning for each task the result and its reliability.

2.3. Functional MRI paradigm

A functional paradigm included a hierarchical auditory test, an imagery test, and for 8 patients we also included a visual task. These tests evaluated different levels of functionality of the patient’s brain — from low levels of stimuli processing till willful modulation of brain activity.

In the hierarchical auditory task, the patients were presented with environmental noises, reversed non-words, frequency rotated non-words, and words as well as their own name. Half the stimuli were presented in familiar voices of family members while half were presented in unfamiliar voices. Stimuli were presented in blocks of 8 s including 5 different sounds. Each condition appeared 4 times in two runs (all together 8 repetitions per condition) and was followed by a quiet block. Each block included an 8 s silent phase when stimuli were presented and two seconds of data acquisition in a sparse sampling design.

Auditory stimuli included 20 common Hebrew nouns, adjectives and adverbs (see list in supplementary data). These words were recorded twice — once by a female family member of the patient (in all cases mother or spouse) and once by a female staff member unfamiliar to the patient. All words were reversed to create unintelligible non-words that sound “word-like”. Then words were frequency rotated to create non-words with a similar frequency pattern as real words but that do not sound like human speech [15]. The fourth condition included the subject’s name recorded both by the familiar family member and the unfamiliar female. The name was recorded seven times and speakers were instructed to use different intonations and nicknames to limit adaptation effect. The fifth condition included 20 environmental sounds — two seconds long each. Sounds were collected from open dataset online. Auditory stimuli were recorded and processed using Goldwave, Audacity® and MATLAB®.

The imagery test was adapted from Monti et al. [4]. Subjects were asked to perform 4 imagery tasks: to imagine themselves playing a ball game, to imagine themselves humming a song, to imagine their way home, and to imagine pictures of objects from their kitchen. Each condition appeared 4 times in two runs (all together 8 repetitions per condition). A condition included a short auditory instruction (for instance, “drive home” or “hum a song”), 14 quiet seconds for the subject to perform the task, and ended with an instruction “stop”. All condition blocks were followed by a rest block. The instruction phase in the imagery task was used to achieve additional information regarding patients’ auditory and language system. Tasks were adjusted according to interviews with family members. For instance, for a subject who did not play sports games we asked her to imagine having a snow-ball fight with her children. In all cases we asked the family to select in advance a song for the patient to hum and to practice the tasks with the patient repeatedly in the week before the scan. Instructions in the imagery tasks included two words each and were recorded in an unfamiliar female voice.

The visual task was one of three paradigms chosen according to patients’ condition: 1) a basic paradigm of a flickering checkerboard (8 Hz) including 5 blocks with each block lasting 12 s; 2) a visual verb generation task including 5 blocks of visual objects, each block lasting 15 s and including 7 objects (In this task the patient was instructed to think of a verb that could be done with the object presented); 3) a high level visual hierarchical paradigm including visually presented words and non-words, neutral faces, emotional faces, famous faces,
and scrambled objects. In this paradigm each condition included 5 blocks lasting 10 s (7 items) each. Patients were instructed to think about the semantic content of the stimuli. The visual images were collected from open resources online, and words printed were common Hebrew nouns. A fixation cross was presented during all rest blocks. As subject cooperation is required for calibration of the eye tracker it was impossible to monitor fixation. Patients were asked to keep their eyes open and this was inspected via the mirror prior to the visual test.

Auditory stimuli were presented using an NNL (NordicNeuroLab) auditory system including noise attenuation of +30 dB. Visual stimuli were presented via an LC projector onto a tangent screen located in the rear part of the magnet. Subjects viewed the screen through a tilted mirror. Stimulus presentation was implemented with Presentation software (http://www.neurobs.com/presentation).

Functional protocol was organized according to the mental load required from the patient: After a brief localizer scan, the subject preformed the imagery tasks (two scans, 8:33 min each), then the visual scan (one scan 2:51 min) and last the auditory scan (two scans, 9 min each). Following the functional scans a T1 anatomical scan was preformed (8:47 min) and a clinical anatomical sequence of scans according to the recommendation of an expert radiologist. Altogether preformed (8:47 min) and a clinical anatomical sequence of scans each). Following the functional scans a T1 anatomical scan was performed the imagery tasks (two scans, 8:33 min each), then the visual task (one scan 2:51 min) and last the auditory scan (two scans, 9 min each).

2.4. Magnetic resonance protocol

The blood oxygenation level dependent (BOLD) fMRI measurements were performed in a whole-body 3 T, Siemens scanner. BOLD contrast was obtained with a gradient-echo echo-planar imaging sequence and a standard head coil. Imaging functional data was obtained using TR = 3 s, TE = 30 ms, flip angle = 90°, imaging matrix = 80 x 80, FOV = 22 x 22 cm (inplane resolution = 2.75 x 2.75 mm) and 40 slices, 3 mm each with 0.3 mm gap between slices. Auditory functional data was obtained using a sparse sampling protocol with TR = 10000 s, TE = 30 ms, flip angle = 90°, imaging matrix = 80 x 80, FOV = 22 x 22 cm (inplane resolution = 2.75 x 2.75 mm) and 30 slices, 3 mm each with 0.5 mm gap between slices. Visual functional data was obtained using TR = 3 s, TE = 30 ms, flip angle = 90°, imaging matrix = 80 x 80, FOV = 22 x 22 cm (inplane resolution = 2.75 x 2.75 mm) and 40 slices, 3 mm each with 0.3 mm gap between slices. Slices were placed oblique to cover most of the brain. A high resolution three-dimensional spoiled gradient echo (SPGR) anatomical sequence was performed in the same session as functional data.

2.5. Data analysis

Data analysis was performed using the BrainVoyager Qx software package (Brain Innovation, Maastricht, The Netherlands, 2000). Prior to the statistical analysis, the raw data were examined for motion and signal artifacts. Head motion correction and high-pass temporal filtering in the frequency domain (3 cycles/total scan time) were applied in order to remove drifts and to improve the signal-to-noise ratio. Motion relative to 1st scan was measured in 6 directions. For each scan we calculated the maximum motion in all of the directions. Then for each patient an average of their motion in the different scans was calculated. Functional images were registered and incorporated into the three-dimensional data sets through trilinear interpolation. Automatic registration was inspected and manually adjusted.

The changes in the BOLD contrast associated with the performance were assessed on a pixel-by-pixel basis, using the general linear model [16]; the hemodynamic response function was modeled using standard parameters [17]. Motion correction parameters were included in GLM to correct for the patients’ movements. The data was analyzed both with and without smoothing (with an 8 mm kernel) to improve signal detection. In Auditory and imagery tasks each scan was processed individually to allow the discarding of noisy scans.

2.6. Contrasts

Auditory related activations were identified by comparing all auditory conditions to the rest condition. Language related activation was identified by comparing words to environmental noise. The response to patient’s own name was identified by comparing the response to patient’s name and words. Voice familiarity effect was identified by comparing response to familiar voice (words and names) with unfamiliar voice (words and names). In the imagery task each condition was compared to the rest condition. However activation was considered only when a region was activated significantly more by one task. In the visual task activation was compared to the rest condition. The statistical threshold was first set to q < 0.05 (FDR correction for multiple comparisons). Then a lenient threshold of 0.05 (uncorrected) was used together with a minimum cluster size of 108 anatomical voxels to identify a possible activation in regions where activation was expected (auditory cortex and inferior frontal lobe in auditory paradigm, motor cortex, auditory cortex, visual cortex and hippocampus in imagery task, and visual cortex and inferior frontal lobe in auditory paradigm).

A final grade (FG) was calculated for each patient including a weighted sum of all tasks, when each task is given one point if related activation was identified:

\[ FG = (\text{auditory} + 2 \times \text{language}) + \text{name} + \text{familiarity} + \text{visual} + 2 \times \text{image tasks} / \text{#tasks preformed}. \]

A t-test was used to check whether the final imagery grade was different between the vegetative state and MCS patients.

In one subject (pat2), the second imagery scan was used for network analysis. Networks were extracted using independent component analysis (ICA, first 30 components) and inspected manually to identify significant functional networks. Additionally both imagery scans were used to identify a region showing deactivation during the imagery task in the medial prefrontal cortex. This region was used as a seed ROI. Time-course in the second imagery scan in this region was used as a predictor to create a connectivity map (p < 0.005).

3. Results

3.1. Technical challenges in implementing the clinical service

Significant motion was detected in all patients and average motion was beyond 4.5 mm in 6 of the patients. Including motion results as predictors allowed correcting to some extent the motion artifacts. Using multiple scans for both auditory and imagery tasks allowed including the better scans for each patient.

Anatomical localization of activation is challenging due to major deformities (see Fig. 1). Deformities include enlargement of ventricles in all patients, trauma related deformities (4 patients), and artifacts created by a VP-shunt.

3.2. Auditory hierarchical paradigm reveals diverse patterns of activation among patients

Results are listed in Table 2. Auditory related activation in the primary auditory cortex was expected to be identified in 4 scans including auditory stimuli (two hierarchical auditory scans and the instruction phase of the two imagery scans). The primary auditory cortex was activated in 9 patients in at least one scan. Of these 9 patients demonstrating auditory related activation, only in one patient could we find consistent activations in all four scans. For the rest
of the patients auditory related activation was found in 2–3 of the scans. The location of activation in 2 patients was consistent only in the left hemisphere, and in 1 patient consistently bilateral. In the other patients activation was inconsistent: in some of the scans, bilateral while in the other scans activation was either in the left (2) or right (4) hemisphere.

Auditory stimuli activated unilateral frontal regions in 7 of the patients. In five patients activation was in the left hemisphere and in two patients activation was in the right hemisphere. Contrasting word stimuli to environmental sounds identified differential activation in 5 patients (pat1, pat2, pat3, pat7, pat11). This activity was in temporal regions and frontal regions. In 4 of the patients activation was in the left hemisphere and in 1 patient (pat3) in the right hemisphere.

Evaluating together auditory and language activation demonstrated clear left hemisphere language lateralization in two patients (pat2, pat11): While low level auditory stimuli activated both hemispheres, language stimuli activated frontal regions solely in the left hemisphere. However in the other patients it was impossible to determine whether lateralization pattern reflects functional organization or rather a result of anatomical deformations. One patient (pat3), demonstrating right hemisphere language activation was left-handed, suggesting that lateralization may reflect a pre-trauma atypical language dominance pattern and not a result of her left hemisphere trauma (Fig. 2).

In 6 patients (pat1, pat2, pat4, pat7, pat9, pat11) differential activation to their own name was found (identified by contrasting word and name conditions). Activated regions were in medial regions as reported by several groups in healthy and unconscious patients (see for review [18]).

Differential activation to a familiar voice was found in 3 patients (pat1, pat2, pat11). Activation in the posterior medial precuneus was greater for the familiar voice compared to an unfamiliar voice. This location is consistent with results of Shah et al. [19]. In the other patients a response to their own name was identified as well.

### 3.3. Visual stimuli can be used to identify visual pathway intactness and higher cortical regions

Visual stimuli were presented in 8 subjects. In three subjects stimuli activated visual-occipital regions (pat5, pat6, pat9). In two of these patients (pat6, pat9) left frontal related language regions were activated as well (see Fig. 3). In both these patients, auditory stimuli failed to activate these frontal regions.

<table>
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<tr>
<th>Patient</th>
<th>Auditory</th>
<th>Language</th>
<th>Name</th>
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<th>Visual</th>
<th>Imagery</th>
<th>Final grade</th>
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### 3.3. Visual stimuli can be used to identify visual pathway intactness and higher cortical regions

Table 2

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<thead>
<tr>
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<th>Language</th>
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<th>Visual</th>
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3.4. Imagery mapping evaluates the ability of willful brain modulation

In 7 patients auditory related activation was identified, thus indicating hearing the instructions. Of those patients, a differential activation located in relevant brain regions was found during the imagery task in 5 patients. In four patients a partial pattern was identified: patients demonstrated differential activation only in one task (pat7),
two tasks (pat4, pat11) or three tasks (pat5). Only one patient, pat2, consistently modulated his brain activation in all four tasks, demonstrating pat2’s ability to comprehend language and willfully perform the instructions (see Fig. 4).

3.5. Relation between clinical diagnosis and final grade

The final grades of all subjects are presented in Table 2. The average grade for MCS was 0.38 and the average for VS was 0.36 and no
significant difference could be found between the groups even using a lenient one tailed t-test ($p = 0.47$ n.s). This effect did not differ even when removing pat2.

3.6. An example of a patient where neuroimaging challenges diagnosis

Pat2, 21 years old, was diagnosed as vegetative state following a non-fatal drowning with prolonged cardiopulmonary resuscitation (CPR). Coma recovery scale — revised CRS-R, [20] was performed half a year post drowning and every three months since. Results from 4 measurements till scanning show little response: Auditory (1/4 Auditory startle), Visual (0–1/4 Non-visual startle), Motor (2/6 Flexion withdrawal), Oromotor (0–1/3: Non-oral reflexive movement), Communication (0/2: None), Arousal (2/3: Eye opening w/o stimulation). Patient’s family had contradictory opinions as to his responsiveness.
In addition to full performance in the imagery tasks, this patient demonstrated a full hierarchal pattern of activation in the auditory task (see Fig. 5), indicating language abilities and autobiographical knowledge. We thereby performed additional analysis to identify biomarkers that have been reported to be correlated with consciousness and to establish the diagnosis.

The patient’s default mode network (DMN) was identified both as deactivated regions during the imagery tasks (Fig. 6) and by using ICA methods (Fig. 7). Clear deactivation in prefrontal regions was found. Using deactivated region as a seed region identified additional regions that were strongly functionally connected to it including the posterior cingulated and bilateral temporo–parietal junction. This Network highly resembled the network identified using ICA. ICA revealed additional functional networks that resembled a visual network composed of occipital regions, a motor network including the primary motor regions around the central gyrus, and an auditory network including bilateral regions in the superior temporal gyrus (Fig. 7).

A follow-up scan four months post the scan was performed and imagery task results were repeated using an identical protocol. However, the clinical outcome improved only marginally over two years.

4. Discussion

In recent years research papers demonstrated the existence of residual brain activity and conscious brain processing in unconscious patients. However, most of those papers focused on isolated aspects of brain activity. In this paper we describe the attempt to implement novel imaging methods to evaluate patients’ condition as a whole, evaluating several brain systems including: auditory and language processing, visual functions, autobiographic memory, and the ability to perform willful brain modulation. Activation in all tasks will allow identifying residual functionality, however only autobiographical recognition and moreover volitional performance of the imagery tasks are related to consciousness. Our results demonstrate the challenges of implementing such a clinical service as well as its advantages to improve diagnosis.

4.1. The patient cohort

The patients we studied are relatively more responsive compared to previous studies. In our cohort, clear auditory responses were found in most patients (9/11), while for instance, Coleman et al. [3] found auditory related activation in 60% of patients. Similarly 5 patients performed the imagery to some extent. This number is significantly high relative to previous published results [4,5]. It should be noted that indications for higher level language processing were less common and were found only in half of the patients. Here our results are similar to numbers previously reported [3,21]. Visual activation was found only in 3 of 8 patients. Since in our study we did not monitor fixation as done by Rodriguez Moreno, Schiff [22], it is impossible to identify if lack of activation reflects patient’s condition or rather patient’s limited cooperation.

The differences between our cohort and those previously reported may be a result of the preparation of the patients for the testing — both the intensive practice, and the encouragement of the family members that emphasized to the patient the importance of cooperation. Another possibility is that this effect is a result of the selection bias induced to our results by the clinical nature of our cohort. Patients were not a random sample but rather in all cases the initiative for the test was of family members who believed that patients were aware and responsive. According to this possibility this effect reflects a true difference between our patients and those previously reported rather
than a methodological difference. In this case this demonstrates the limitation of the classical behavioral diagnosis of patients.

In this study we did not find a significant difference between MCS and VS patients. In the literature, the correspondence between the imaging results and the clinical diagnosis (vegetative state vs. minimal consciousness) is puzzling. While some studies found correlations between imaging parameters and clinical diagnosis [7,11,23,24], other studies report higher levels of activity in single VS patients compared to patients with MCS [4,9,21]. This discrepancy is well expressed by Crone, Ladurner [25] who found correspondence between imaging results and behavioral diagnosis on the group level but not on the single subject level (for another example see: [111]). This disagreement between behavioral measures and imaging may reflect the difficulties of the current clinical evaluation that is known to be erroneous in many cases [26]. Nevertheless dissociations are found even when thoroughly comparing behavioral abilities and imaging results within a single subject [27], thereby suggesting that not all cases can be explained by hyper-diagnosis and that it is necessary to revise the diagnosis and create new definitions and diagnosis criteria. Thereby it was suggested that DOC patients showing imaging non-behavioral evidence of consciousness should be considered “functionally locked-in” regardless of their clinical diagnosis (see: [28]).

4.2. The scanning protocol

Using a wide range of tests increased our sensitivity and supplied a broad view to patients’ abilities and their brain activity. The use of multiple scans allows discarding of scans with intensive motion and relying on the scans with the better results. Thus, accumulating evidence allows achieving a reliable diagnosis even when results from each scan individually are noisy. For instance, the replication of auditory activation in at least two scans for all patients responding to auditory stimuli increases the reliability of this result. On the other hand it is hard to evaluate the reliability of the imagery results when a partial pattern of activation was identified (as is the case in all patients except pat2). These inconsistencies may be a result of noise and motion artifacts or changes in the level of arousal or cooperation of the patient. However they may reflect the differences between the cognitive demands of the different tasks, demonstrating the importance of using a wide variety of tasks to fit the different abilities of the patients. A similar inconsistent pattern of activation was found in Yu, Lang [5]: of 5 patients demonstrating imagery related activation only 1 activated relevant regions in both tasks.

Using a multi-modal paradigm allowed the assessment of language function not only from the auditory modality but also from the visual modality. This can supply supporting evidence for the auditory language evaluation, and moreover accommodate possible auditory deficits that may prevent identifying language related activation through the auditory modality (an additional example for the importance of using multiple paradigms can be found in Monti et al [29] see discussion). Nevertheless, unlike auditory stimuli, visual stimuli require the cooperation of the patient to keep their eyes open and attend to the stimuli; therefore we chose to perform most of the evaluation using the auditory modality.

Using advanced connectivity analysis we evaluated the DMN of pat2 in order to further establish the evidence of consciousness. Recent studies suggested that the DMN is a key player in DOC. Specifically, identifying deactivation in the DMN while performing a task [25], the ability to identify the DMN using ICA [6,8] and the level of connectivity within the network [7] were found to correlate with consciousness. Identifying an intact DMN for pat 2, in addition to a full pattern of activation in the hierarchal auditory testing and complete performance of the imagery task supported the notion that pat2 is conscious and that his diagnosis should be reconsidered.

Using patients own name and the voice familiarity test we were able to evaluate patients’ autobiographical knowledge. While most research focus on the cognitive domain, autobiographical knowledge is extremely important to family members. However, while these results may be interpreted as evidence of an intact sense of “self”, they may reflect a frequency effect. Nevertheless, effect demonstrates intact memory that even if the patient may not be necessarily aware of is of much meaning to the family.

The sensitivity of our test may not be sufficient and the option of false negatives must be considered: while auditory processing is automatic, visual processing depends on patient’s cooperation to keep his eyes open and fixate on the stimuli. However in this study we did not monitor fixation. Moreover we did not evaluate the intactness of visual and auditory pathways (using BERA or VEP recordings). Thereby the lack of signal may be a result of the lack of peripheral input rather than a brain damage. Additionally fMRI requires patient cooperation. However, as drift in awareness in chronic vegetative patients are common [2], the limited scanning time may fail to detect awareness. These drawbacks must be considered when interpreting results, nevertheless as they do not induce false positives but rather limit our ability to detect awareness, they do not limit the validity of our results.

These drawbacks may be addressed in several ways: Although in some of the patients it is technically difficult, it may be advisable to test the intactness of the peripheral nerve system (using tests such as BERA or VEP) before entering the magnet and adjusting the scanning accordingly. Fixation should be monitored manually and used in interpreting the results. The drifts in awareness require developing methods that won’t require patient cooperation such as resting state fMRI (e.g. [7,9,11], for review and discussion see: [12,13]). The relationship between resting-state parameters and patient abilities requires still additional research and establishing norms that can be used to evaluate patients. An alternative solution is to develop bedside evaluation methods such as EEG ([30,31], however see: [32]). A more available method can allow repetitive evaluation and thereby achieving a diagnosis that is not dependent on patient’s abilities in one given (and very uncomfortable) situation.

4.3. Technical caveats and the interpretation of results

The fMRI signal is influenced by many factors that may induce noise and diminish patient’s brain activity. These include artifacts caused by damaged structure and medical tools. Additionally, similar to what is reported in the literature [3], our patients produced substantial movement of their heads during the scanning. These uncontrollable movements pose a significant challenge in this patient population and the current methods for motion correction are sub-optimal.

Anatomical deformations impose severe difficulties on the interpretation of results. Identifying the location of activation and comparing it to previous knowledge is critical in establishing the reliability of activation and understanding its meaning. In some of the patients, anatomical structure was so damaged, that experienced neurologists could not clearly identify the different brain regions.

The clinical setup of this study required searching for existing effects even when data was noisy and difficult to interpret. Reliable effects must be identified in the individual subject (rather than in the group level as common in the research) and discarding problematic subjects is not an option. We thereby included data with severe motion and considered activation in expected ROI even at uncorrected thresholds.

Beyond the technical difficulties the interpretation of results is a major issue in implementing methods from research to a clinical service. What does the fMRI activation tell us about the level of consciousness of the patient? Response to auditory stimuli and even differential activation for language or one’s own name does not necessarily imply understanding. Moreover the ability of the imagery task to identify consciousness was doubted, as the cue words themselves might trigger some of the measured activity in relevant regions. Similarly in the autobiographical test it is impossible to reject the possibility that observations reflect frequency effects.
Addressing these issues involves both methodological and theoretical issues. The clinical setup and our choice to use multiple tests limited our ability to adopt from research sophisticated designs and detailed contrasts to separate effects for each task individually. Nevertheless we believe that although each result on its own may be difficult to interpret, the accumulating evidences do suggest an interpretation. For instance, while “play ball” may automatically trigger some motor activity, it is less likely that all four imagery tasks triggered the relevant activity.

The definition of “consciousness” and understanding the relationship between detectable brain activation and awareness are still under debate not only in neuroscience but also in the fields of philosophy and religion. Thereby, we did not attempt to define consciousness or perception. Rather, results were presented to patients’ family in detail. Beyond explaining the limitation of the test to patients’ family prior to scanning we met with the family and delivered the results personally. The meeting allows describing the findings in detail to the family members and while we do present possible interpretations, this is done in caution and limitations are stressed.

The case of pat2 well demonstrates the limitation of the current clinical diagnosis and the gap between the lack of evidence of functionality in the behavioral diagnosis and the evidence achieved by imaging. A joining evidence of residual language functionality, the volitional activity from the imagery result and the connectivity results allow the clinical diagnosis and the evidence achieved by imaging. The gap between the lack of evidence of functionality and religion. Thereby, we did not attempt to define consciousness or perception. Rather, results were presented to patients’ family in detail. Beyond explaining the limitation of the test to patients’ family prior to scanning we met with the family and delivered the results personally. The meeting allows describing the findings in detail to the family members and while we do present possible interpretations, this is done in caution and limitations are stressed.

The recent breakthrough of the ability to better diagnose the status of awareness of the DOC patient preceded treatment progress. This of course raises major ethical concerns[33]. However, these results change the way clinicians and scientists perceive disorders of consciousness and their clinical implications. Brain 2011;134(Pt 3):769–82 [Epub 2012/01/31].


