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

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ABSTRACT

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.

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

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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.

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.

Table 1
Details of patients. M: male, F: female, TBI: traumatic brain injury, y: year, m: months, VS: vegetative state, MCS: minimal conscious state.

Patient	Age	Sex	Etiology	Diagnosis	Time
1	34	F	TBI	VS	5 y
2	22	M	Anoxic	VS	1 y
3	11	F	TBI	VS	6 m
4	34	M	TBI	MCS	3 y
5	44	M	Anoxic	MCS	2 y
6	68	M	Anoxic	VS	3.5 y
7	65	M	Anoxic	VS	3.5 y
8	21	M	TBI	VS	2 y
9	29	F	TBI	MCS	2 y
10	40	F	TBI	MCS	12 y
11	49	M	TBI	MCS	3 y

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 *hierarchal 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 snowball 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 (8hez) 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,