Case Report

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Effect of amantadine on vegetative state after traumatic brain injury: a functional magnetic resonance imaging study

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Abstract

Objective: We assessed the use of functional magnetic resonance imaging (fMRI) to observe residual brain function and responsiveness to amantadine in a patient in a vegetative state (VS) following traumatic brain injury.

Method: We observed cerebral cortex activation in a 52-year-old man in a VS, and in a healthy individual using fMRI during passive listening and motor-imagery tasks. The patient received oral amantadine for 3 months. fMRI was repeated after treatment.

Results: Activation around the left insular regions occurred during stimulation by a familiar voice, and activity in the left temporal and bi-occipital cortices occurred during stimulation by a familiar/unfamiliar voice. Activity in the bilateral frontal and parietal cortices occurred during the motor-imagination task. Brain cortex activation was reduced in the VS patient compared with the healthy volunteer. However, the patient responded to certain auditory stimuli and motor imagery, suggesting that he retained some intact auditory and motor cortical functions. fMRI scans after 3 months of treatment showed increased activation of brain areas corresponding to task instructions.

Conclusion: fMRI could be used to observe the effects of amantadine on brain function, and to aid the diagnosis and prognostic prediction in VS patients in terms of recovery and rehabilitation planning.

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Keywords

Vegetative state, traumatic brain injury, fMRI, amantadine, rehabilitation, brain function

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Introduction

Patients experiencing acute disorders of consciousness following severe craniocerebral injury generally recover between a few days and several weeks after the injury. If the patient does not recover within 3 months, they are considered to be in a vegetative state (VS), while no recovery within a year represents a persistent vegetative state.[1] The incidence of VS in the United States is 19 per million individuals, with the associated medical expenses reaching several billion US dollars.[2] Because patients in a VS can still exhibit a certain degree of recovery of consciousness, early identification of the signs of VS recovery is crucial for making appropriate clinical decisions, saving medical resources, and reducing family burden. VS is also known as unresponsive wakefulness syndrome, and patients in a VS exhibit a normal sleep–wake cycle and do not require mechanical support for their vital functions; however, they do not respond to external stimuli or perceive the external environment, and are unable to communicate verbally or by using body language.[3]

It is difficult to determine the state of consciousness clinically in patients with consciousness disturbances. Although family members may observe clinical responses, such as emotional excitement, when they call the patient's name, or frowning and grimacing under pain stimulation, these reactions may not be reflected accurately by clinical rating scales such as the Glasgow Coma Scale (GCS). The patient's state of consciousness is thus misdiagnosed in more than 40% of cases.[4] Recent studies have shown that residual cerebral cortical function and response to external stimuli in VS patients can be observed by functional magnetic resonance imaging (fMRI), which has demonstrated a sensitivity and specificity for the diagnosis of VS disturbance of 44% to 67%.[5] Although it is difficult to determine if fMRI is superior to neurobehavioral assessments for diagnosing disorders of consciousness, some evidence suggests that fMRI can successfully addresses such diagnostic issues.[6,7] fMRI allows clinicians to assess residual brain function in VS patients accurately, thus allowing them to develop individualized rehabilitation treatment programs for different states of consciousness, and providing an objective basis for continuing medical support. However, research on VS status assessment based on fMRI in China in currently lacking. In this case study, we evaluated fMRI outcomes following external cortical stimulation and task imaging stimulation in a patient in a VS, and in a healthy individual. We formulated an awakening rehabilitation plan for the patient based on the fMRI results, and monitored the effects of amantadine therapy on wakefulness by repeat fMRI. This case suggests that fMRI can be used to provide an objective basis for determining the waking of patients from a VS.

Case report and clinical data

Patient information

The patient was a 52-year-old right-handed man in VS, according to the standardized

VS diagnostic criteria developed by the American Medical Association.[8] He had developed a trauma-induced brain injury (TBI) leading to a disturbance of consciousness, quadriplegia lasting 45 days, a GCS score of 6 (2 blinks, 1 verbal response, 3 motor response),[9] and Rancho Los Amigos rating level I.[10,11] Head computed tomography showed left temporal bone fracture with temporal, parietal, and occipital epidural hematoma, subarachnoid hemorrhage, and cerebral herniation. The right medial orbital wall was irregularly shaped, which was considered to be due to a prior fracture. His past illness history included craniotomy and tracheotomy 45 days before admission, and traumatic right eye injury 9 years earlier, without sequelae. The healthy subject was a 45-year-old right-handed man who drove for a living, and who had no previous history of head injury or cerebrovascular disease.

Brainstem auditory evoked potential (BAEP) examination

BAEP was performed on the healthy subject and VS patient to rule out lesions to the auditory pathway.

fMRI scans

fMRI was performed in the healthy subject and VS patient during sound stimulation and movement-imagination tasks. Sound stimuli were divided into familiar–rest and familiar–unfamiliar sound stimuli. The movement-imagination tasks were designed to promote the imagining of playing tennis. The fMRI imaging data were analyzed using the FSL software package (https://fsl.fmrib.ox.ac.uk).

The subjects were asked to alternate 30-s periods of task activity with 30 s of rest for a total of 3 minutes and 30 s. For sound stimulation, a familiar voice was provided by the closest family member to the individual prior to the onset of illness. The family member was instructed to speak the patient's name and describe things that were of interest to the patient before the onset of their illness. The unfamiliar voice was provided by a person who had never been in contact with the patient. The instructions for the movement-imagination tasks were explained to the subject before scanning. The patient was instructed to imagine himself standing in the middle of a tennis court and playing tennis. The beginning of the movement-imagination period was cued with the word "tennis", and the rest periods were cued with the word "relax".

fMRI was performed using an Ingenia 3.0T magnetic resonance system (Philips Healthcare, Best, the Netherlands), with conventional axial position T2 ($TR = 2369$ ms, $TE = 107$ ms), FLAIR ($TR = 7000$ ms, $TE = 93$ ms, $TI = 2215$ ms), T1 ($TR = 2600$ ms, $TE = 20$ ms, $TI = 1040$ ms), resting state brain scan ($TR = 2500$ ms, $TE = 27$ ms, $NSA = 1$, $FOV = 230$ mm), and task-oriented dynamic scan.

We obtained informed consent and support from the patient's family to develop a rehabilitation and wake-up treatment plan. Rehabilitation treatment included rehabilitative nursing (e.g., optimal limb placement, nursing care for urine and intestinal function, air incision care), arousal therapy (e.g., environmental stimulation, sensory stimulation of sound, light, electricity, exercise therapy), joint mobility, standing bed, MOTOmed exercise trainer (RECK Technik GmbH, Betzenweiler, Germany), electrical stimulation of swallowing function, and acupuncture treatment. Amantadine was administered orally for 4 weeks according to the following schedule: 100 mg twice daily in week 1, 150 mg twice daily in week 2, and 200 mg twice daily in weeks 3 and 4.[12] fMRI scans were repeated after treatment for 3 months.

Ethics and patient consent

This project was approved by the institutional review board of the First Hospital of Jilin University. This research did not increase the risk and economic burden of the patient; the patient's rights were fully protected; and the project design was conducted in line with scientific and ethical principles. The patient's relatives provided written informed consent to publish this case.

Results

BAEP (Figure 1)

The latencies of stimulation of waves I to V were within the normal range on both the right and left sides in the healthy individual. In contrast, the latencies of left-side stimulation waves I to V were prolonged in the VS patient (2.3, 3.5, 4.5, 5.4, and 6.1 ms, respectively) suggesting that the left auditory pathway was slightly damaged. The latencies of the right waves I to V were within the normal range.

fMRI results for different stimuli and task instructions

During familiar–rest sound stimulation, the healthy individual showed bilateral activation of the temporal and occipital lobe functional areas (Figure 2A), whereas the VS patient exhibited only partial activation in the functional areas near the medial insula of the left temporal lobe (Figure 2B).

During familiar–unfamiliar sound stimulation, the functional areas of the bilateral temporal lobes and deep gray matter nuclei were activated in the healthy individual (Figure 2C). Meanwhile, the left temporal and bilateral occipital lobe functional areas were activated in the VS patient (Figure 2D), related to the activation of compensatory coordination zones of the bilateral occipital lobes following left temporal lobe injury. The bilateral frontal lobe, parietal lobe, and cortical functional areas

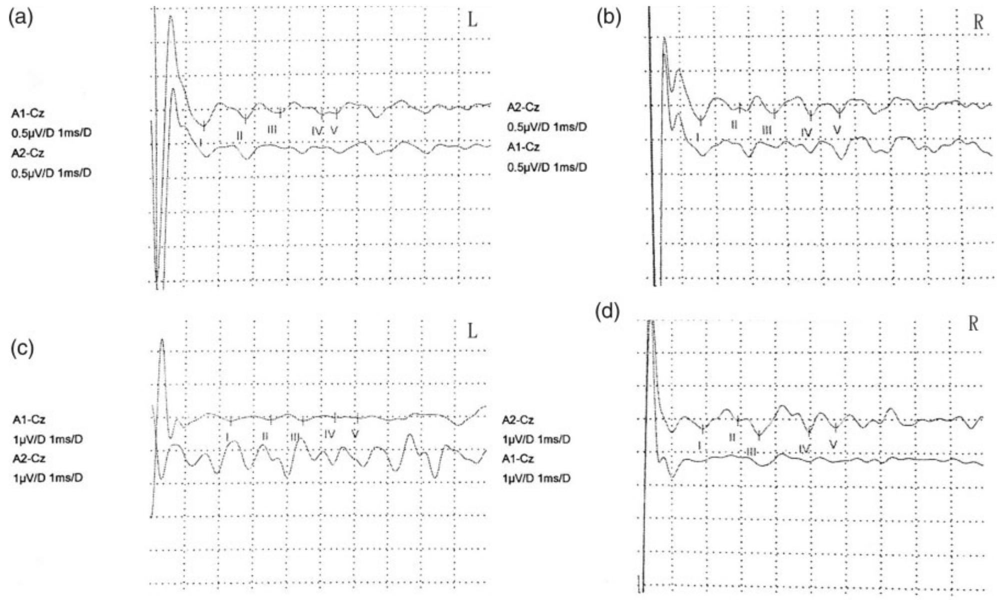

Figure 1. BAEP results in a healthy individual (A, B) and in a patient in a VS (C, D).

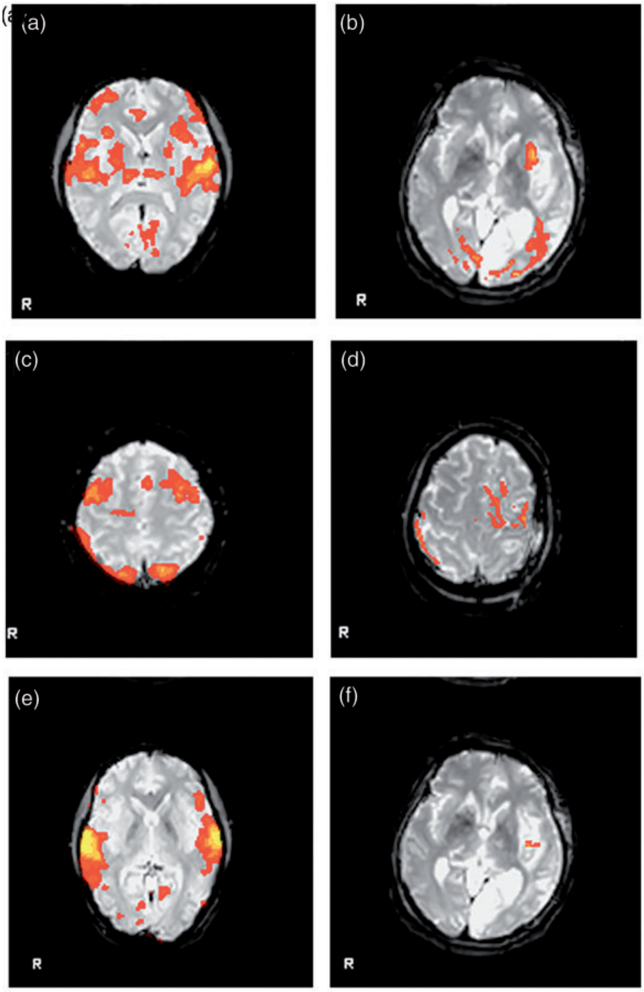

Figure 2. fMRI image of response to familiar–rest sound under auditory stimulation in (A) a healthy individual and (B) the VS patient. fMRI image of response to familiar–unfamiliar sounds under auditory stimulation tasks in (C) a healthy individual and (D) the VS patient. Dynamic fMRI image under movement-imagination tasks in (E) a healthy individual and (F) the VS patient.

were activated in the healthy subject in response to the exercise-imagination task command (Figure 2E). The left semi-oval central functional area of the right parietal cortex was activated in the VS patient (Figure 2F), but the activation range was significantly smaller than normal. Activation of the left motor functional areas and auxiliary motion function area was consistent with the patient's right-handed habit.

We formulated a wake-up treatment plan for the VS patient based on these fMRI results. Members of the patient's immediate family were instructed to provide the described voice stimuli, and the family's sound stimulation was incorporated into the daily rehabilitation program.

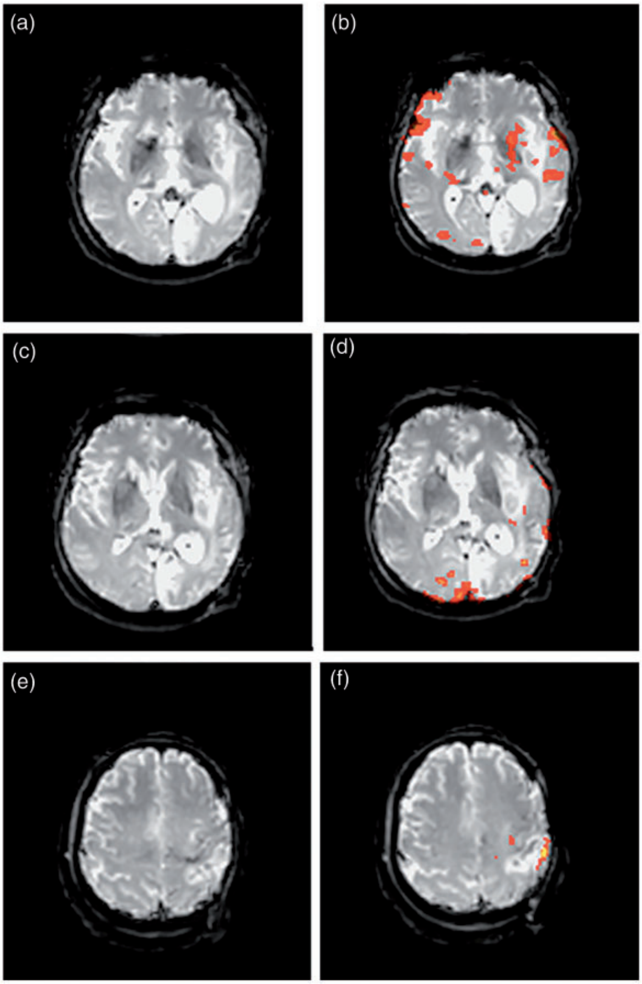

Figure 3. fMRI response to familiar–rest sound stimuli (A) before and (B) 3 months after treatment. Red areas indicate sites of increased activation compared with pre-treatment. fMRI response to familiar–unfamiliar sound stimulation (C) before and (D) 3 months after treatment. fMRI image under movement-imagination tasks (E) before and (F) 3 months after treatment.

The patient underwent repeat fMRI with different stimuli and task commands after 3 months of treatment. The activation zones in the right frontal lobe, bilateral temporal lobe, right occipital cortex, and left basal ganglia region were visible during familiar–rest sound stimulation, indicating increased activity compared with before treatment (Figure 3A, B). Part of the left temporal and right occipital lobes were also activated after treatment, and the activation area was significantly increased by familiar–unfamiliar sound stimulation (Figure 3C, D). In addition, the active area of the left parietal lobe showed a markedly increased response to the movement-imagination task command (Figure 3E, F). The patient's post-treatment GCS was 8 (4 points for eye response, 1 for verbal response, and 3 for motor response), and the patient tracked both sound and visual cues.

Discussion

It has recently been reported that some VS patients have implicit perceptual functions but are unable to communicate with the outside world due to speech or motor dysfunction; these patients are therefore mistakenly assumed to still be in a VS. Determining if a patient is indeed in a VS is of great ethical importance in light of clinical decisions regarding the continuation of medical support and treatment.[13,14] However, assessments such as the GCS are unable to evaluate subtle changes in the state of consciousness. In contrast, fMRI can not only observe spontaneous resting brain activity, but can also detect brain responses to task instructions dynamically to identify hidden residual brain functions.[6,15–18] Rodriguez Moreno et al. performed an fMRI study in 10 patients with consciousness disorders using a picture-naming task, and found that one patient with atresia syndrome, six patients with minimally conscious state (MCS), and two patients with VS retained all or part of the naming function, thus confirming the ability of fMRI to detect hidden brain functions in patients with consciousness disturbances.[19] Bekinschtein et al. performed an fMRI study during movement-imagination tasks in five patients with VS, who were instructed to complete a left/right hand movement, and the study documented activation of the functional area of the corresponding contralateral cerebral cortex in two patients with VS.[20] In the current study, we performed voice stimulation and exercise-imagination tasks in one healthy subject and a patient in a VS, and found that the functional areas of the brain were significantly reduced in the VS patient compared with the healthy subject. Although the results of this study did not reveal signs of wakefulness or perception in the VS patient, reduced activation of functional areas in the primary auditory cortex and activation of partial motor cortices suggested that the patient not only responded to auditory stimuli to some degree, but also that the motor cortex may still be functional. These results indicate that fMRI may be used to observe potential cerebral cortical responses in patients in a VS.

Monti et al.[21] studied the correlation between fMRI and rating scales in 54 patients with consciousness disturbance and found that five patients had mental awareness of fMRI, three had sensory signs indicated by the clinical scale, and one correctly responded to given instructions. Vogel et al.[7] performed fMRI prognostic studies in 10 VS and 12 MCS patients and found that five VS patients whose brain-related functional areas were significantly activated during the exercise-imagination and space migration-imagination tasks all progressed to MCS. Five other patients showed no activation responses suggesting that they were still in a VS, indicating that fMRI had a sensitivity of 100% for judging VS prognosis. Six of nine MCS patients with activation in the relevant brain functional areas recovered consciousness, compared with only one of three MCS patients without activation, with a sensitivity of fMRI for determining the prognosis of MCS of 85%. fMRI is thus one method for determining the prognosis in VS patients,[22] with VS patients with positive fMRI results deriving greater benefits from clinical rehabilitation interventions.[22] The dopamine agonist, amantadine, may have beneficial effects in patients with TBI. Ghalaenovi et al.[23] showed that TBI patients in VS scored ≤ 9 on the GCS. They treated patients with amantadine or placebo for 6 weeks, and evaluated the patients using the GCS and FOUR scoring scales on days 1, 3, and 7 after the start of drug treatment.

The patients were then evaluated 6 months later by Mini-Mental State Examination, Glasgow Outcome Study, Disability Rating Scale, and Karnofsky Performance Scale. The researchers found that patients in the amantadine group showed arousal between days 1 and 7, though amantadine was not associated with reportable effects on the level of consciousness, memory, disability, cognition, mortality, or performance either during the first week or at 6 months of follow-up.[23] In contrast, Sawyer et al.[24] reviewed studies of amantadine (used <6 months after injury) for enhancement of arousal or cognition in patients with TBI and concluded that amantadine at 200–400 mg/day could safely improve these conditions. However, most previous studies have evaluated the effects of amantadine by neurobehavioral tests, and no definite conclusions were drawn.[24] Additional studies are therefore needed to clarify the role of amantadine in arousal and to develop better tools for assessing the level of consciousness.

On the basis of the above findings, we conducted an fMRI scan in a VS patient and found that the patient showed some responses to sound and movement-imagination. We then developed a rehabilitation and wake-up treatment plan, with the support and consent of the patient's family, involving interventions based on auditory stimulation and movement imagination. fMRI scans after 3 months of treatment showed significantly increased activation of the brain function areas corresponding to all task instructions, as well as an increase in GCS from 6 to 8 points, with occasional clinical manifestations such as eye tracking of sound stimulation. Although we could not rule out the possibility of natural recovery in this patient, we believe that the development of an fMRI-guided rehabilitation program supported the implementation of more effective wake-up measures to strengthen residual brain function and promote the restoration of consciousness in patients in a VS. Current opinions regarding VS drug and rehabilitation wake-up treatments differ, owing to a lack of evidence for their effectiveness. Some studies have shown that amantadine can improve recovery of consciousness after brain injury, and can significantly improve executive function in patients with cognitive dysfunction after TBI.[25] Positron emission tomography-computed tomography showed that increased left prefrontal cortex glucose metabolism was positively correlated with improvements in cognitive function.[25]

In the current study, we used amantadine in combination with rehabilitation training as wake-up treatment in a patient with VS after brain injury, and observed subsequent changes in brain function by fMRI. We conclude that fMRI, combined with clinical assessment scales, can not only serve as a tool for assessing awareness in VS patients, but can also provide an objective basis for developing wake-up rehabilitation treatment plans and new avenues for assessing patient consciousness and rehabilitation.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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