Clinical Neurophysiology 126 (2015) 1539–1547

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Brain response to thermal stimulation predicts outcome of patients with chronic disorders of consciousness

Li Li [a,1], Xiao-gang Kang [a,1], Shun Qi [b,1], Xiao-xia Xu [a], Li-ze Xiong [c], Gang Zhao [a], Hong Yin [b,*], Wen Jiang [a,*]

[a] Department of Neurology, Xijing Hospital, Fourth Military Medical University, Xi'an, China
[b] Department of Radiology, Xijing Hospital, Fourth Military Medical University, Xi'an, China
[c] Department of Anaesthesia, Xijing Hospital, Fourth Military Medical University, Xi'an, China

See Editorial, pages 1462–1463

ARTICLE INFO

Article history:
Accepted 5 October 2014
Available online 30 October 2014

Keywords:
Vegetative state
Minimally conscious state
Prognosis
Electroencephalogram
Functional magnetic resonance imaging

HIGHLIGHTS

- We report here a new somatosensory stimulation method termed thermal stimulation for use in fMRI and EEG reactivity tests.
- EEG reactivity and fMRI activation patterns to thermal stimulation can predict improved outcomes in patients with chronic disorders of consciousness.
- fMRI high-order activation to thermal stimulation is highly correlated with the favorable outcomes in patients with chronic disorders of consciousness.

ABSTRACT

Objective: To study the role of brain responses to thermal stimulation in outcome prediction of patients in either vegetative or minimally conscious states.
Methods: We performed a prospective study with 22 patients and used functional magnetic resonance imaging (fMRI) and EEG reactivity (EEG-R) tests in conjunction with thermal stimulation. We conducted thermal stimulation on patients by stimulating either their feet (fMRI) or hands (EEEG-R) with warm water (42 ± 2 °C). Each patient received a 1-year follow-up.
Results: Among the 22 patients, 1 was lost to follow- up, 10 had improved outcomes, and the remaining 11 patients showed no improvement. Thermal stimulation induced three different fMRI brain activation patterns: (1) high-order activation in 4 patients, (2) primary activation in 6 patients, and (3) no activation in 11 patients. Eight of the 10 patients with either high-order or primary activation had an improved outcome. Contrastingly, only 2 of the 11 patients with no activation pattern showed improvement. EEG-R was elicited in 11 patients and 9 of them showed improved outcomes. However, among the 10 patients with no EEG-R, 9 patients did not improve.
Conclusions: Using fMRI and EEG to measure brain responses to thermal stimulation is capable of predicting patient outcomes with a high degree of predictive accuracy.
Significance: Thermal stimulation can be used as an objective and quantifiable somatosensory stimulation mode for clinical EEG-R and fMRI tests.

1. Introduction

Recent progress in critical care has increased the survival of patients who sustain severe brain injury. Consequently, these increased rates have led to a greater incidence of patients with chronic disorders of consciousness, including a vegetative state

* Corresponding authors at: Department of Radiology, Xijing Hospital, Fourth Military Medical University, Xi'an 710032, China (H. Yin). Department of Neurology, Xijing Hospital, Fourth Military Medical University, Xi'an 710032, China. Tel./fax: +86 029 84771319 (W. Jiang).
E-mail addresses: yinhong@fmmu.edu.cn (H. Yin), jiangwen@fmmu.edu.cn (W. Jiang).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.clinph.2014.10.148
1388-2457/

(VS) or minimally conscious state (MCS) (Beaumont and Kenealy, 2005). Management of patients with either VS or MCS inevitably raises difficult economic, ethical, and legal issues about whether to continue or withdraw care and/or the extent of care to be provided. Thus, accurate outcome prediction for recovery of awareness in patients in either VS or MCS is important for family counseling and decision-making.

A prominent feature of patients with chronic disorders of consciousness is a behaviorally unresponsiveness (in VS) or a limited and intermittent responsiveness (in MCS) to external stimuli while remaining in a normal sleep--wake cycle (Bernat, 2006). The underlying neuroanatomical basis that contributes to such phenomenon is widespread damage to the cerebral cortex or the disconnection of cortical networks (Laureys et al., 2005; Bernat, 2006; Giacino et al., 2006). Accordingly, the evaluation of residual brain function in patients in VS or MCS may provide important information about future prognoses.

Currently, functional magnetic resonance imaging (fMRI) and electroencephalography reactivity (EEG-R) have offered the possibility of objectively detecting residual brain function in patients in VS or MCS (Owen et al., 2007b; Monti et al., 2010; Cruse et al., 2011). Moreover, past work has shown that brain responses to external stimuli presented while patients undergo fMRI and/or EEG were related to patient outcomes (Coleman et al., 2007; Di et al., 2008; Thenayan et al., 2010; Logi et al., 2011).

However, external stimuli conducted through primary senses, such as pain and olfaction, are often difficult to quantify in clinical practice. These difficulties in determining accurate stimulation intensity and duration unavoidably result in deviations in the assessment of residual brain function, thereby decreasing the sensibility and specificity of outcome measures using fMRI and EEG-R. For example, intense or prolonged painful stimuli often cause detectable artifacts in fMRI and EEG due to muscle contraction whereas weak or brief stimuli cannot create reliable information about brain activation. Therefore, an objective and quantifiable sensory stimulation is needed for fMRI and EEG-R tests to achieve better prognostic accuracy for patients in VS and MCS.

Given that thermal and painful sensations share the same neural transduction pathway (i.e. spinothalamocortical pathway) and that thermal stimuli can be quantified, here we employed a thermal stimulation paradigm and assessed brain responses using fMRI and EEG. Subjects were patients who were either in VS or in MCS for more than 3 weeks post-onset. We then took this methodology and further explored its role in determining future patient outcomes.

2. Methods

2.1. Subjects

From March 2010 until March of 2012, we prospectively enrolled all consecutive patients diagnosed with either VS or MCS who were referred to the Department of Neurology in Xijing Hospital of the Fourth Military Medical University, one of the largest hospitals in Northwestern China. Patients were eligible for inclusion if they met the standard clinical diagnostic criteria for VS or MCS (The Multi-Society Task Force on PVS, 1994; Giacino et al., 2002; Bernat, 2006) in addition to a post-injury time longer than 3 weeks, but less than 3 months. Exclusion criteria were as follows: (1) premorbid history of developmental, psychiatric, or neurological illness resulting in documented functional disabilities up to time of the injury, (2) spinal cord injury, and/or (3) severe coexisting systemic disease with a limited life expectancy. Control fMRI subjects consisted of 7 healthy, right-handed individuals (2 men and 5 women, age range 19–40 years) with no history of any neurological disorder. All patients and controls were studied while in the awake/alert state for fMRI and EEG-R tests.

The present study was carried out in agreement with all Chinese laws and the Helsinki Declaration relative to patients' rights and was approved by the ethics committee of Xijing hospital. Written informed consent was obtained from each healthy volunteer and each patient's legal surrogate.

2.2. Procedures

After admission, all patients were assessed at two different time points by two neurologists for separate confirmation of the diagnosis of VS and MCS. The Coma Recovery Scale-Revised (CRS-R) was used once a day during the first week after admission to differentiate between MCS and VS. Twenty-two inpatients (5 female, 17 male; age range of 17–70 years) fulfilled all inclusion and exclusion criteria. These patients were separated into two groups: 10 patients with MCS and 12 patients with VS.

Within two weeks after their inclusion in the study, we performed fMRI and EEG-R tests. After patients were discharged from Xijing Hospital, they were transferred to secondary hospitals around Xijing, where they received basic medical care. During their stays at these secondary hospitals, local physicians assessed patients at least once a week. These physicians had been specifically prompted to search for signs of awareness, including (1) simple command-following, (2) intelligible verbalization, (3) recognizable verbal or gestural "yes/no" responses, and/or (4) movements or emotional responses not attributed to reflexive activity (Giacino et al., 2002). All patients were followed up for at least 12 months after inclusion in the study. The neurological outcomes at the study endpoint were assessed and adjudicated by two trained neurologists who were blinded to the fMRI and EEG-R results. These assessments entailed a review of all the patients' medical records and a discussion with the physicians in charge of the patients. It should be noted that the study protocol contained no guidelines for withholding or withdrawing treatment.

2.3. Thermal stimulation/fMRI protocol

Our thermal stimulation consisted of a block-designed functional paradigm. This block design consisted of 30 s of thermal stimuli alternating with a 60 s resting condition. This block was then repeated for a total of 6 times during each functional scan. The stimulation temperature was kept at 42 ± 2 °C and the baseline temperature was 21 °C (room temperature). Thermal stimulation was carried out by putting a plastic bag containing warm water to the whole plantar surface of one of the subject's feet for 30 s. This ensured that each subject received abundant stimulation, but would suffer no adverse consequences (Moulton et al., 2005; Tseng et al., 2010).

2.4. Image acquisition

All fMRI scans were performed on a 3.0 T MR scanner (MAGNETOM Trio, Siemens AG, Erlangen, Germany). The coil was foam-padded to restrict head motion and improve subject comfort. Each subject was provided with ear plugs to minimize stimulation from scanning sounds. Functional images with blood oxygenation level-dependent (BOLD) contrast were acquired using a T2-weighted single-shot gradient-recalled echo planar imaging (EPI) sequence. Axial slices were acquired to provide full-brain coverage (35 slices for each subject) with the following parameters: TR = 3000 ms, TE = 28 ms, flip angle = 80°, acquisition matrix = 64 × 64, field of view = 220 × 220 mm^2, and 3.00 mm slice thickness with a 0.3 mm gap. To improve the signal-to-noise ratio in areas prone to susceptibility artifacts, shimming was applied to lessen the field heterogeneity during data collection.