Original Investigation

Evidence of Resting-state Activity in Propofol-anesthetized Patients with Intracranial Tumors

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Rationale and Objectives: Resting-state (RS) networks, revealed by functional magnetic resonance imaging (fMRI) studies in healthy volunteers, have never been evaluated in anesthetized patients with brain tumors. Our purpose was to examine the presence of residual brain activity on the auditory network during propofol-induced loss of consciousness in patients with brain tumors.

Materials and Methods: Twenty subjects with intracranial masses were prospectively studied by means of intraoperative RS-fMRI acquisitions before any craniectomy. After performing single-subject independent component analysis, spatial maps and time courses were assigned to an auditory RS network template from the literature and compared via spatial regression coefficients.

Results: All fMRI data were of sufficient quality for further postprocessing. In all but two patients, the RS functional activity of the auditory network could be successfully mapped. In almost all patients, contralateral activation of the auditory network was present. No significant difference was found between the mean distance of the RS activity clusters and the lesion periphery for tumors located in the temporal gyri vs. those in other brain regions. The spatial deviation between the activated cluster in our experiment and the template was significantly ($P = 0.04$) higher in patients with tumors located in the temporal gyri than in patients with tumors located in other regions.

Conclusions: Propofol-induced anesthesia in patients with intracranial lesions does not alter the blood-oxygenation level-depended signal, and independent component analysis of intraoperative RS-fMRI may allow assessment of the auditory network in a clinical setting.

Key Words: Functional MRI (fMRI); resting state; brain tumor; auditory cortex; independent component analysis.

INTRODUCTION

Resting-state functional magnetic resonance imaging (RS-fMRI) acquisitions, based on system-wide coherent blood-oxygenation level dependent (BOLD) signal fluctuations, visualize a set of regions suggesting an underlying functional relationship despite deprivation of external stimuli (1). In humans, fMRI-visualized RS activity has been shown to be stable throughout light sleep/wake cycles (2,3), during light sleep, deep sleep, or sedation (4–6), as well as during different levels of consciousness including propofol-induced loss of consciousness (5,7–9). The partial preservation of functional connectivity in the absence of consciousness has been attributed to preserved anatomical connections dissociated from higher cognitive functions (10).

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Thus far, however, these RS networks, revealed by fMRI studies mostly in healthy volunteers, have never been evaluated in anesthetized patients with brain tumors. The present study investigated the feasibility of acquiring whole-brain RS-fMRI measurements in patients with brain tumors by means of intraoperative fMRI during pharmacological modulation of the level of consciousness. The anesthetic drug used was propofol because of its advantage over isoflurane/sevoflurane in keeping low subdural intracranial pressure and arteriovenous oxygen difference while keeping higher cerebral perfusion pressure in patients with brain tumors (11). Under the proof-of-principle study design, we orientated in the RS activity of the auditory cortex because it has been shown in many studies to be robustly identifiable across healthy subjects and patients (12,13), its analysis is relatively simple compared to other networks (14), and previous works have tested the influence of different anesthetics on its activation (7,15,16) in healthy subjects. The auditory network involves the superior temporal gyrus, the transverse temporal gyrus (Heschl's gyrus), the insula, and the postcentral gyrus. The primary auditory cortex has also known interactions with the angular gyrus, the supramarginal gyrus, Broca's, and Wernicke's areas.

We postulated that fMRI during propofol-induced loss of consciousness in patients with brain tumors may reproduce brain activity shown in healthy subjects, resorting to the same

conditions of anesthesia (7); however, we were uncertain whether these BOLD fluctuations will be decreased as well as associated with further disorganization of brain activity, mostly in the vicinity of tumor tissue.

MATERIALS AND METHODS

Ethics Statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. The local institutional ethics review board approved this feasibility study and written informed consent was obtained from all participants.

Subjects

After thorough explanation of the study plan, all subjects provided informed consent for the intraoperative fMRI and the evaluation of the data. The patients (11 males and nine females; mean age 39.8 ± 16.5 years; age range 19–77 years; all right handed) were considered eligible for the study after fulfillment of the following inclusion criteria: (1) MRI evidence of supratentorial gliomas or extensive pituitary gland tumors (macroadenomas); (2) neuro-oncology board request for intraoperative MRI pursuing margin-free tumor resection, which would be beneficial for the patient; (3) medical and physical conditions permitting prolonged operation and anesthesia according to the internationally accepted guidelines; (4) lack of previous history of head trauma or surgery, mental illness, or drug addiction; and (5) no contraindication for MRI examination. Before the initiation of the study-related examinations, identical RS-fMRI experiments (in terms of imaging parameters and at the same scanner) were conducted in three awake healthy volunteers.

Intraoperative MRI

Propofol was infused through an intravenous catheter placed into the left antecubital vein. Sedation was achieved using intravenous infusion of propofol to obtain constant effect-site concentrations. The electrocardiogram, blood pressure, pulse oxymetry (Spo_2), and breathing frequency were continuously monitored (Magnitude 3150M; Invivo Research, Inc., Orlando, FL) in all patients during the study. MR-compatible anesthetic monitoring was used throughout the MR scanning. Intraoperative MRI was performed in an intraoperative MR suite (IMRIS Visius Surgical Theatre, IMRIS Inc., Winnipeg, Canada) with a modified ceiling-mounted 1.5T moveable magnet (Espree; Siemens Medical Systems, Erlangen, Germany), described previously in the work of Chen et al. (17). The patient's head was fixed in an MR-compatible DORO skull clamp with disposable cranial pins (ProMed Instruments GmbH, Freiburg, Germany). The conventional MRI protocol included three-dimensional T2-FLAIR (repetition time/echo time/inversion time (TR/TE/TI)), 8800/356/2500 ms, field of view (FOV), 240 mm^2; matrix size, 256 × 256; section thickness, 1.5 mm; 3D MPRAGE (TR/TE/TI, 1650/3/1100 ms, FOV, 240 mm^2; matrix size, 256 × 256; section thickness, 1 mm) before and after intravenous contrast agent injection (0.1 mL/kg/body weight, Gadovist, Bayer Schering, Berlin, Germany). The fMRI experiment (TR/TE, 2000/50 ms, FOV, 250 mm^2; matrix size, 64 × 64; section thickness, 3 mm; number of slices, 24; number of images, 220) lasted 7 min and was performed before any gadolinium administration. Subjects wore earplugs during the whole MR acquisition.

Anesthesia Protocol

Total intravenous general anesthesia was maintained by continuous administration of propofol (5 mg/kg body weight/h) and remifentanil (0.5 μg/kg body weight/min). During the surgery, electrocardiogram, blood pressure, pulse oxymetry, blood gas, and breathing frequency were continuously monitored. Mean arterial pressure and heart rate were kept stable between 70–90 mmHg 60–80 beats/min, respectively.

Image Processing and Data Analysis

RS-fMRI data were analyzed by using software package (SPM8, Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk) running in MATLAB (The MathWorks Inc.). All images were manually corrected through re-orientation of the original images, which were shifted in the yaw direction, and then entered the preprocessing stage. Preprocessing comprised slice time correction for interleaved acquisition, motion correction, and segmentation of anatomical data. Functional and anatomical images were co-registered and normalized to the T1 standard template in Montreal Neurological Institute space (14). After that, functional data were smoothed using a Gaussian kernel of 10 mm full width at half maximum.

After preprocessing, single-subject independent component analysis (ICA) of 20 subjects was carried out using the Infomax algorithm, which was proposed by Bell and Sejnowski (18) within the GIFT software (http://icatb.sourceforge.net, version1.3b). For each subject, preprocessed data were decomposed into a chosen number of 75 independent components by this algorithm. This number was also used by Allen et al. (14). For each of those components, characteristic time courses and spatial maps were generated. These maps provided z-scores as intensity values, describing the similarity of the time course within the voxel with the characteristic time course. A two-step process was used to determine individual components corresponding to the auditory network. First, a spatial template matching technique provided by the GIFT toolbox was applied. This technique identifies one or more components by comparing the spatial maps to the selected template. It selects one or more components by comparing the spatial maps to the auditory network template and selecting the ones that show a high spatial correlation coefficient to it (14). In the reference data set, auditory network consists of one single component, which is no. 17.