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Propofol attenuates low-frequency fluctuations of resting-state fMRI BOLD signal in the anterior frontal cortex upon loss of consciousness

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ABSTRACT

Recent studies indicate that spontaneous low-frequency fluctuations (LFFs) of resting-state functional magnetic resonance imaging (rs-fMRI) blood oxygen level-dependent (BOLD) signals are driven by the slow (< 0.1 Hz) modulation of ongoing neuronal activity synchronized locally and across remote brain regions. How regional LFFs of the BOLD fMRI signal are altered during anesthetic-induced alteration of consciousness is not well understood. Using rs-fMRI in 15 healthy participants, we show that during administration of propofol to achieve loss of behavioral responsiveness indexing unconsciousness, the fractional amplitude of LFF (fALFF index) was reduced in comparison to wakeful baseline in the anterior frontal regions, temporal pole, hippocampus, parahippocampal gyrus, and amygdala. Such changes were absent in large areas of the motor, parietal, and sensory cortices. During light sedation characterized by the preservation of overt responsiveness and therefore consciousness, fALFF was reduced in the subcortical areas, temporal pole, medial orbital frontal cortex, cingulate cortex, and cerebellum. Between light sedation and deep sedation, fALFF was reduced primarily in the medial and dorsolateral frontal areas. The preferential reduction of LFFs in the anterior frontal regions is consistent with frontal to sensory-motor cortical disconnection and may contribute to the suppression of consciousness during general anesthesia.

1. Introduction

Resting-state functional magnetic resonance imaging (rs-fMRI) is a powerful and unique tool for the noninvasive mapping of spontaneous neuronal activity and regional functional interactions in the brain in the absence of exogenous stimulation or task (Biswal 2012; Buckner et al. 2013). Accumulating experimental evidence indicates that the low-frequency (< 0.1 Hz) fluctuations (LFFs) of blood oxygen-dependent (BOLD) fMRI signals in the resting state are correlated with spontaneous neuronal activity synchronized locally or over long distances in the brain (Cabral et al. 2014; Foster et al. 2016). Rapid neuronal dynamics like spiking and gamma-band activity are modulated by neuronal processes occurring at a slower time scale, and it is this slow modulation that gives rise to the observed BOLD fMRI dynamics (Fox et al. 2005; Raichle 2011; Foster et al. 2016). Moreover, the long-range synchrony of network activity as revealed by rs-fMRI has been specifically linked to the slow modulation (< 0.1 Hz) of local field potentials in the gamma-band (Nir et al. 2008).

General anesthesia alters ongoing brain activity, regional cerebral metabolism and hemodynamics, with characteristic patterns depending on the anesthetic agent and dose (Alkire et al. 2008). In the past decade, numerous neuroimaging studies sought a better understanding of functional connectivity changes in anesthetic-induced altered states of consciousness (Hudetz 2012). However, with few exceptions, little attention has been given to the local or regional modulation of low-frequency fluctuations of BOLD fMRI signals by anesthesia (Guldenmund et al. 2016). This is important because functional connectivity is generally derived from the temporal correlation of BOLD signals between a pair of spatially remote brain regions, indexing the degree of their temporal coactivation. This derivation of

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functional connectivity does not reveal which of the involved brain regions are altered during any intervention. For example, an anesthetic may alter functional connectivity via the suppression or augmentation of local neuronal-hemodynamic fluctuations in either or both regions and may influence those in a similar or opposing manner. This argument motivated us to examine the effect of anesthesia on low-frequency BOLD fluctuations across various regions of the brain.

To quantify the intensity of regional spontaneous brain activity, a suitable index, the fractional amplitude of low-frequency fluctuations, or fALFF, was previously introduced (Zou et al. 2008) based on the similar index ALFF (Zang et al. 2007). The fALFF measures the ratio of power within the low-frequency range (e.g., 0.01–0.1 Hz) of BOLD signal fluctuations relative to total power in the entire measurable frequency range. It has been applied to detect abnormal spontaneous brain activity in various cognitive and neuropsychiatric disorders such as mild cognitive impairment (Han et al. 2012), schizophrenia (Hoptman et al. 2010), aging (La et al. 2016), and depression (Tadayonnejad et al. 2015). To our knowledge, fALFF has not been used to characterize the effect of general anesthesia on brain activity.

In this study, we used the fALFF index to quantify region-specific changes of spontaneous LFFs of the BOLD signal during propofol-induced alterations of consciousness. To delineate the important changes in fALFF associated with the transition between conscious and unconscious states, we used two levels of sedation, as called here, light and deep sedation. Memory and consciousness are two expressions of brain functioning that are suppressed by anesthetics (Hudetz and Pearce 2010). Memory is diminished at a light sedative dose of anesthetic at which responsiveness and consciousness are still present (Sanders et al. 2012). Overt behavioral responsiveness and, by inference, consciousness are abolished at a deep sedative dose.

Prior findings suggested that general anesthetics at a deep sedative dose preferentially reduce brain activation in higher-order information-processing regions but leave the reactivity of primary sensory cortices to stimuli unchanged (Hudetz 2006; Alkire et al. 2008; Hudetz and Mashour 2016). Accordingly, we hypothesized that during light sedation with propofol, fALFF would be reduced in memory-related brain areas, and while in deep sedation consistent with loss of consciousness, it would show preferential reduction in the frontal association regions involved in higher-order executive functions.

2. Materials and methods

2.1. Data acquisition

Fifteen healthy volunteers aged 19–35 years old (nine males and six females, mean age 26.7 years, standard deviation 4.8, body mass index < 25) participated in this study. The anesthetic agent propofol was administered with a bolus dose followed by a target-controlled continuous infusion (STANPUMP (Shafer 1996)). We targeted a plasma concentration of 0.98 ± 0.18 μg ml^{-1} for light sedation and 1.88 ± 0.24 μg ml^{-1} for deep sedation (the targeted plasma concentration varied slightly in individual participants in order to achieve a desired state of sedation). The lower dose for light sedation was intended to induce lethargic response to questions in participants (OAAS [observer's assessment of alertness/sedation] score: 4; (Chernik et al. 1990)). The higher dose for deep sedation was chosen to achieve the desired endpoint, at which the participant showed no response when his/her name was called loudly at the scanner bedside and did not respond to mild prodding and shaking (OAAS score: 2–1). The order of administering light and deep sedation was counterbalanced in study participants. Standard American Society of Anesthesiologists monitoring was conducted during the experiment, including electrocardiogram, noninvasive blood pressure cuff, pulse oximetry, and end-tidal carbon dioxide gas monitoring. Supplemental oxygen was administered prophylactically via nasal cannula.

Resting-state structural and functional MRI data were acquired using a whole-body 3 T Signa GE 750 scanner (GE Healthcare, Waukesha, Wisconsin, USA) with a standard 32-channel transmit-receive head coil. Functional imaging data were acquired during each of four 15-minute scans in wakefulness, light sedation, deep sedation, and recovery, respectively, with repetition time, 2 s; echo time, 25 ms; slice thickness, 3.5 mm; in-plane resolution, 3.5×3.5 mm; number of slices, 41; flip angle, 77°; field of view, 22.4 cm; matrix size, 64×64. High-resolution spoiled gradient-recalled echo (SPGR) anatomical images were acquired before functional scans with TE/TR/TI, 8.2/3.2/450 ms; slice thickness, 1 mm; number of slices, 150; flip angle, 12°; field of view, 24 cm; matrix size, 256×256.

2.2. Data preprocessing

Imaging data were preprocessed using a collection of Analysis of Functional NeuroImages (AFNI, http://afni.nimh.nih.gov/afni), FSL (http://www.fmrib.ox.ac.uk/fsl), FreeSurfer (http://freesurfer.net), and Matlab (The MathWorks, Natick, MA) software. Raw functional images were first retrospectively corrected for cardiac and respiratory motion (*3dretroicor* in AFNI). The first five data points were discarded to reduce the initial transient effects in data acquisition. Subsequent data preprocessing included despiking, detrending, and motion correction. No significant differences of head motion ranges were found between the four functional scan conditions. Physiological noise was estimated using the average BOLD time series from the regions of white matter (WM) and cerebrospinal fluid (CSF), which were determined in each individual's anatomical images. The voxelwise BOLD time series from each run was then analyzed with a general linear regression model (*3dDeconvolve* in AFNI) using the eight regressors representing noise artifacts from the motion parameters, WM, and CSF, respectively. Each participant's high-resolution anatomical images were spatially transformed to the standard MNI (Montreal Neuroimaging Institute) space (MNI152) (*flirt* in FSL); then, the functional data were coregistered into the MNI space with a sampling to a 3-mm cubic voxel size. In the MNI space, functional data were further cleaned by regressing out artifacts originating from subregions of the WM, CSF, and major vein (e.g., superior sagittal sinus) areas.

2.3. Computation of fALFF and statistical analysis

Computation of fALFF was performed in voxel-wise manner using the volumetric fMRI data. The BOLD time series of all brain voxels were converted to the frequency domain via the Fast Fourier Transform (FFT, Matlab), and normalized power spectrums were subsequently obtained. The fALFF index was computed in a voxel-wise manner as the sum of power in the frequency band of 0.01–0.1 Hz divided by the sum of power of the entire frequency range (0.01–0.25 Hz). To investigate the effect of propofol-induced differences in fALFF at the group level, two-sided paired *t*-tests were performed on the individual fALFF maps between different states of consciousness. The threshold of significance was set at a P=0.01 combined with correction for multiple comparisons using the *AlphaSim* method in AFNI (a minimum cluster threshold of 153 voxels of 3-mm cubic in the MNI space).

We found that standardization of voxel BOLD time series (normalizing to zero mean and standard deviation, i.e., z-score) did not affect the fALFF index results. This is because fALFF represents the relative power of low-frequency fluctuations to that of a wider frequency range, whereas the ALFF index measures the absolute power of LFFs. For the purpose of comparison, we also computed the ALFF index and compared the changes in ALFF across the four states of consciousness (see Supplemental Information). However, standardizing the voxel BOLD time series became a critical factor that substantially influenced the results for ALFF. In our experiments, BOLD fMRI signals were acquired using a standard 32-channel transmit-receive head coil with a