NeuroImage 148 (2017) 130–140

Contents lists available at ScienceDirect

NeuroImage

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

Multi-modal analysis of functional connectivity and cerebral blood flow reveals shared and unique effects of propofol in large-scale brain networks

Maolin Qiu[a,1], Dustin Scheinost[a,*,1], Ramachandran Ramani[b], R. Todd Constable[a,c]

[a] Department of Radiology and Biomedical Imaging, Yale School of Medicine, New Haven, CT 06520, USA
[b] Anesthesiology, Yale School of Medicine, New Haven, CT 06520, USA
[c] Neurosurgery, Yale School of Medicine, New Haven, CT 06520, USA

ARTICLE INFO

Keyword:
Multi-modal
Functional connectivity
Cerebral blood flow
Reduced consciousness
Propofol
Large-scale brain networks

ABSTRACT

Anesthesia-induced changes in functional connectivity and cerebral blow flow (CBF) in large-scale brain networks have emerged as key markers of reduced consciousness. However, studies of functional connectivity disagree on which large-scale networks are altered or preserved during anesthesia, making it difficult to find a consensus amount studies. Additionally, pharmacological alterations in CBF could amplify or occlude changes in connectivity due to the shared variance between CBF and connectivity. Here, we used data-driven connectivity methods and multi-modal imaging to investigate shared and unique neural correlates of reduced consciousness for connectivity in large-scale brain networks. Rs-fMRI and CBF data were collected from the same subjects during an awake and deep sedation condition induced by propofol. We measured whole-brain connectivity using the intrinsic connectivity distribution (ICD), a method not reliant on pre-defined seed regions, networks of interest, or connectivity thresholds. The shared and unique variance between connectivity and CBF were investigated. Finally, to account for shared variance, we present a novel extension to ICD that incorporates cerebral blood flow (CBF) as a scaling factor in the calculation of global connectivity, labeled CBF-adjusted ICD). We observed altered connectivity in multiple large-scale brain networks including the default mode (DMN), salience, visual, and motor networks and reduced CBF in the DMN, frontoparietal network, and thalamus. Regional connectivity and CBF were significantly correlated during both the awake and propofol condition. Nevertheless changes in connectivity and CBF between the awake and deep sedation condition were only significantly correlated in a subsystem of the DMN, suggesting that, while there is significant shared variance between the modalities, changes due to propofol are relatively unique. Similar, but less significant, results were observed in the CBF-adjusted ICD analysis, providing additional evidence that connectivity differences were not fully explained by CBF. In conclusion, these results provide further evidence of alterations in large-scale brain networks are associated with reduced consciousness and suggest that different modalities capture unique aspects of these large scale changes.

Introduction

Consciousness is a hallmark of normal human life, yet its breadth and complexity make consciousness remarkably difficult to study. Anesthetic agents are designed to suppress levels of consciousness and such agents provide a powerful tool to relate changes in consciousness to changes in brain properties (Mashour, 2006). With a few exceptions such as ketamine, anesthetics suppress baseline metabolism (Franks, 2008), suggesting a brain energetic pathway for consciousness (Shulman et al., 2009). Similarly, electroencephalogram (EEG) data shows a transition from high-frequency electrical activity to slow cortical waves as anesthesia takes effect, reflecting a reduction in neuronal firing rate (Alkire et al., 2008). For both metabolism and electrical activity, the greatest changes are observed large-scale brain networks spanning cortical and subcortical regions (Franks, 2008; Hudetz, 2012).

Changes in functional connectivity also point towards similar disruption of large-scale brain networks in anesthesia-based reduced consciousness (Boveroux et al., 2010; Gili et al., 2013; Liang et al., 2012; Liu et al., 2013; Martuzzi et al., 2010; Monti et al., 2013). Cortical regions commonly reported include regions of the default mode network (DMN; Greicius et al., 2008; Martuzzi et al., 2010; Mhuircheartaigh et al., 2010; Stamatakis et al., 2010), the frontoparietal network (FPN: Boveroux et al., 2010; Schrouff et al., 2011), and

* Correspondence to: Magnetic Resonance Research Center, 300 Cedar St, PO Box 208043, New Haven, CT 06520-8043, USA.
[1] Authors contributed equally.

http://dx.doi.org/10.1016/j.neuroimage.2016.12.080
Received 5 October 2016; Accepted 28 December 2016
Available online 06 January 2017

motor-sensory networks (Martuzzi et al., 2010; Peltier et al., 2005).

However, studies of functional connectivity disagree on which large-scale networks are altered or persevered during anesthesia, making it difficult to find a consensus among studies (Hudetz, 2012). Many functional connectivity techniques applied to investigations of anesthetics have focused on a limited number of seed regions or a predefined network (such as a component derived from independent component analysis), making it difficult to detect changes in more than one network. Focusing on pre-defined specific regions or canonical resting-state networks potentially yields an incomplete picture of the large-scale network changes due to anesthesia-related changes in consciousness.

Additionally, connectivity studies often employ only a single modality (typically resting-state functional magnetic resonance imaging or rs-fMRI) and do not account for changes in metabolism or blood flow. Variations in these factors can modulate the rs-fMRI signal (Jo et al., 2010; Khalili-Mahani et al., 2014; Liu, 2013), leading to mischaracterization of the shared or unique aspect of functional connectivity correlates of reduced consciousness.

In this work, we used data-driven connectivity methods and multimodal imaging to investigate neural correlates of reduced consciousness for connectivity in large-scale brain networks. Rs-fMRI and CBF data, as measured by pulsed arterial spin labeling (ASL), were collected from the same subjects during an awake and a deep sedation condition. We measured whole-brain connectivity using the intrinsic connectivity distribution (ICD (Scheinost et al., 2012)), a method not reliant on predefined seed regions, networks of interest, or connectivity thresholds. The shared and unique variance of connectivity and CBF were investigated using a high-resolution, 268 node functional atlas (Finn et al., 2015). Finally, to account for the shared variance, we present a novel extension to ICD that incorporates cerebral blood flow (CBF) as a scaling factor in the calculation of global connectivity, labeled CBF-adjusted ICD. We hypothesized that unique connectivity differences due to reduced consciousness will span multiple large-scale brain networks when accounting for the shared variance with CBF.

Materials and methods

Subjects

Thirty-two healthy subjects (19–35 years) underwent imaging that included resting state blood oxygenation level dependent (BOLD) fMRI and pulsed arterial spin labeling (PASL) acquisitions during an awake condition and a propofol anesthesia condition within the same imaging session. Fig. 1 shows a timeline of image acquisition. The BOLD fMRI scans were always acquired before the ASL scans. The sample included 19 males and 13 females with an average age of 23.3 ± 3.1 years. Subjects on psychoactive drugs or centrally acting medications and those with a history of renal disease were excluded. MRI experiments were performed under research protocols approved by the Institutional Review Board of Yale University. All patients fasted for more than 8 h before the study.

Propofol administration

Propofol was infused to induce an anesthetized state. For propofol administration, an intravenous (IV) cannula was inserted under sterile conditions, and an IV infusion line was used for maintenance infusion (lactated ringer at 100 ml/h). Propofol infusion was administered through a target-controlled infusion (TCI) pump (Stanpump, Stanford University, Palo Alto, CA), which is based on a kinetic model that uses the age, sex, weight and height of the subject as model inputs. The target plasma concentration for TCI was 2 μg/ml plasma level. This concentration produces unresponsiveness to verbal commands and global loss of memory (Purdon et al., 2009) and corresponds to "Deep Sedation" as defined by American Society of Anesthesiologist (ASA) continuum of sedation. As a confirmation of level of consciousness, all subjects did not respond to verbal call. Painful stimuli were not performed to arouse the participants.

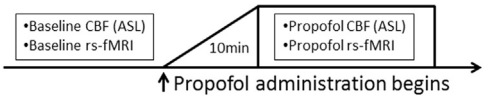

Fig. 1. Schematic of image acquisition timeline. Baseline resting-state fMRI (rs-fMRI) and cerebral blood flow (CBF) data were acquired while subjects were awake in the resting state. Next, within the same imaging session, a low dose of propofol was administered to the participant with a maintenance infusion target plasma concentration of 2 μg/ml. After allowing the subject to reach an anesthetized state (approximately 10 min), the same sequence of CBF and rs-fMRI data was acquired.

For the deep sedation condition, the MRI scans began at least 10 min after the start of propofol infusion. To assess the variability in propofol delivery as determined by plasma level for each subject, two blood samples (5 ml each) were drawn on 23 of the 32 participants. One sample was drawn at least 10 min after the start of propofol infusion and the other right before the end of the propofol infusion. For subject safety, physiological parameters were monitored throughout the imaging session. Blood pressure was monitored every 5 min using a standard blood pressure cuff. Respiratory rate, heart rate, end-tidal CO2, and blood hemoglobin oxygenation were continuously monitored with standard ASA monitors. Oxygen was delivered to the subjects through a nasal cannula at a rate of 4 l per minute for both the awake and deep sedation conditions. During the experiment, subjects were instructed to lie still in the scanner with their eyes closed.

BOLD fMRI acquisition

Magnetic resonance imaging data were acquired on a 3 T whole-body scanner Siemens TIM Trio with a 12-channel phased array head coil. During the awake and the propofol conditions, two functional BOLD runs of 210 volumes each were acquired using a T2*-sensitive gradient-recalled, single-shot echoplanar imaging pulse sequence (TR=2 s, TE=30 ms, FOV=256×256 mm^2, flip angle=90°, matrix size 64×64). Each volume consisted of 33 AC-PC aligned slices, with a slice thickness of 4 mm and no gap.

PASL CBF acquisition

The Quantitative Imaging of Perfusion using a Single Subtraction (QUIPSS) pulsed arterial spin labeling (PASL) sequence was used for measuring resting-state CBF in the anesthesia-free and anesthesia conditions (Luh et al., 1999). A slab-selective (100 mm) hypersecant inversion radiofrequency (RF) pulse was used for labeling the in-flow arterial blood water. The RF pulse was applied to a slab 25 mm inferior to the imaging slab for labeling, and the same RF pulse was applied to a slab 25 mm superior to the imaging slab to control for off-resonance effects. The paired labeling and control images were acquired in an alternating manner. A 20-slice ASL acquisition was implemented, and all slices were acquired parallel to the AC-PC line and positioned to provide full brain coverage. The ASL acquisition parameters were: field of view FOV=256×256 mm^2; matrix=64×64; bandwidth=2004 Hz/pixel; slice thickness=5 mm with an interslice gap of 2.5 mm. The repetition time was TR=3000 ms; the echo time was TE=26 ms. The acquisition of each slice took approximately 60 ms, therefore the post-labeling inversion time for each slice i, i=1, 2, ..., TI(i)=1400+60 (i-1) ms, which was used in CBF quantification, resulting in a post-labeling data acquisition window from 1.4 to 2.6 s. A bipolar gradient of encoding velocity Venc=5 cm/s was applied to the imaging slices to suppress the signal contamination from the labeled arterial water within large vessels. Proton density weighted images were collected using the same perfusion sequence, except for the following changes: TR was set to 10 s; the delay time TD was set to 0 ms; and the inversion time TI was set to maximum to allow a full longitudinal magnetization