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Volitional eyes opening perturbs brain dynamics and functional connectivity regardless of light input

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ABSTRACT

The act of opening (or closing) one's eyes has long been demonstrated to impact on brain function. However, the eyes open condition is usually accompanied by visual input, and this effect may have been a significant confounding factor in previous studies. To clarify this situation, we extended the traditional eyes open/closed study to a two-factor balanced, repeated measures resting state fMRI (rs-fMRI) experiment, in which light on/off was also included as a factor. In 16 healthy participants, we estimated the univariate properties of the BOLD signal, as well as a bivariate measure of functional connectivity and multivariate network topology measures. Across all these measures, we demonstrate that human brain adopts a distinctive configuration when eyes are open (compared to when eyes are closed) independently of exogenous light input: (i) the eyes open states were associated with decreased BOLD signal variance (P-value = 0.0004), decreased fractional amplitude of low frequency fluctuation (fALFF. P-value = 0.0061), and decreased Hurst exponent (H. P-value = 0.0321) mainly in the primary and secondary sensory cortical areas, the insula, and the thalamus. (ii) The strength of functional connectivity (FC) between the posterior cingulate cortex (PCC), a major component of the default mode network (DMN), and the bilateral perisylvian and perirolandic regions was also significantly decreased during eyes open states. (iii) On the other hand, the average network connection distance increased during eyes open states (P-value = 0.0139). Additionally, the metrics of univariate, bivariate, and multivariate analyses in this study are significantly correlated. In short, we have shown that the marked effects on the dynamics and connectivity of fMRI time series brought by volitional eyes open or closed are simply endogenous and irrespective of exogenous visual stimulus. The state of eyes open (or closed) may thus be an important factor to control in design of rs-fMRI and even other cognitive block or event-related experiments.

Introduction

The state of having one's eyes open or closed has long been linked to changes in brain physiology (Berger, 1929). For example, the eyes closed condition is known to play a critical role in the generation of the alpha rhythm observed in electroencephalography (EEG) experiments (Berger, 1929; Fisch and Spehlmann, 1999; Goldman et al., 2002; Jann et al., 2009). In recent decades, other modalities like positron emission tomography (PET), magnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI) have also been applied to study the effects of opening or closing eyes on endogenous brain dynamics.

As described below, several univariate, bivariate and multivariate methods of fMRI analysis have previously been used to detect changes

Abbreviations: CID, eyes Closed In the Dark; OID, eyes Open In the Dark; CIL, eyes Closed In the Light; OIL, eyes Open In the Light; AG, Angular Gyrus; APC, Anterior Prefrontal Cortex; DLPFC, Dorsolateral Prefrontal Cortex; FEF, Frontal Eye Field; FG, Fusiform Gyrus; HG, Heschl's Gyrus; IFG, Inferior Frontal Gyrus; IOG, Inferior Occipital Gyrus; IPL, Inferior Parietal Lobule; ITG, Inferior Temporal Gyrus; LOG, Lateral Occipital Gyrus; MFG, Middle Frontal Gyrus; MTG, Middle Temporal Gyrus; PCC, Posterior Cingulate Cortex; PCL, Paracentral Lobule; PHG, Parahippocampal Gyrus; Post-CG, Postcentral Gyrus; Pre-CG, Precentral Gyrus; SFG, Superior Frontal Gyrus; SPL, Superior Parietal Lobule; STG, Superior Temporal Gyrus; TTG, Transverse Temporal Gyrus.

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across conditions, including the eyes open/closed states. However, such prior measurements may have been confounded by the effect of visual input concomitant with the eyes open condition. In this study, we disambiguate these effects for the first time and, within this context, apply a wide range of functional MRI time series analysis methods, of increasing sophistication. A brief overview of each method used and related prior findings is given below.

The magnitude of spontaneous blood oxygen level-dependent (BOLD) fluctuations are known to correlate with various physiological conditions, metabolic status (Biswal et al., 1997), cognitive activities (Birn et al., 2001; Fox et al., 2005a; Gilden et al., 1995; McGonigle et al., 2003; Smith et al., 2005), and medications (Kiviniemi et al., 2005; Li et al., 2000). Several fMRI studies have also pointed out differences in the spontaneous BOLD oscillations between the eyes open/closed conditions (Bianciardi et al., 2009; Burr, 2005; Goldman et al., 2002; Marx et al., 2003, 2004; McAvoy et al., 2008; Yang et al., 2007). For example, Bianciardi et al. (2009) and McAvoy et al. (2008) reported reduced amplitude of spontaneous BOLD fluctuations in visual areas under eyes open conditions relative to the eyes closed condition. Marx et al. (2003) reported that the eyes closed condition relatively activated visual, somatosensory, vestibular, and auditory systems using a blocked design fMRI paradigm.

Spectral properties of interest of the BOLD signal include for example the power spectrum and the amplitude of low frequency fluctuation (ALFF), and both of which are widely used in neuroimaging studies (Sun et al., 2004; Yan et al., 2009; Yang et al., 2007; Yu-Feng et al., 2007). For example, it has previously been reported, using specific region of interest (ROI) analysis, that the ALFF in the frequency range of 0.01–0.08 Hz was higher in the eyes open than in the eyes closed state (Yan et al., 2009; Yang et al., 2007). Here, we will be using the ratio of the power spectrum at low frequency, the fractional ALFF (fALFF), which is less sensitive to physiological noise and thus improves the sensitivity and specificity in detecting spontaneous brain activity (Zou et al., 2008, 2010).

Furthermore, fractal scaling parameters like the Hurst exponent (H) have been used to investigate randomness and self-similarity of fMRI time series from different brain areas in various states in both normal and diseased people (Barnes et al., 2009; Lai et al., 2010; Maxim et al., 2005; Pritchard, 1992; Wink, 2008). However, little is known about the sensitivity of this parameter to changes in endogenous fMRI dynamics induced by the difference between eyes open and eyes closed states.

Besides univariate analysis, bivariate functional connectivity estimated from temporal correlations between distributed brain regions has also enabled a greater understanding of brain organization (Friston, 1994). In addition, brain functional networks constructed from multivariate time series are widely used to study alterations in the organization of the brain as a whole. Information processing in these large-scale brain networks is often characterized using metrics of network topology like clustering coefficient, local efficiency, and modularity (which measure brain functional segregation) and/or topological measures such as characteristic path length or global efficiency (which quantify functional integration) (Achard et al., 2006; Bullmore and Sporns, 2009; Meunier et al., 2009b; Rubinov and Sporns, 2010). In addition, connection distance can be measured, to get some sense of the economical aspect (or cost) of information processing within brain networks (Bullmore and Sporns, 2012; Niven and Laughlin, 2008; Rubinov and Sporns, 2010; Sepulcre et al., 2010). Overall, brain functional networks revealed by fMRI studies have been found to be modified by various brain activities ranging from simple finger tapping (Biswal et al., 1995) to memory tasks (Bassett et al., 2009), various neuropsychiatric disorders (Alexander-Bloch et al., 2010; Liu et al., 2007; Lynall et al., 2010; Seeley et al., 2009), and even various physiological states ranging from aging (Meunier et al., 2009a) to the eyes open/closed conditions (Yan et al., 2009; Zou et al., 2009). In particular, studies using certain ROIs showed that in the eyes closed versus the eyes open condition, there were negative linear correlations between the thalamus and the visual cortex (Zou et al., 2009, with global signal regression), and also lower seed-based functional connectivity within the default mode network (DMN) (using posterior cingulate cortex, PCC, and medial prefrontal cortex, MPFC, as the seed respectively) (Yan et al., 2009).

Given this wealth of previous work focusing on the effect of open versus closed eyes, it is somewhat surprising that little attention has so far been paid to the effects of exogenous visual input in the eyes open condition. The neuroanatomical pathways of motor control for opening and closing eyes (Baehr et al., 2005; Brazis et al., 2007; Schmidtke and Buttner-Ennever, 1992) are distinct from those of visual perception (Baehr et al., 2005; Brazis et al., 2007; FitzGerald and Folan-Curran, 2002) and may therefore reasonably be expected to have distinct effects on brain dynamics. These conditions have so far not been strictly controlled and were thus perhaps incompletely disambiguated in the previous EEG and fMRI eyes open/closed studies (Bianciardi et al., 2009; Fukunaga et al., 2006; Goldman et al., 2002; Marx et al., 2003; Mazoyer et al., 2001; McAvoy et al., 2008; Nir et al., 2006; Pritchard, 1992; Sewards and Sewards, 1999; Singh et al., 1998; Yan et al., 2009; Yang et al., 2007).

To clarify this situation, we extended the traditional eyes open/closed study to a balanced, two-factor, repeated measures, resting state fMRI experiment, in which light on/off was also included as an experimental factor. Moreover, to explore the physiological effects of both factors and the interaction between them on fMRI time series, we investigated a range of metrics including local measures of fMRI dynamics, such as regional variance, fALFF, Hurst exponent, as well as measures of functional connectivity and functional network organization. We expected hypothetically that it would be possible to demonstrate significant effects of eyes open/closed on brain function, that could not be explained by changes in visual input, and that these brain functional effects would be represented by correlated changes in several measures of resting state fMRI time series. Please see Fig. 1 for schematic overview.

Materials and methods

Sample

16 healthy right-handed volunteers (8 male, 8 female) were recruited by local advertising on campus (mean age = 26.75 years; standard deviation 5.1 years). All subjects were screened by a questionnaire and a board-certified neurologist to exclude possible history of neurological illness, psychiatric disorders, or current drug use. Informed written consent was obtained from all participants in agreement with the protocol approved by the National Taiwan University Institutional Review Board.

Experimental design

Each subject underwent four separate scanning sessions under the following conditions: (1) eyes closed in darkness, CID; (2) eyes open in darkness, OID; (3) eyes closed in light, CIL; and (4) eyes open in light, OIL. The order of scanning under these conditions was counterbalanced across subjects by a Latin square design. Each of the scanning sessions lasted for 8 minutes with a few minutes of break between sessions. During the eyes open conditions, subjects were instructed to blink normally but keep their eyes open; during the eyes closed condition they were instructed not to fall asleep. During the conditions of darkness, we created a completely dark environment by covering the window of the MRI scan room meticulously with opaque black canvas. We also draft-proofed the door and covered the bore of the MRI machine tunnel. Any other dim light sources, like the buttons on the machine console, were also covered during the scan. Opaque lightproof goggles were not used because