Reliability of sleep deprivation-associated spontaneous brain activity and behavior postprint

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Abstract

Recent studies have indicated that sleep deprivation (SD) alters intrinsic low-frequency connectivity in the resting brain, mainly focusing on the default mode network (DMN) and its anticorrelated network (ACN). These networks hold key functions in segregating internally and externally directed awareness. However, far less attention has been paid to investigation of the altered amplitude of these low-frequency fluctuations (ALFF) at the whole-brain level and more importantly by what extent the sleep-deprived resting brain pattern can be reproducible and predict individual behavioral performance. The aim of this study was to characterize more clearly the influence of sleep on the whole brain level of ALFF changes and its relation with the performance of a lexical decision task in the sleep deprivation. Sixteen healthy participants underwent fMRI three times: once after a normal night of sleep in the rested wakefulness (RW) state and two following approximately 24 h of total SD separated by an interval of two weeks (SD1 and SD2). Our behavioral results showed that sleep stabilizes performance whereas two sleep deprivation even at an interval of two weeks consistently deteriorates it. Sleep deprivation attenuated the ALFF mainly in the bilateral orbitofrontal cortex (OFC), bilateral dorsolateral prefrontal cortex (DLPFC) and right inferior parietal lobule (IPL). By contrast, the enhanced ALFF emerged in the left sensorimotor cortex (SMA), visual cortex and left fusiform gyrus. Conjunction analysis of SD1 and SD2 versus the control maps and voxel-wise ICC analysis revealed that these SD induced ALFF changes showed a significantly high reliability (ICC $>$ 0.5). Particularly, the attenuation of the right IPL presents a significant negative relation with the behavior performance and can be reproducible for two SD at an interval of two weeks. Our results suggest that ALFF is a stable measure in study of SD, and the right IPL may represent a stable biomarker that responds to sleep loss.

Full Text

Reliability of Sleep Deprivation-Associated Spontaneous Brain Activity and Behavior

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Abstract

Recent studies have indicated that sleep deprivation (SD) alters intrinsic low-frequency connectivity in the resting brain, with most research focusing on the default mode network (DMN) and its anticorrelated network (ACN). These networks play key roles in segregating internally and externally directed awareness. However, far less attention has been paid to investigating altered amplitude of low-frequency fluctuations (ALFF) at the whole-brain level, and more importantly, the extent to which sleep-deprived resting brain patterns are reproducible and can predict individual behavioral performance.

This study aimed to characterize more clearly how sleep influences whole-brain ALFF changes and their relationship to performance on a lexical decision task

following sleep deprivation. Sixteen healthy participants underwent fMRI scanning three times: once after a normal night of sleep in a rested wakefulness (RW) state, and twice following approximately 24 hours of total SD, with the two SD sessions separated by a two-week interval (SD1 and SD2). Behavioral results showed that sleep stabilizes performance, whereas two sessions of sleep deprivation, even when separated by two weeks, consistently deteriorate it. Sleep deprivation attenuated ALFF primarily in the bilateral orbitofrontal cortex (OFC), bilateral dorsolateral prefrontal cortex (DLPFC), and right inferior parietal lobule (IPL). By contrast, enhanced ALFF emerged in the left sensorimotor cortex (SMA), visual cortex, and left fusiform gyrus.

Conjunction analysis of SD1 and SD2 versus control maps, along with voxel-wise ICC analysis, revealed that these SD-induced ALFF changes showed significantly high reliability (ICC $>$ 0.5). Particularly, the attenuation in the right IPL demonstrated a significant negative relationship with behavioral performance and was reproducible across the two SD sessions separated by two weeks. Our results suggest that ALFF is a stable measure for studying SD, and the right IPL may represent a stable biomarker that responds to sleep loss.

Keywords: sleep deprivation, resting-state fMRI, ALFF, test-retest, reliability

Introduction

Sleep deprivation (SD) repeatedly demonstrates a variable negative impact on mood, cognitive performance, and motor function due to increasing sleep propensity and destabilization of wakefulness (Goel et al., 2009). Previous neuroimaging studies have shown that insufficient sleep adversely affects brain functioning. Although investigation of the neural mechanisms underlying SD using fMRI remains in its early stages, this research has already provided substantial information about sleep-deprived brain networks and the various functions that support normal wakeful behavior.

Neuroimaging studies have identified altered activation patterns in the sleep-deprived brain during numerous tasks, including memory (Chee and Choo, 2004; Chee et al., 2006; Mu et al., 2005; Sterpenich et al., 2009; Van Dongen, 2005), attention (Chee and Tan, 2010; Chee et al., 2008; Kong et al., 2012), executive functioning (Drummond and Brown, 2001; Muto et al., 2012), and decision making (Chee et al., 2010; Kong et al., 2011; Libedinsky et al., 2011). Several brain regions—including the prefrontal cortex, parietal cortex, sensorimotor areas, visual cortex, thalamus, and cingulate cortex—have been frequently reported to associate with SD.

Prolonged wakefulness has been linked to altered functional integration in the resting brain. The default mode network (DMN), characterized by relatively high regional cerebral blood flow (rCBF) (Gusnard et al., 2001; Raichle et al., 2001) and high levels of correlated BOLD signal fluctuations at rest (Greicius et

al., 2003; Raichle, 2011), is thought to support self-awareness (Gusnard et al., 2001) and conscious self-representation (Lou et al., 2004). Investigations of SD's influence on the DMN have shown significantly disrupted deactivations, leading to double dissociations within both anterior and posterior midline DMN regions (Gujar et al., 2010). These findings suggest that decreased DMN connectivity could be intrinsic to sleep deprivation or a reflection of vigilance changes (De Havas et al., 2012; Samann et al., 2010).

Additionally, the DMN is anticorrelated with the cognitive control network (CCN), a corresponding task-positive network encompassing bilateral fronto-cingulo-parietal structures including lateral prefrontal and superior parietal areas (Niendam et al., 2012). Abnormal connectivity within the DMN and its anticorrelated networks has also been reduced following SD (Bosch et al., 2013; De Havas et al., 2012; Samann et al., 2010; Shao et al., 2013). DMN-CCN interactions may reflect the level of consciousness required for information integration (Heine et al., 2012; Larson-Prior et al., 2011). More recently, two studies noted that enhanced functional connectivity between the dorsal nexus and dorsolateral prefrontal cortex, as well as attenuated functional connectivity within thalamocortical networks, also occur after SD (Bosch et al., 2013; Shao et al., 2013). These findings indicate disrupted temporal synchronization of the global resting-state network in the sleep-deprived brain.

However, these investigations generally adopted seed-based functional connectivity methods that did not allow direct assessment of regional activity during rest. In other words, abnormal functional interactions between remote areas cannot address which area is responsible for such connectivity alterations. Given this limitation, we aimed to measure the amplitude of low-frequency fluctuation (ALFF) in the sleep-deprived resting brain. ALFF, without a priori selection of regions of interest, can be used to study BOLD signal dynamics at the local, voxel-wise level without assessing inter-regional relationships (Zang et al., 2007). This method has demonstrated test-retest reliability across time (Li et al., 2012; Turner et al., 2012; Yan et al., 2013; Zuo et al., 2010) and can successfully predict magnitudes of task-evoked activity (Mennes et al., 2011; Zou et al., 2013).

The present study addressed three issues: (i) how the sleep-deprived brain exhibits abnormal ALFF patterns; (ii) whether such patterns are reproducible across a two-week interval between SD sessions; and (iii) to what extent inter-individual differences in ALFF during rest may predict behavioral performance. For this purpose, we used a lexical decision task to test the effects of sleep loss and fatigue on the dynamic time-course of responses to cognitive load (Babkoff et al., 1985; Forster and Forster, 2003; Lopez-Zunini et al., 2014).

Materials and Methods

Subjects

Sixteen healthy volunteers (8 females, mean age 22.1 ± 0.8 years) were recruited after providing informed consent. Participants were selected from respondents to a web-based questionnaire and met the following criteria: (1) right-handed according to the modified Edinburgh Handedness Questionnaire (Oldfield, 1971); (2) aged 20-24 years; (3) good sleeping habits (sleeping no less than 6.5 hours each night for the past month); (4) not extreme morning or evening chronotypes (score $ $22 on a modified Morningness-Eveningness scale; Horne and Ostberg, 1976); (5) no long-term medication use; (6) no symptoms associated with sleep disorders; (7) no history of psychiatric or neurologic disorders; and (8) no history of drug abuse or current use of antidepressant or hypnotic medications.

Participants averaged 15.7 ± 1.2 years of education. All participants showed normal sleep quality as assessed by the Pittsburgh Sleep Quality Index (PSQI) (mean ± SD: 1.5 ± 0.97) and normal daytime sleepiness as assessed by the Epworth Sleepiness Scale (ESS) (mean ± SD: 6.44 ± 2.07). Body mass index ranged from 17.5-22 kg/m^2, and participants were free of nightshift work. Approximately four weeks before the experiment, subjects were required to sleep 7-9 hours per night (typically before 00:10 a.m.) and maintain sleep logs. The study was approved by the medical research ethics committee and institutional review board of The First Affiliated Hospital of Nanchang University.

Sleep Deprivation and Experimental Protocol

All subjects completed three fMRI scans starting at 7:00 PM: one after normal sleep (RW group) and two after a night of total SD (SD1 and SD2 groups). The two SD sessions were separated by approximately two weeks, with the experimental sequence counterbalanced across sessions to minimize possible residual SD effects on cognition. Subjects were prohibited from consuming tea, coffee, caffeine-containing drinks, and alcohol for 72 hours before fMRI examinations. Sleep logs were maintained for one week prior to the study night. During SD, subjects were monitored in the laboratory and engaged only in non-strenuous activities such as reading and watching videos. Vigorous physical activity before scanning was forbidden.

A behavioral test was administered to each subject before fMRI scanning. Word stimuli were presented using DMDX v.3.0.4 experimental software (Forster and Forster, 2003). White words (10 mm size) appeared on a black background monitor in a dimly lit room. Each stimulus pair was presented for 900 ms, separated by a 500 ms blank screen. Subjects had 2,500 ms between trials to judge whether the two words were semantically related. Positive responses were indicated by pressing the right button with the right middle finger, while negative responses were indicated by pressing the left button with the right index finger. Participants were instructed to respond as quickly and accurately as possible. Accuracy and reaction times (RTs) were recorded to the nearest

millisecond. Before formal testing, participants practiced with a different set of sentences.

Data Acquisition

fMRI data were collected on a Siemens Trio 3.0 T scanner. Each subject lay supine with the head in a neutral position, comfortably secured with a belt and foam pads. Scanning sessions included: (1) localizer; (2) T1 MPRAGE anatomy (176 sagittal slices, thickness/gap = 1.0/0 mm, in-plane resolution = 256 × 256, field of view (FOV) = 240 mm × 240 mm, repetition time (TR) = 1,900 ms, echo time (TE) = 2.26 ms, flip angle = 15°); and (3) EPI-BOLD (36 axial slices, echo-planar imaging pulse sequence, thickness/gap = 5.0/1 mm, in-plane resolution = 64 × 64, TR = 3,000 ms, TE = 30 ms, flip angle = 90°, FOV = 240 mm × 240 mm). During resting-state fMRI, subjects were instructed to remain as calm as possible, keep their eyes closed, and avoid falling asleep to ensure successful image acquisition.

Behavioral Analysis

To examine behavioral performance changes across SD sessions, we computed mean RT and error rates (incorrect button presses) as measures of performance accuracy.

Data Preprocessing

All preprocessing was performed using Data Processing Assistant for Resting-State fMRI (DPARSF, Yan and Zang, 2010, http://www.restfmri.net), based on Statistical Parametric Mapping (SPM8) (http://www.fil.ion.ucl.ac.uk/spm) and Resting-State fMRI Data Analysis Toolkit (REST, Song et al., 2011, http://www.restfmri.net). For each subject' s resting-state fMRI data, the first two volumes were discarded to avoid scanner instability and subject adaptation effects.

The preprocessing sequence included: (i) slice timing correction for within-scan acquisition time differences between slices; (ii) head motion correction (realignment and six-parameter spatial transformation). Recent studies indicate that head motion can significantly influence resting-state fMRI measures (Power et al., 2012; Van Dijk et al., 2012; Yan et al., 2013). Therefore, we computed voxel-specific head motion parameters, including voxel-specific framewise displacement (FDvox) and voxel-specific total displacement (TDvox) values for each subject using the DPARSF toolbox. Group differences in mean FDvox were assessed with two-sample t-tests, revealing no significant group differences. Mean FD was subsequently used as a covariate in group ALFF comparisons. In our study, absolute head movement remained below 0.5 mm and 0.5° for all subjects; (iii) spatial normalization to Montreal Neurological Institute (MNI) template (resampling voxel size = 3 × 3 × 3 mm^3); (iv) spatial smoothing

(full width at half maximum (FWHM) = 6 mm Gaussian kernel); (v) linear detrending; and (vi) voxel-wise bandpass filtering (0.01-0.08 Hz).

ALFF Analysis

For a given voxel, the time series was converted to the frequency domain (0.01-0.1 Hz) using Fast Fourier Transform (FFT). The square root of the power spectrum was computed and averaged across a predefined frequency interval. This averaged square root was termed ALFF at that voxel, measuring the absolute strength or intensity of low-frequency fluctuations. ALFF was computed for each voxel in each participant and divided by the global mean value to reduce global variability across participants.

Test-Retest Reliability Analyses

Reliable test-retest measurements are crucial for drawing convincing conclusions. To investigate test-retest reliability of SD effects, we calculated voxel-wise intraclass correlation coefficients (ICC) between the two SD sessions (Zuo et al., 2010).

Statistical Analyses

We used paired t-tests to compare SD versus RW groups for RT performance measures. For ALFF, one-sample one-sided t-tests were performed within groups to determine whether ALFF differed from 1 (Raichle et al., 2001; Zang et al., 2007), and paired t-tests identified between-group differences. Voxels with $p < 0.01$ and cluster size $> 1{,}053$ mm^3 (39 voxels) were considered statistically significant, corresponding to multiple-corrected $p < 0.05$ using the AlphaSim program (http://afni.nih.gov/afni/docpdf/AlphaSim.pdf).

Conjunction Analysis

A conjunction of SD1 and SD2 versus control maps was calculated to identify brain areas that showed consistent, similar differences in both SD sessions.

Brain-Behavior Relationships

To evaluate relationships between ALFF changes and behavioral performance after SD, we examined Pearson correlations between mean ALFF values of peak voxels from inter-group comparisons and RT performance measures.

Results

Performance Findings

No significant differences in accuracy rates were observed between SD and RW groups. However, both SD groups showed significantly longer reaction times than the RW group (RW = 2,010.4 ± 227.17 ms; SD1 = 2,275.1 ± 176.66 ms, T = -3.858, d.f. = 15, P < 0.002; SD2 = 2,172.2 ± 166.51 ms, T = -2.584, p < 0.021) [Figure 1: see original paper].

ALFF Differences in Two SD Sessions

Compared with the RW group, both SD groups showed ALFF decreases primarily in bilateral orbitofrontal cortex (OFC) (BA 11/47), bilateral dorsolateral prefrontal cortex (DLPFC) (BA 46), and right inferior parietal lobule (IPL, BA39/40), while ALFF increases emerged mainly in the somatosensory cortex (SMC), fusiform gyrus (BA 37), and middle occipital gyrus (MOG) (BA 18/19) [Figure 2: see original paper] and .

Conjunction Analysis and Voxel-Wise ICC Analysis

The overlap between SD1 and SD2 compared to the control group shared common areas primarily in the precuneus/posterior cingulate cortex (Pcu/PCC), OFC, SMC, bilateral occipital cortex, and right IPL [Figure 3: see original paper]. High reliability derived from intra-subject test-retest analysis was observed in most brain areas (ICC ≥ 0.5) [Figure 3: see original paper]. These areas were located primarily in the precuneus/PCC, cingulate cortex, bilateral SMC, bilateral parietal cortex, bilateral medial prefrontal cortex (MPFC), and bilateral occipital cortex.

Correlations Between ALFF and Behavioral Performance in the SD Group

Greater RT prolongation from rest to SD was associated with greater ALFF decreases in the right IPL that were reproducible across the two SD sessions separated by two weeks (for SD1: r = -0.561, p < 0.024; for SD2: r = -0.499, p < 0.05) [Figure 4: see original paper].

Discussion

Several key observations emerged from examining spontaneous low-frequency fluctuations in the sleep-deprived resting brain. Beyond confirming altered intrinsic patterns in the "off-line" brain, we found that even one night of sleep loss can alter ALFF, particularly showing attenuations in bilateral OFC, bilateral DLPFC, and right IPL, alongside enhancements in SMC, thalamus, fusiform gyrus, and visual cortices. Moreover, ALFF measurements in the sleep-deprived

brain demonstrated considerable reliability over a two-week interval. These relatively high stability coefficients provide conservative estimates of ALFF test-retest reliability in SD. Additionally, inter-individual differences in ALFF measures provide clues for predicting behavioral performance, showing a significant negative relationship between RT and ALFF in the right IPL.

Significantly different ALFF patterns were found between SD and RW states. Consistent with previous task-evoked activation studies using varied cognitive stimuli, our findings showed that altered ALFF changes were located primarily in DLPFC, OFC, and IPL. Frontal-parietal areas appear particularly vulnerable to SD (Bosch et al., 2013; Chee and Tan, 2010; Chuah et al., 2010; Lythe et al., 2012). Decreased prefrontal and parietal activity has been especially noted in working memory studies, with parietal activity representing a biomarker of individual response to sleep debt (De Havas et al., 2012). Inadequate sleep is also associated with exaggerated emotional responses (Chuah et al., 2010; Goldstein et al., 2013; Killgore, 2013; Menz et al., 2012; Minkel et al., 2012; Mullin et al., 2013). The OFC, part of the limbic system, is thought critical for mediating interactions between emotional processes and cognitive functions such as decision making (Azzi et al., 2012; Kahnt et al., 2012; Parsons et al., 2013; Zald et al., 2012). We speculate that SD may influence emotion and cognition regulation circuitry, leading to deficient capacity for regulating emotional arousal and cognitive load.

Beyond impairments in the sleep-deprived resting brain, it is noteworthy that enhanced ALFF emerged primarily in SMC, fusiform gyrus, and visual cortex, possibly reflecting compensatory mechanisms following sleep loss and attempts to maintain hyperarousal. Early PET and fMRI studies investigating brain responses to attention tasks after SD also found such hypermetabolism in visual cortex and sensorimotor areas (Thomas et al., 2000). These researchers inferred that enhanced brain activity might indicate a homeostatic drive for recovery in brain areas involved in attention and higher-order cognitive processes, interpreted as compensatory mechanisms to maintain alertness and cognitive performance during extended wakefulness. A recent study of enhanced functional connectivity between primary sensory processing and motor planning regions in insomnia provides further evidence consistent with our results (Killgore et al., 2013). This may imply that ALFF encodes tendencies for task response even during resting states.

As expected, we found highly reproducible ALFF patterns at a two-week interval in the sleep-deprived brain. Overlapped areas identified through conjunction analysis included the PCC, OFC, IPL, SMC, visual cortex, and right insula. Voxel-wise ICC maps showed the spatial distribution of ALFF reliability, primarily along midline brain structures, lateral prefrontal cortex, and parietal cortex ($p < 0.001$). This finding aligns with previous task-fMRI research (Lim et al., 2007) showing reproducible brain activations highly correlated across sessions in a frontoparietal network during working memory tasks. As in previous studies showing stable decreases in left parietal activation over time, we sug-

gest that these task-evoked brain activity and behavioral changes may reflect underlying intrinsic brain activity. The reliability of resting spontaneous activity patterns, which serve as a functional framework for moment-to-moment responses, has remained unclear. The present study confirms this stability over a two-week interval. Along similar lines, other studies have found ALFF reliability in chronic schizophrenia (Turner et al., 2012) and healthy states (Li et al., 2012) over short periods. This supports the notion that intra-individual resting dynamics in response to SD load remain stable over relatively short durations.

At rest, the brain exhibits intrinsic organization including both "task-negative" (DMN) and its anticorrelated "task-positive" networks (ACN) (Fox et al., 2005). The DMN, characterized by more energetic metabolic and neural activity at rest, engages in internally focused tasks such as autobiographical memory retrieval, implicit learning, prospection, monitoring, and other internally directed thought processes (Braga et al., 2013; Raichle et al., 2001; Uddin et al., 2009). Decreased ALFF signals in the PCC, bilateral OFC (BA 11/47), and right IPL following 24-hour SD may be associated with maladaptive ability to switch default mode activity when task conditions require attention.

The DLPFC, one of the "task-positive" regions (ACN), has been implicated in working memory failure during SD (Goel et al., 2009). In our study, reduced DLPFC activity may suggest dysfunctional integration between DMN and ACN, consistent with reduced anti-correlation between DMN and ACN nodes during both task and resting states (De Havas et al., 2012). Moreover, the notable finding of increased ALFF in SMC, visual cortex, and left fusiform gyrus may be explained by the sleep homeostatic hypothesis (Born and Feld, 2012; Tononi and Cirelli, 2003, 2006) as compensatory reallocation—the resting brain reallocates its oscillatory dynamic resources. This reconfiguration reduces neural resource adaptation in response to increased cognitive challenges and emotion regulation demands.

We obtained reproducible behavioral performance following SD at a two-week interval. Beyond this reliability, a significant negative linear correlation existed between ALFF decreases in the right IPL and RT during the lexical decision task. Numerous studies have found that sleep loss significantly degrades performance on tasks incorporating working memory components or requiring contributions from frontoparietal cortical regions (Goel et al., 2009). The IPL, as an important association area for integrating sensory information, plays a prominent role in visuospatial attention. Successful semantic priming task performance demands sustained mental effort, strategic control, rapid attentional focusing to accurately register transient stimulus events, and rapid comparison of incoming information to that maintained in working memory. Our significant negative linear correlation suggests that spontaneous IPL activity was impaired by sleep loss load. Many reports, despite some divergence, have associated reduced task-evoked parietal activation with declining behavioral performance. One recent resting functional connectivity study also supports the notion that IPL activity changes may reflect early SD effects (De Havas et al., 2012). Therefore, it is

reasonable to suggest that reduced resting-state intrinsic activity in the IPL may relate to declining cognitive capacity during SD.

Limitations

This study has several limitations. First, the relatively small sample size limits statistical power, preventing results from surviving strict multiple comparison corrections (e.g., FDR or FWE). Future studies should use larger samples to increase statistical power. Second, we lacked objective assessment of self-reported sleepiness and mood. Further investigations should incorporate more detailed frequency-dependent analyses.

Conclusion

Our findings of high test-retest reliability in ALFF patterns highlight that sleep burden reshapes low-frequency dynamics in the resting brain, and that this sleep-deprived brain pattern can predict individual behavioral performance. This may provide deeper insights into the neurological underpinnings of SD-related cognitive decline.

Conflict of Interests: The authors declare no competing interests.

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Table and Figure Legends

Table 1 . Brain areas showing ALFF differences between RW and SD groups. Coordinates x, y, z (mm) are given in standard stereotactic MNI space. All regions listed are statistically significant at $p < 0.05$, AlphaSim corrected. L: left; R: right.

Figure 1 [Figure 1: see original paper]. Effects of 24-hour sleep deprivation on reaction time for semantic tasks. Y-axes show mean ($±$2 SD) RT for each group. X-axes indicate group. Significantly different groups are indicated (*p < 0.05, **p < 0.01).

Figure 2 [Figure 2: see original paper]. Group ALFF differences in the two SD sessions. Effects are significant at $p < 0.05$, AlphaSim corrected. Cool colors indicate decreased ALFF in SD groups compared with controls; hot colors indicate increased ALFF. Results were visualized with BrainNet Viewer (http://www.nitrc.org/projects/bnv/).

Figure 3 [Figure 3: see original paper]. Overlap of SD1 and SD2 compared to control differences. Areas shared across both SD sessions are shown in brown and blue. Voxel-wise ICC: intra-subject test-retest reliability for two SD sessions, with regions showing high reliability (ICC > 0.5) displayed. Results were visualized with BrainNet Viewer (http://www.nitrc.org/projects/bnv/).

Figure 4 [Figure 4: see original paper]. Correlation between RTs and ALFF change in the right IPL in the sleep deprivation group. Greater RT prolongation from rest to sleep deprivation was associated with greater ALFF decreases in the right IPL. Results were visualized with BrainNet Viewer (http://www.nitrc.org/projects/bnv/).

Note: Figure translations are in progress. See original paper for figures.