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Microstructure of frontoparietal connections predicts individual resistance to sleep deprivation

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ABSTRACT

Sleep deprivation (SD) can degrade cognitive functioning, but growing evidence suggests that there are large individual differences in the vulnerability to this effect. Some evidence suggests that baseline differences in the responsiveness of a fronto-parietal attention system that is activated during working memory (WM) tasks may be associated with the ability to sustain vigilance during sleep deprivation. However, the neurocircuitry underlying this network remains virtually unexplored. In this study, we employed diffusion tensor imaging (DTI) to investigate the association between the microstructure of the axonal pathway connecting the frontal and parietal regions—i.e., the superior longitudinal fasciculus (SLF)—and individual resistance to SD. Thirty healthy participants (15 males) aged 20–43 years underwent functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) at rested wakefulness prior to a 28-hour period of SD. Task-related fronto-parietal fMRI activation clusters during a Sternberg WM Task were localized and used as seed regions for probabilistic fiber tractography. DTI metrics, including fractional anisotropy, mean diffusivity, axial and radial diffusivity were measured in the SLF. The psychomotor vigilance test (PVT) was used to evaluate resistance to SD. We found that activation in the left inferior parietal lobule (IPL) and dorsolateral prefrontal cortex (DLPFC) positively correlated with resistance. Higher fractional anisotropy of the left SLF comprising the primary axons connecting IPL and DLPFC was also associated with better resistance. These findings suggest that individual differences in resistance to SD are associated with the functional responsiveness of a fronto-parietal attention system and the microstructural properties of the axonal interconnections.

Introduction

Sleep deprivation (SD), even for one night, can lead to impairments in cognitive function and performance (Killgore, 2010). It has been found that individual differences in resistance to cognitive performance impairment following SD are consistent, trait-like, and stable over time (Rupp et al., 2012; Van Dongen et al., 2004). Numerous neuroimaging studies suggest that task-related activation in frontal and parietal cortices is particularly susceptible to the effects of SD and related to alterations in cognitive performance during SD (Chee and Choo, 2004; Choo et al., 2005). Moreover, several studies have reported that the extent of fronto-parietal activation in response to a working memory (WM) task under normal well-rested conditions can predict the magnitude of activation change and performance decline after SD (Caldwell et al., 2005; Chee et al., 2006; Lythe et al., 2012; Mu et al., 2005). However, the structure–function relationship underlying this fronto-parietal network in SD is not well understood. Most studies regarding the effects of SD on cognitive functioning have focused primarily on changes in functional brain activation, but much less is known about the microstructural properties of white matter fiber tracts underlying the fronto-parietal brain regions typically affected by sleep loss. Of particular interest is the association between individual resistance to SD and the microstructure of the superior longitudinal fasciculus (SLF), a primary and direct tract supporting bidirectional information transfer between the frontal and parietal cortices (Schmahmann and Pandya, 2006).

Diffusion tensor imaging (DTI) enables an in vivo characterization of microstructural properties of white matter based on water molecular diffusion (Basser et al., 1994; Hagmann et al., 2006). Water tends to diffuse preferentially in a direction parallel to the orientation of axons (Basser, 1995; Beaulieu, 2002). This phenomenon is called diffusion anisotropy and is represented by a diffusion tensor model. The tensor has

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three eigenvalues that represent the magnitude of diffusion in three axis directions (Hagmann et al., 2006). The most commonly used parameter in DTI analysis, fractional anisotropy (FA), is calculated from the three eigenvalues to indicate the degree of anisotropy of the diffusion tensor. FA is a scalar value that ranges from 0 (low) to 1 (high) and reflects axon caliber, degree of myelination, and axon density within a voxel (Beaulieu, 2002). Higher FA values represent better microarchitecture of the white matter tracts. The average of the three eigenvalues is called mean diffusivity and is considered an estimation of membrane density (Schmithorst and Yuan, 2010). The largest eigenvalue, indicating diffusion along the direction of the axons, is termed axial diffusivity (AD), which may reflect aspects of axon morphology and pathology including axon diameter, loss, or damage (Budde et al., 2007; Song et al., 2003). The average of the other two eigenvalues provides a measure of radial diffusivity (RD), which is considered to reflect the degree of myelination (Nair et al., 2005; Song et al., 2002).

To our knowledge, only one study has used DTI to investigate the relationship between white matter integrity and cognitive vulnerability to SD (Rocklage et al., 2009). Higher FA values were found in SD-resilient compared to SD-vulnerable groups in multiple white matter regions, including the corpus callosum, forceps major, posterior limb of the internal capsule, retrolenticular portion of the internal capsule, superior corona radiata, posterior corona radiata, SLF, posterior thalamic radiation, and corticospinal tract (CST), but these were not linked to functional responses in that study. No DTI studies have yet explored the specific relationship between resistance to SD and microstructural architecture of white matter fiber tracts, and none have linked structural indices with known functional regions, such as those involved in sustained attention or working memory, to identify potential structure–function networks that may predict cognitive resistance to sleep loss. In this study, we aimed to determine if the microstructural properties of the SLF, which connects primary attention and vigilance regions, might be associated with SD resistance. At rested baseline, we measured the DTI metrics of this tract of interest (TOI) using the Johns Hopkins University (JHU) white matter atlas and also employed probabilistic fiber tractography to reconstruct the specific white matter tracts connecting fronto-parietal activated regions identified with WM task-related functional MRI (fMRI). Participants were then sleep deprived for one night and their cognitive vigilance was monitored hourly throughout the night using the gold standard psychomotor vigilance test (PVT) to determine individual resistance to SD (Dinges and Powell, 1985). For each participant, a simple resistance score was calculated by determining the mean percent decline in PVT performance speed during the overnight sleep deprivation period compared to baseline. After identifying functionally defined frontal–parietal attention regions, we correlated the DTI metrics of the SLF with individual resistance scores. We hypothesized that individuals with higher FA values of the SLF tracts connecting functionally activated fronto-parietal attention regions would demonstrate greater resistance to SD.

Methods

Participants

Thirty-four right-handed, healthy, native English-speaking adults (mean age 25.4 ± 5.8 years, range 20–43; 17 males, 16 females) were recruited from the greater Boston area and underwent neuroimaging. Exclusion criteria included any history of self-reported medical, neurological, psychiatric, or sleep disorders. Data from four participants were excluded due to poor image quality. The final analyzed group consisted of 30 subjects (mean age 25.8 ± 6.0 years, range 20–43; 15 males, 15 females). All participants provided written informed consent prior to participation and were compensated for their time. This research protocol was reviewed and approved by the Institutional Review Board of McLean Hospital and the U.S. Army Human Research Protection Office.

Materials and procedure

Participants were scheduled for three visits. The procedure for this experiment can be seen in Fig. 1A. The first visit was a baseline session during which volunteers were informed of the study procedures and underwent screening for the presence of psychopathology using the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998).

After seven to ten days (M = 8.44, SD = 3.19), participants returned to the lab for the imaging session. Caffeine use was determined via a questionnaire that asked participants to list their frequency of use of caffeine related products per day, including from coffee (8 oz), brewed tea (8 oz), caffeinated soda (cans), caffeinated sports drinks (per bottle/can), and over the counter caffeine supplements. We scored these according to the values provided in Killgore (2011). Based on these criteria, participants were found to be low to moderate users of caffeine, with an average intake of 62.1 mg per day (SD = 83.8; range = 0–266 mg). Of the sample, 13 participants (43.3%) reported no regular consumption of caffeine containing products, with 8 participants (26.7%) reporting greater than 100 mg of caffeine per day. On the day of the scan, participants were not asked to refrain from caffeine consumption. Instead, they were asked to consume their "normal" morning caffeine, so that they would not be in any form of withdrawal during the scan. On the day of the scan, participants consumed an average of 46.7 mg (SD = 78.7 mg) prior to arrival to the neuroimaging session. In order to control for fluctuations due to menstrual hormones, all female participants were either on monophasic contraceptives or were scheduled to undergo neuroimaging during the follicular phase of the menstrual cycle. In addition, participants were asked not to take any over-the-counter medication on the day of this session.

The third lab visit, a 28-hour sleep deprivation session, began on the Friday following the second visit. The time between the scan and the overnight sleep deprivation session ranged from one to four days (M = 2.23, SD = 1.45). On the two nights before the final sleep deprivation session, participants were instructed to go to bed between 10 and 11 pm and remain in bed for 8 h each night and were asked to abstain from any caffeine-containing products or other stimulants. On the morning of the third visit day, participants were required to rise between 7:00 am and 8:00 am (verified by actigraphy sleep data and sleep diaries). Every participant was given a wake-up call at 7:30 am and was required to remain awake for the next 28 to 30 h until being released from the study at 12:00 pm the following day. Participants arrived at the McLean Hospital Sleep Research Laboratory by 6:30 pm and completed the overnight SD sessions in pairs (1 male and 1 female). Beginning at 7:15 pm, a modified 10-minute version of the psychomotor vigilance test (PVT) was administered on a laptop computer every hour throughout the SD session (Dinges and Powell, 1985). The testing sessions were run simultaneously for both participants in separate rooms. During the PVT, participants monitored a screen and pressed a response button as quickly as possible each time a target stimulus appeared. Response time feedback was given after each response. The interstimulus interval was varied pseudorandomly between presentations to minimize anticipation of the stimulus (ITI range: 2 to 10 s). Reaction time (RT) and number of attentional lapses (RT ≥ 500 ms) for all trials were collected.

Sternberg working memory task (SWMT)

The SWMT was performed during the fMRI scan and the behavioral data were acquired within the scanner. Each functional scan lasted for 12 min and 58 s, consisting of an initial 10-second fixation cross followed by twelve (12) 64-second stimulus blocks. Each block included a 32-second control task followed by a 32-second Sternberg task. Each task comprised two 16-second trials. During the task, participants were asked to press an MR compatible button box to respond *YES* or *NO* to each trial following a visual prompt. The RT was defined as the time