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Functional connectivity during rested wakefulness predicts vulnerability to sleep deprivation

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ABSTRACT

Significant inter-individual differences in vigilance decline following sleep deprivation exist. We characterized functional connectivity in 68 healthy young adult participants in rested wakefulness and following a night of total sleep deprivation. After whole brain signal regression, functionally connected cortical networks during the well-rested state exhibited reduced correlation following sleep deprivation, suggesting that highly integrated brain regions become less integrated during sleep deprivation. In contrast, anti-correlations in the well-rested state became less so following sleep deprivation, suggesting that highly segregated networks become less segregated during sleep deprivation. Subjects more resilient to vigilance decline following sleep deprivation showed stronger anti-correlations among several networks. The weaker anti-correlations overlapped with connectivity alterations following sleep deprivation. Resilient individuals thus evidence clearer separation of highly segregated cortical networks in the well-rested state. In contrast to corticocortical connectivity, subcortical–cortical connectivity was comparable across resilient and vulnerable groups despite prominent state-related changes in both groups. Because sleep deprivation results in a significant elevation of whole brain signal amplitude, the aforesaid signal changes and group contrasts may be masked in analyses omitting their regression, suggesting possible value in regressing whole brain signal in certain experimental contexts.

Introduction

Inter-individual differences in performance decline following sleep deprivation are trait-like (Lim et al., 2007; Rupp et al., 2012; Van Dongen et al., 2004). Being able to identify vulnerable persons prior to their undergoing sleep deprivation could prove invaluable in a world that has become increasingly dependent on 24/7 service delivery. Drift diffusion in psychomotor vigilance response times (Patanaik et al., 2014), decreased heart rate variability (Chua et al., 2012) and lower task-related fMRI activation (Caldwell et al., 2005; Chee et al., 2006; Mu et al., 2005) have been suggested as candidate predictive markers but are uninformative regarding why they predict neurobehavioral vulnerability.

Task-based fMRI shows how brain regions are differentially affected by sleep deprivation (Bell-McGinty et al., 2004; Drummond et al., 2005; Tomasi et al., 2009). Reduced fronto-parietal activation following a night of total sleep deprivation correlated with various types of attentional decline (Chee and Tan, 2010; Chuah and Chee, 2008). However, few task-based fMRI studies have examined the neural correlates of sleep deprivation vulnerability *in rested participants*. In these studies, lower frontoparietal activation in the well-rested state was associated with greater vulnerability to cognitive performance decline (Caldwell et al., 2005; Chee et al., 2006; Mu et al., 2005), suggesting lowered cognitive reserve. However the 'predictive' aspect of one of the working memory experiments (Chee et al., 2006) was not subsequently replicated (Lim et al., 2007). Additionally, task-based fMRI inferences are typically restricted to brain regions recruited by the task. Other areas in the same individuals may show sleep deprivation effects when a different task is used (Chuah and Chee, 2008). As such, resting-state fMRI is attractive since connectivity of multiple networks can be assessed concurrently (Biswal et al., 1995; Smith et al., 2009; Buckner et al., 2013).

Functional connectivity studies of sleep-deprived persons have mostly focused on the Default network and its anti-correlations with the Attention and Control networks[1] (De Havas et al., 2012; Sämann

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[1] The Attention and Control networks are sometimes collectively referred to as the task-positive or anti-correlated network (Fox et al., 2005, 2006; Spreng, 2012).

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et al., 2010). There were also studies that evaluated connectivity alterations with the dorsal prefrontal cortex (Bosch et al., 2013) and thalamocortical connections (Picchioni et al., 2014; Shao et al., 2013). Of these, only one (De Havas et al., 2012) attempted to uncover associations between connectivity disruption and behavior, but did not find significant association.

The present study uses a recently published resting-state network parcellation (Yeo et al., 2011) to characterize connectivity changes associated with sleep deprivation. First, we evaluated the effects of sleep deprivation on connectivity of hitherto unstudied networks at a high resolution. Second, we examined how functional connectivity in the rested state might predict vulnerability to performance decline in the psychomotor vigilance task (PVT; Dinges and Powell, 1985). The PVT is a highly reproducible assay for vigilance that has been validated in multiple settings (Basner et al., 2011; Dorrian et al., 2005) and utilized by many military and transport authorities to determine fitness for duty around the world (Russo et al., 2005). Finally, we evaluated differences in state-related network changes in participants that are more vulnerable and participants that are more resilient to sleep deprivation, expecting that these would resemble features differentiating participants in the well-rested state. We performed our analyses with and without regressing whole brain signal in order to test recent observations that increased amplitude of this signal is informative about decreased vigilance (Thompson et al., 2013; Wong et al., 2013).

Methods

Participants

82 participants provided informed consent in compliance with a protocol approved by the National University of Singapore Institutional Review Board. Participants were selected from respondents of a web-based questionnaire who (1) were right-handed, (2) had regular sleeping habits, (3) slept no less than an average of 6.5 h/night, (4) were not on any long-term medications, (5) had neither symptoms nor history of sleep disorders, (6) had no history of psychiatric or neurologic disorders, (7) drank less than 3 caffeinated drinks per day and (8) were not of an extreme chronotype as assessed by the Horne–Östberg Morningness–Eveningness questionnaire (Horne and Östberg, 1976), i.e., selected subjects had scores between 35 and 65. 14 participants were subsequently excluded due to high motion (see motion scrubbing), incomplete data or outlier analysis.

The final set of 68 participants (mean age of 22 ± 2.5 years, 32 females) consisted of three groups. Group A and Group B consisted of 19 and 22 subjects scanned in conjunction with two previously published studies (Kong et al., 2014; Ong et al., 2013). Group C consisted of 27 subjects collected solely for this study. While most of the analyses combined all three groups of participants to increase power, steps were taken to ensure that results were not driven by any one group.

Study procedure

Participants made three visits to the laboratory. On the first visit, they were briefed on the study protocol. To monitor their sleep pattern, each person was given a wrist actiwatch (Actiwatch, Philips Respironics, USA) that had to be worn until they completed the experiment. Only subjects with good sleep habit (slept for more than 6.5 h per night, slept no later than 1:00 am and woke up no later than 9:00 am) were invited to participate in the subsequent sessions.

The second and third visits were rested wakefulness (RW) or sleep deprivation (SD) sessions. During the sleep deprivation session, participants arrived at 7:00 pm and stayed awake the entire night. They completed the 9-point Karolinska Sleepiness Scale (KSS) (Åkerstedt and Gillberg, 1990) and the 10-minute psychomotor vigilance task (PVT) every hour (Dinges et al., 1997) to measure their alertness. All three groups were scanned at 6:00 am.

In the PVT, subjects had to fixate on a screen and place their dominant index finger on the button/key to minimize delayed response. Subjects were to press the button/key as soon as a number appeared. A warning was triggered if subjects did not respond for a long period of time. Across all three groups of subjects, the temporal distribution of the stimulus was a uniform distribution from 2 to 10 s.

During the rested wakefulness session, participants arrived at 9:30 pm and were given a 9 h sleep opportunity in a dark, quiet, air-conditioned room. They were awakened at 7:00 am to wash up and have a light snack. Groups A and B performed the PVT at 8:00 am and were scanned after its completion. Subjects from Group C performed a 10-minute PVT at 7:30 am and were scanned at 8:00 am.

There were three main differences in the PVT procedure among the three groups of subjects. First, Group A utilized the PVT-192 (Ambulatory Monitoring Inc., Ardsley, NY), a portable hand-held device with a LED display, while Groups B and C utilized computer-based testing (i.e., keyboard and 20.8″ × 17.7″ monitor). This resulted in systematically slower RT in Groups B and C compared with Group A. For computer-based testing, subjects were required to maintain an approximate distance of 60 cm from the screen keeping their eyes level with the fixation dot. Secondly, the PVT in Group C during the rested wakefulness session was conducted at 7.30 am instead of 8 am. Lastly, all subjects performed a PVT every hour from 8:00 pm until 5:00 am (inclusive) during the sleep deprivation session. Group C performed an additional PVT at 5:45 am.

The rested wakefulness scan time was chosen to be representative of a typical work day start time, while the sleep deprivation scan time was chosen when vigilance hits a nadir following a night of sleep deprivation (Doran et al., 2001). The rested wakefulness and sleep deprivation sessions were separated by a minimum of one week and the order of test sessions was counterbalanced across participants.

While there were variations in behavioral experiments across the three groups (Groups B and C performed additional behavioral experiments, whose details can be found in Kong et al., 2014; Ong et al., 2013), the scan times in the well-rested and sleep-deprived states were separated by less than an hour across the three groups. Guidelines for allowable activity through the study night were common across the groups. In particular main meals were taken at the same time across participants. All the participants in the rested wakefulness session were observed overnight in the sleep lab so that their wake time was regularized across participants in the three groups.

MRI acquisition

24 min (4 runs × 6 min) and 12 min (2 runs × 6 min) resting-state fMRI data were collected during the rested wakefulness and sleep deprivation sessions respectively. Three participants from Group A were scanned for shorter duration: two participants with 1 run of 8 min and one participant with 2 runs of 6 min for both sessions. Participants were instructed to keep their eyes open, relax and stay still. They were monitored through an eye tracker system and given a pre-recorded wake-up call if their eyes were closed for more than 10 s to prevent them from falling asleep. Wake-up calls were automatically recorded and utilized for further control analyses.

Structural and functional images were acquired on a 3-Tesla Tim Trio system (Siemens, Erlangen, Germany) using a 12-channel head coil. Functional images were collected using a gradient echo-planar imaging sequence (TR = 2000 ms, TE = 30 ms, FA = 90°, FOV = 192 × 192 mm and matrix size = 64 × 64). For each functional volume, 36 oblique axial slices (3 mm thick with no gap between slices) parallel to the AC–PC line were acquired with interleaved acquisition. High-resolution structural images were acquired using MPRAGE sequence (TR = 2300 ms, TI = 900 ms, TE = 2.98 ms, FA = 9°, BW = 240 Hz/pixel, voxel dimension: 1.0 × 1.0 × 1.0 mm, FOV = 256 × 240 mm).

MRI preprocessing

fMRI processing steps included 1) discarding the first four frames of each run, 2) correcting for slice acquisition-dependent time shifts in each volume with SPM (Wellcome Department of Cognitive Neurology, London, UK), and 3) correcting for head motion using rigid body translation and rotation parameters (FSL; Jenkinson et al., 2002; Smith et al., 2004).

Individual participants' structural scans were reconstructed into surface representations using FreeSurfer 4.5.0 (http://surfer.nmr.mgh.harvard.edu; Fischl, 2012). Functional data were registered to structural images using FreeSurfer's FsFast package (http://surfer.nmr.mgh.harvard.edu/fswiki/FsFast; Greve and Fischl, 2009). The structural preprocessing and structural–functional data alignment steps have been described in Yeo et al. (2011). Quality of image registration and cortical surface extraction was visually assessed for each subject.

Standard functional connectivity preprocessing was then performed on the fMRI data (Fox et al., 2005; Van Dijk et al., 2010; Vincent et al., 2006). Linear trends over each run were removed and a low-pass temporal filter retained frequencies below 0.08 Hz. Spurious variance was removed using linear regression with terms for head motion, whole brain signal, ventricle signal, white matter signal and their derivatives. The whole brain, white matter and ventricular masks were defined based on FreeSurfer segmentation of individual subjects' anatomical scan and transformed into the native T2* space of individual subjects. The white matter segmentation was eroded by one voxel. Erosion was not performed for the ventricular segmentation because this would result in some subjects not having any ventricular voxels.

Functional data were projected onto the FreeSurfer surface space (2 mm mesh), smoothed on the surface using a 6 mm full-width half-maximum kernel, and then downsampled to a 4 mm mesh.

In addition, structural data of individual subjects were nonlinearly registered to MNI152 space using FreeSurfer (Fischl et al., 2002, 2004; Han and Fischl, 2007). More details can be found in Buckner et al. (2011). Visual inspection of the structural data suggested that the deformation were adequate for all subjects. Functional data of individual subjects were then projected to MNI152 space, downsampled to 2 mm voxels and then smoothed with a 6 mm full-width half maximum kernel.

Motion scrubbing

Head motion affects measures of functional connectivity (Power et al., 2012; Satterthwaite et al., 2012; Van Dijk et al., 2012; Yan et al., 2013; Zeng et al., 2014) and can be a confounding factor when comparing groups with differential head motion. To reduce the effects of motion on functional connectivity, motion scrubbing (Power et al., 2012) was applied to the preprocessed fMRI data. Briefly, this technique included selective removal of volumes (time points) based on two measures, framewise displacement (FD) and variance of temporal derivative of time courses over voxels (DVARS). Here, only volumes with FD < 0.2 mm and DVARS < 5% were included. One volume before and two volumes after each volume that failed the criteria were also discarded. A functional run was excluded if less than 50% of the volumes remained after motion scrubbing. Based on these criteria, 2 subjects were excluded due to high motion during sleep-deprivation. There were 164.9 ± 17.4 and 158.0 ± 21.4 volumes per run per subject after motion scrubbing in the rested and sleep-deprived states respectively. We note that there were more runs during the rested state than during the sleep-deprived state, so that there were an overall average of 633.0 ± 102.7 and 302.1 ± 52.8 volumes per subject after motion scrubbing in the rested and sleep-deprived states respectively.

Functional connectivity

Functional connectivity was evaluated on motion scrubbed preprocessed resting-state fMRI data in fsaverage surface space (for cortical regions) and MNI152 volumetric space (for subcortical regions). Cortical regions were represented by 114 regions of interest (ROIs) extracted from a 17-network cortical parcellation estimated in 1000 young adults (Yeo et al., 2011; also see Baker et al., 2014; Betzel et al., 2014). Subcortical regions were represented by 8 ROIs corresponding to the left and right hemispherical thalamus, striatum, hippocampus, and amygdala extracted from the FreeSurfer segmentation of the FSL MNI152 template. This resulted in a total of 122 ROIs. For each functional run, time courses were averaged across vertices (for cortical regions) or voxels (for subcortical regions) within each ROI. The mean time course of each ROI was correlated to the mean time courses of all other ROIs, resulting in a 122×122 correlation matrix, with 7381 ($=122 \times 121 / 2$) unique Pearson's correlation values. Fisher r-to-z transform was applied to the correlation values to encourage normality (Van Dijk et al., 2010). For each rested wakefulness and sleep deprivation session, the resulting z-transformed correlation matrices were averaged across all runs of each subject.

Finally, two sets of nuisance factors were jointly regressed from each entry of the correlation matrices. To reduce possible inter-group differences, the first set of regressors consisted of three binary vectors indicating Group A, Group B, or Group C membership. The second set of regressors consisted of average motion of each individual subject to further reduce residual motion-related effects (Van Dijk et al., 2012).

Effects of sleep deprivation on functional connectivity

For each entry in the (z-transformed and regressed) correlation matrix, a within-subject (paired) t-test was performed to test for stronger correlations during the well-rested state than during the sleep-deprived state. Network-based statistic was used to correct for multiple comparisons (Zalesky et al., 2010). The network-based statistic is the graph analog of cluster-based thresholding and controls the family-wise error rate (in the weak sense). Like cluster-based thresholding (Nichols and Holmes, 2002), the network-based statistic requires thresholding of the t-statistics generated by the initial univariate t-tests. To ensure our results were robust to the choice of this initial threshold, we tested three initial thresholds corresponding to $p = 0.05$, $p = 0.01$, and $p = 0.005$ uncorrected. The analysis was repeated to test for weaker correlations during the rested wakefulness session than during the sleep deprivation session. The separate testing of stronger and weaker correlations followed previous network-based statistic convention (Zalesky et al., 2010).

Categorization of subjects into resilient and vulnerable groups

The 68 subjects were divided into two groups based on the number of psychomotor vigilance task (PVT) lapses in the sleep deprivation session. The number of lapses in a single PVT run was defined as the number of trials with reaction time (RT) slower than twice the subject's mean RT during the rested wakefulness PVT run. While PVT lapses correlate strongly with reaction time, PVT lapses are thought to reflect both slower mental processing as well as state instabilities (micro-sleeps) during sleep deprivation (Doran et al., 2001).

The number of sleep deprivation lapses in Group C subjects was obtained by averaging across the last three PVT runs (4:00 am, 5:00 am and 5:45 am). For Group B and Group C subjects, the last PVT run was at 5:00 am. Consequently, the number of sleep deprivation lapses was averaged across the last two runs (4:00 am and 5:00 am).

The 68 subjects were categorized as either more vulnerable (VUL) or more resilient (RES) based on a median split of the average number of sleep deprivation lapses. This categorization was performed separately for each of the three groups of subjects because of systematic RT differences across groups (see results) due to differences in PVT procedures (see the Study procedure section). The categorization resulted in a total of 34 resilient and 34 vulnerable subjects.

Functional connectivity differences between vulnerable and resilient subjects

The 122 × 122 correlation matrices of resilient and vulnerable subjects during rested wakefulness were compared. We tested whether the more resilient subjects had stronger (or weaker) correlations than the more vulnerable subjects using network-based statistics. The procedure is the same as the analysis of connectivity changes due to sleep deprivation, except the initial univariate tests utilized unpaired (instead of paired) t-tests.

We also compared connectivity changes after sleep deprivation between resilient and vulnerable subjects. Network-based statistics were again utilized to correct for multiple comparisons.

Prediction of sleep deprivation vulnerability with functional connectivity during the well-rested state

A leave-one-out cross-validation procedure was employed to test if functional connectivity during the rested state can predict whether a subject is more vulnerable or more resilient to cognitive decline during sleep deprivation. More specifically, a linear support vector machine (SVM) classifier was trained with the 122 × 122 functional connectivity matrix of 67 subjects and tested on the leave-one-out subject. The leave-one-out procedure was repeated for each of the 68 subjects. A permutation test (500 permutations) was performed to determine whether the resulting classification accuracy was better than chance.

Whole brain signal regression

Whole brain signal regression can introduce negative correlations between brain regions (Fox et al., 2009; Murphy et al., 2009), resulting in ongoing debate about the appropriateness of whole brain signal regression in fcMRI preprocessing. We hold the position that whether to regress whole brain signal (just like regressing the age of subjects) varies with context. Given that the whole brain fMRI signal has been correlated with vigilance decline and accompanying increase in EEG delta activity (Wong et al., 2013), regressing the whole brain signal might remove valuable information about sleep deprivation. To explore this, we repeated previous analyses omitting whole brain signal regression. Critically, analyses with whole brain signal regression examines the relationship of fMRI fluctuations *relative to* the whole brain signal with sleep deprivation (and resilience to sleep deprivation). In contrast, omitting this step evaluates *total* fMRI shift and fluctuation (whole brain signal plus fluctuations relative to the whole brain signal). To foreshadow the results, omitting whole brain signal regression resulted in weaker differentiation of resilient and vulnerable subjects.

Controlling for confounding factors

There were several confounding factors when comparing functional connectivity in the well-rested and sleep-deprived states. First, subjects exhibited higher motion following sleep deprivation than during rested wakefulness. Second, there was twice as much data for the rested wakefulness session (24 min) compared with the sleep deprivation session (12 min), which is a possible confounding factor (Giessing et al., 2013). Third, subjects received more wake-up calls in the sleep-deprived state, which might temporally redirect their attention to the external environment.

Here a control analysis was performed that considered all three confounding factors. First, recall that subjects were given wake-up calls if their eyes were closed for more than 10 s. Therefore we removed 10 s of data before and after the wake-up call (20 s in total). A functional run was excluded if fewer than 50% of the volumes remained after the removal, resulting in 6 subjects being excluded. Four subjects were also excluded because wake-up call data was incomplete, so we were left with 58 subjects. Second, a subset of the rested wakefulness runs was then selected to match the number of remaining sleep-deprived runs based on the number of volumes remained after wake-up calls removal. Rested wakefulness runs with similar number of volumes as sleep deprived runs were chosen and then volumes in each run were further discarded (randomly) such that both states had equal number of volumes. Finally, a subset of subjects with comparable motion during rested wakefulness and sleep deprivation states was isolated. The analysis of connectivity changes due to sleep deprivation was repeated using this subset of subjects (N = 43).

To foreshadow the results, there were no difference in the amount of motion and the number of wake-up calls between the more resilient and the more vulnerable subjects during the well-rested state, so no additional analyses were performed to control for these factors in the vulnerability analysis. However, we did explore various strategies in categorizing resilient and vulnerable subjects. First, we investigated whether categorizing resilient and vulnerable subjects within each group and then combining the subjects was acceptable. The analysis comparing resilient and vulnerable subjects during rested wakefulness was repeated for each of the three groups separately. Second, we performed a ternary (instead of a median) split within each group of subjects. Third, we directly correlated functional connectivity during the well-rested state with the number of lapses during sleep deprivation.

Finally, to ensure our results are robust to preprocessing strategies, we also utilized CompCor (Behzadi et al., 2007; Chai et al., 2012) in place of whole brain, white matter and ventricular regression. Briefly, this involves regressing the top five principal components of ventricular and white matter time courses instead of whole brain, white matter and ventricular signals. Both connectivity changes due to sleep deprivation and sleep-deprivation vulnerability were investigated.

Comparison of different analyses

To compare the similarity between two analyses, let us suppose the first analysis resulted in matrix A, while the second analysis resulted in matrix B. For example, the first analysis might utilize whole brain signal regression, while the second analysis might utilize CompCor. The similarity between the two analyses was quantified by the correlation of the entries of matrices A and B.

Results

PVT performance decreases during sleep deprivation

Table 1 summarizes PVT performance of subjects. The number of PVT trials for each subject was 84 ± 9 and 83 ± 10 during rested wakefulness and sleep deprivation respectively. As a group, participants showed the expected decline in psychomotor vigilance following sleep deprivation as evidenced by slower response times (mean RT = 371.5 ms, 511.7 ms, 603.5 ms for Groups A, B and C respectively) as compared to rested wakefulness (mean RT = 256.9 ms, 314.0 ms, 345.5 ms, $p < 0.001$). There were also an increased number of lapses during sleep deprivation: 7 lapses during sleep deprivation versus 1 lapse during rested wakefulness.

There were systematic inter-group RT differences during rested wakefulness ($F(2, 65) = 32.8$, $p < 0.001$) and sleep deprivation ($F(2, 65) = 4.54$, $p < 0.05$), leading us to categorize sleep deprivation vulnerability separately within each group of subjects.

Corticocortical connectivity during rested wakefulness and sleep deprivation

Fig. 1a shows the 17-network parcellation of the right cerebral cortex (Yeo et al., 2011). The 17 networks were divided into eight groups (Default, Control, Limbic, Salience/Ventral Attention, Dorsal Attention, Somatomotor, Visual and TempPar), which broadly correspond to

Table 1
Statistics of reaction times and lapses of subjects in all three groups in both the well-rested and sleep-deprived states.

	Group A	Group B	Group C
Mean reaction time (in ms)			
Rested wakefulness			
Mean ± standard deviation	256.9 ± 29.7	314.0 ± 43.6	345.5 ± 34.6
Range (min–max)	208.6–315.2	265.0–425.9	287.1–444.9
More resilient subjects			
Mean ± standard deviation	246.2 ± 32.6	306.6 ± 25.3	347.5 ± 37.4
Range (min–max)	208.6–315.2	271.8–355.9	307.7–444.9
More vulnerable subjects			
Mean ± standard deviation	264.7 ± 26.3	322.9 ± 59.1	343.3 ± 32.7
Range (min–max)	233.2–303.4	265.0–425.9	287.1–389.7
Sleep deprivation			
Mean ± standard deviation	371.5 ± 112.6	511.7 ± 337.9	603.5 ± 253.3
Range (min–max)	237.0–731.3	297.3–1406.1	321.2–1322.6
More resilient subjects			
Mean ± standard deviation	290.8 ± 47.6	326.8 ± 18.2	439.5 ± 61.9
Range (min–max)	237.0–395.4	297.3–356.6	321.2–540.0
More vulnerable subjects			
Mean ± standard deviation	430.2 ± 110.6	733.6 ± 407.0	780.2 ± 264.0
Range (min–max)	333.0–731.3	316.0–1406.1	423.2–1322.6
Number of lapses during sleep deprivation			
Mean ± standard deviation	7.1 ± 5.2	5.7 ± 8.2	9.2 ± 8.2
Median	7.0	1.5	7.3
More resilient subjects			
Mean ± standard deviation	2.2 ± 1.6	0.8 ± 0.6	3.0 ± 2.3
Range (min–max)	0–4.5	0–1.5	0–7.3
More vulnerable subjects			
Mean ± standard deviation	10.6 ± 3.7	11.5 ± 9.3	15.9 ± 6.8
Range (min–max)	7.0–20.0	2.0–27.5	8.7–27.7

major networks discussed in the literature. The 17 networks are referred to as "Default A", "Default B" and so on (Fig. 1a).

114 regions of interest (ROIs) in the cortical regions were derived from the 17 networks. The pairwise functional connectivity (with whole brain signal regression) among the 114 cortical ROIs during rested wakefulness and during sleep deprivation is shown in Figs. 1b and c respectively.

Connectivity patterns among the cortical networks during rested wakefulness and sleep-deprivation share some common features in that high within-network and low between-network correlations can be observed. We quantify connectivity differences between the two states in the following sections.

Distributed brain-wide connectivity changes after sleep deprivation

Functional connectivity differences (with whole brain signal regression) among 122 cortical and subcortical ROIs between the well-rested and sleep-deprived states were computed. Consistent with previous work (De Havas et al., 2012; Sämann et al., 2010), we found both increased and decreased connectivity within and across distributed large-scale brain networks resulting from sleep deprivation. The state-related changes in connectivity were significant across all three network-based statistics thresholds ($p < 0.0001$ corrected). In the following sections, we first focus on cortical connectivity changes before considering subcortical connectivity changes.

Corticocortical connectivity changes after sleep deprivation

Differences in functional connectivity (with whole brain signal regression) among the 114 cortical ROIs between rested wakefulness and sleep deprivation are shown in Fig. 2. Cool (hot) colors indicate decreased (increased) connectivity in the well-rested state compared with the sleep-deprived state.

Three previous results (De Havas et al., 2012; Sämann et al., 2010) were replicated. First, stronger anti-correlations (cool colors) between Default and Attention networks were observed during the rested state relative to the sleep-deprived state, i.e., the negative correlations were more negative during rested wakefulness. The stronger anti-correlations were especially prominent between Default networks (A and B) and Dorsal Attention networks (A and B): 171 out of 252 ROIs pairs with $p < 0.05$ corrected. Second, subjects exhibited stronger correlations (hot colors) within Default network A during the well-rested state relative to the sleep-deprived state: 28 out of 36 ROIs pairs with $p < 0.05$ corrected. Third, there were stronger anti-correlations between Default networks (A and B) and Salience/Ventral Attention A during wakefulness: 139 out of 198 ROIs pairs with $p < 0.05$ corrected.

A previously unreported finding is stronger functional connectivity (hot colors) between Dorsal Attention and Ventral Attention networks during the rested state relative to the sleep-deprived state. The higher correlations were especially prominent between Salience/Ventral

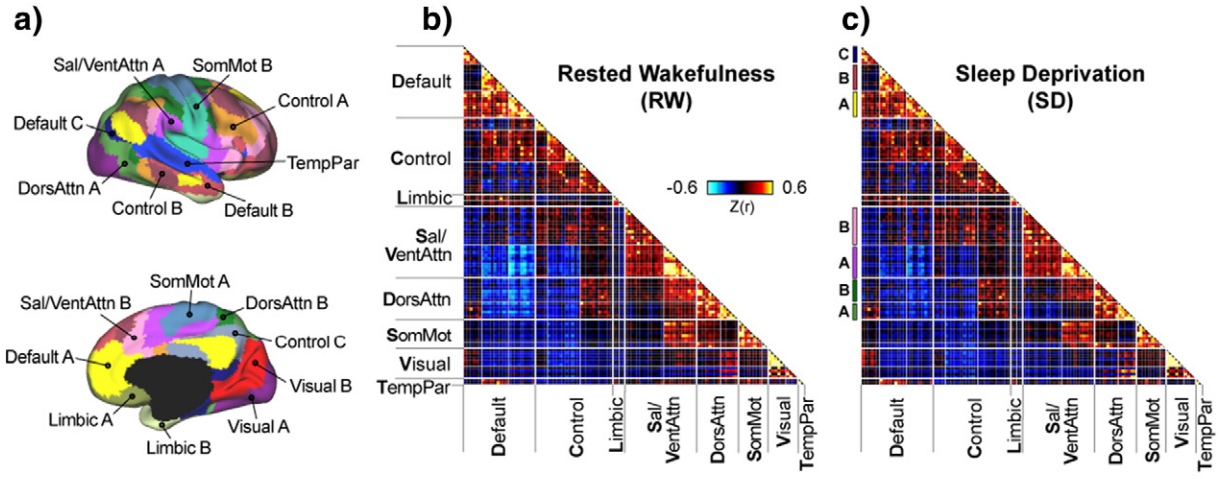

Fig. 1. Similar functional coupling among cortical regions during rested wakefulness and after sleep deprivation. (a) 17-network cortical parcellation (Yeo et al., 2011). The 17 networks are divided into eight groups (Default, Control, Limbic, Salience/Ventral Attention, Dorsal Attention, Somatomotor, Visual and TempPar), roughly corresponding to major networks discussed in the literature. 114 ROIs were derived from the 17 networks. Z-transformed pairwise functional connectivity among the 114 cortical ROIs during (b) rested wakefulness and during (c) sleep deprivation. Hot (cool) colors represent positive (negative) correlation. Thick white lines separate the eight groups of networks, while thin white lines separate the 17 networks. The networks within each of the eight groups are ordered in alphabetical order from bottom to top. For example, ROIs belonging to Default networks A, B, and C are arranged from bottom to top (c). Within each network, left hemispherical ROIs are at the bottom while right hemispherical ROIs are at the top. Similar connectivity patterns are seen for both well-rested and sleep-deprived states.

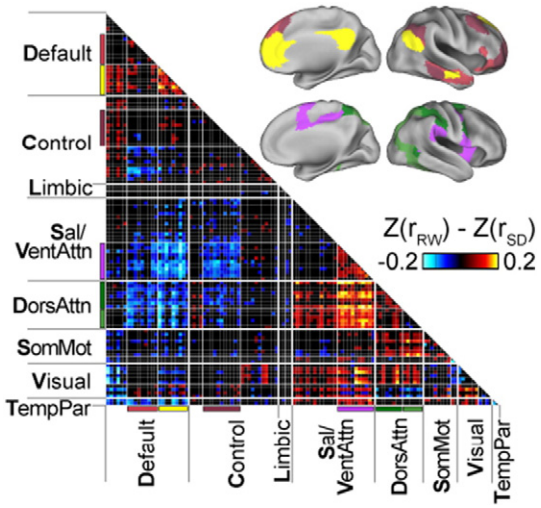

Fig. 2. Corticocortical connectivity differences between rested wakefulness and sleep deprivation. ROI arrangement follows Figs. 1b and c. Hot (cool) colors indicate stronger (weaker) correlations during rested wakefulness (relative to sleep deprivation). Both stronger and weaker correlations after sleep-deprivation were statistically significant ($p < 0.0001$, corrected for multiple comparisons). Only ROI pairs with $p < 0.05$ corrected using network-based statistic initial threshold of $p < 0.01$ are colored. One prominent difference is that during rested wakefulness, subjects exhibited stronger anti-correlations between Default networks (A and B) and Attention networks (Salience/Ventral Attention network A, and Dorsal Attention networks A and B). There were also stronger correlations during rested wakefulness within Default network A and between Dorsal Attention networks (A and B) and Salience/Ventral Attention network A. Networks that were significantly affected by sleep deprivation are illustrated on the right.

Attention network A and Dorsal Attention networks (A and B): 136 out of 154 pairs of ROIs with $p < 0.05$ corrected.

Subcortical–cortical connectivity changes after sleep deprivation

Functional connectivity between the 114 cortical ROIs and 8 subcortical ROIs (with whole brain signal regression) during rested wakefulness and sleep deprivation is shown in Fig. 3 (top two panels).

Differences in functional connectivity (with whole brain signal regression) among subcortical and cortical ROIs between rested wakefulness and sleep deprivation are shown in Fig. 3 (bottom panel).

During rested wakefulness, subjects exhibited (1) higher correlations between the thalamus and Default networks A and C: 25 out of 30 ROI pairs with $p < 0.05$ corrected, (2) lower correlations between the thalamus and Salience/Ventral Attention networks: 39 out of 48 ROI pairs with $p < 0.05$ corrected, and (3) weaker anti-correlations between thalamus and Dorsal Attention network A: 12 out of 12 ROIs pairs with $p < 0.05$ corrected.

During rested wakefulness, subjects also exhibited (1) higher correlations between hippocampus and Default network A (14 out of 18 ROIs pairs with $p < 0.05$ corrected) and (2) higher anti-correlations between hippocampus and Salience/Ventral Attention A (15 out of 22 ROIs pairs with $p < 0.05$ corrected).

Vulnerability to sleep deprivation can be predicted during rested wakefulness

The more resilient and the more vulnerable subjects performed on average 84 ± 9 and 83 ± 10 PVT trials respectively. This difference was not significant ($p = 0.79$). Resilient participants averaged 2 lapses in the sleep-deprived state compared to 13 for the vulnerable subjects. The difference of 11 lapses between resilient and vulnerable subjects constitutes 13% of the PVT trials, suggesting a significant difference in vigilance decline between the two groups of subjects. There was no significant difference in PVT reaction time between resilient and vulnerable subjects during the well-rested state ($p = 0.187$ for Group A, $p = 0.396$ for Group B and $p = 0.758$ for Group C; Table 1).

Functional connectivity differences (with whole brain signal regression) among 122 cortical and subcortical ROIs between resilient and vulnerable subjects during the well-rested state were computed. Resilient subjects exhibited significantly lower connectivity compared to vulnerable subjects ($p < 0.005$ corrected across all network-based statistic thresholds).

Differences in functional connectivity among cortical ROIs between resilient and vulnerable subjects during the well-rested state are shown in Fig. 4a. Resilient subjects exhibited stronger anti-correlations (more negative) between Default and Attention networks. Stronger anti-

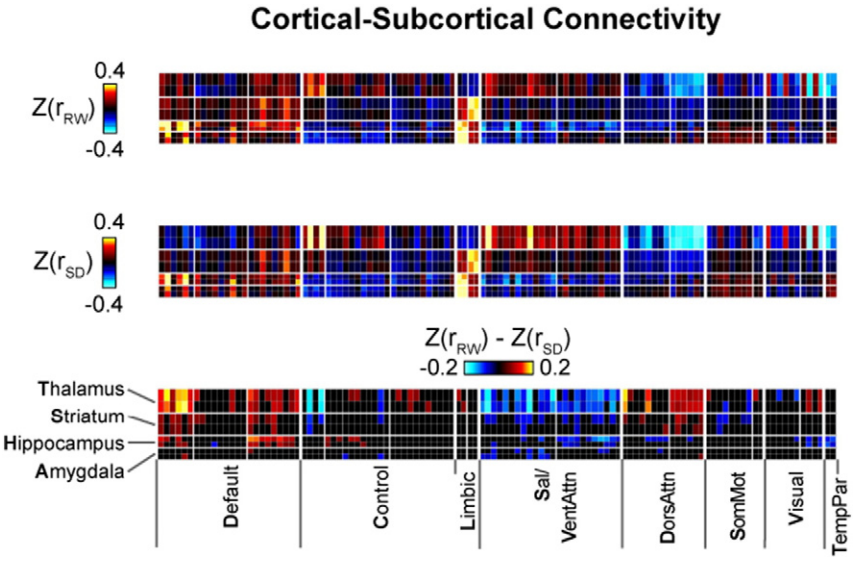

Fig. 3. Effect of sleep deprivation on connectivity between subcortical and cortical regions. Connectivity between 8 subcortical ROIs and 114 cortical ROIs during rested wakefulness (top) and sleep deprivation (middle), as well as connectivity changes between cortical and subcortical regions following sleep deprivation (bottom). Thalamus and striatum are represented in rectangles of larger size to illustrate their larger volumes compared to hippocampus and amygdala. During rested wakefulness, subjects exhibited weaker correlations between thalamus and Salience/Ventral Attention networks (cool colors; $p < 0.0001$, corrected for multiple comparisons) and weaker anti-correlations between thalamus and Dorsal Attention network A (hot colors; $p < 0.0001$, corrected for multiple comparisons).

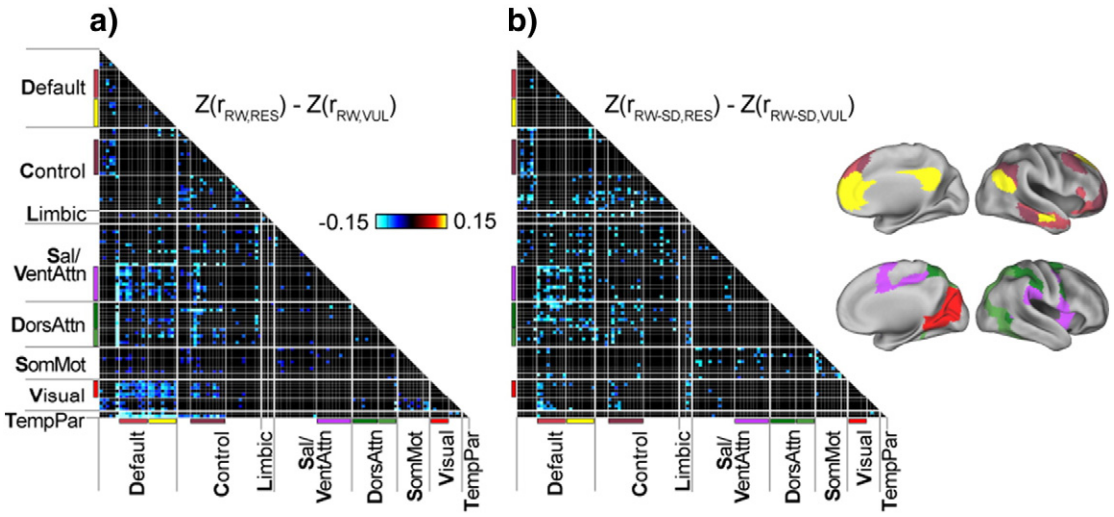

Fig. 4. Vulnerability to sleep deprivation is predictable during rested wakefulness. (a) Connectivity differences between resilient (RES) and vulnerable (VUL) subjects during rested wakefulness. ROI arrangement follows Figs. 1b and c and only ROI pairs showing weaker correlations for resilient subjects with $p < 0.05$ corrected (using network-based statistic threshold of $p < 0.05$) are colored. Only weaker correlations (cool colors) are statistically significant ($p < 0.005$ corrected for multiple comparisons). One prominent difference is that resilient subjects have stronger anti-correlations (more negative) between Default networks (A and B) and Attention networks (Dorsal Attention A and B, Salience/Ventral Attention A). Resilient persons also showed greater anti-correlations between both Attention networks and Control network B as well as between Default networks (A and B) and Visual network B. (b) Differences in functional connectivity changes (after sleep deprivation) between resilient and vulnerable subjects. Only ROI pairs with $p < 0.05$ corrected using network-based statistic initial threshold of $p < 0.05$ are colored (c.f. Fig. 2). Compared to vulnerable subjects, resilient subjects exhibited greater increase in anti-correlations (cool colors) in the well-rested state relative to the sleep-deprived state with borderline significance ($p < 0.05$ corrected for multiple comparisons for one of the three network-based statistic thresholds; $p = 0.06$ for the remaining thresholds). The converse is not statistically significant when corrected for multiple comparisons.

correlations were especially prominent between Default networks (A and B) and Attention networks (Dorsal Attention A and B, Salience/Ventral Attention A): 112 out of 450 ROI pairs with $p < 0.05$ corrected. These were more prominent with respect to the Salience/Ventral Attention A network. Resilient persons also showed greater anti-correlation between both Attention networks and Control network B (58 out of 275 ROI pairs with $p < 0.05$ corrected) as well as between Default networks (A and B) and Visual network B (80 out of 108 ROI pairs with $p < 0.05$ corrected).

There were no significant subcortical–cortical or between-subcortical connectivity differences between resilient and vulnerable subjects in the rested wakefulness state.

By training a SVM classifier on the functional connectivity data in the well-rested state, we were able to correctly classify 41 of the 68 subjects as either more vulnerable or more resilient during sleep deprivation. This corresponded to a classification accuracy of 60.3% ($p < 0.05$).

Comparison of connectivity differences between resilient and vulnerable subjects during rested wakefulness and across states

Comparison between Figs. 2 and 4a suggests that network differences between the more vulnerable and the more resilient subjects during rested wakefulness shared features observed in network alterations following sleep deprivation ($r = 0.31$, $p < 0.05$). Specifically, resilient participants evidenced more pronounced anti-correlations between Default networks (A and B) and Attention networks (Dorsal Attention A and B, Salience/Ventral Attention A).

However, other aspects of connectivity that showed significant state-changes (specifically connectivity within Default A and connectivity between Dorsal and Ventral Attention networks) did not differentiate resilient and vulnerable individuals. Conversely, connectivity differences between Default and Visual networks were predictive of vulnerability, but were not significant features of state-related changes in connectivity.

Connectivity changes following sleep deprivation were different in vulnerable and resilient subjects

The more resilient and the more vulnerable persons did not show significant differences in connectivity (with whole brain signal regression) during the sleep-deprived state. Therefore the matrix showing the direct comparison of state-related connectivity alterations between these groups (Fig. 4b) thus resembles connectivity differences observed in the rested state (Fig. 4a).

Indeed, compared to vulnerable subjects, resilient subjects exhibited greater increase in anti-correlations (cool colors) in the well-rested state relative to the sleep-deprived state with borderline significance (Fig. 4b; $p < 0.05$ corrected for multiple comparisons for one of the three network-based statistic thresholds; $p = 0.06$ for the remaining thresholds).

Another way of describing this finding is to note that the resilient subjects who exhibited greater anti-correlations (cool colors) between Default and Attention networks in the rested wakefulness state evidenced a relatively larger reduction in anti-correlation following sleep deprivation (119 out of 450 ROI pairs with $p < 0.05$ corrected for multiple comparisons).

Analyses without whole brain signal regression

The pairwise functional connectivity (without whole brain signal regression) among the 114 cortical ROIs during rested wakefulness is shown in Fig. 5a. Correlations were stronger within networks than between networks, consistent with the fact that almost identical cortical parcellations were obtained with and without whole brain signal regression (Yeo et al., 2014).

Functional connectivity differences (without whole brain signal regression) among 122 cortical and subcortical ROIs between the well-rested and sleep-deprived states were computed. Functional connectivity within the cerebral cortex was significantly higher when participants were sleep-deprived ($p < 0.005$ corrected). The increase in functional

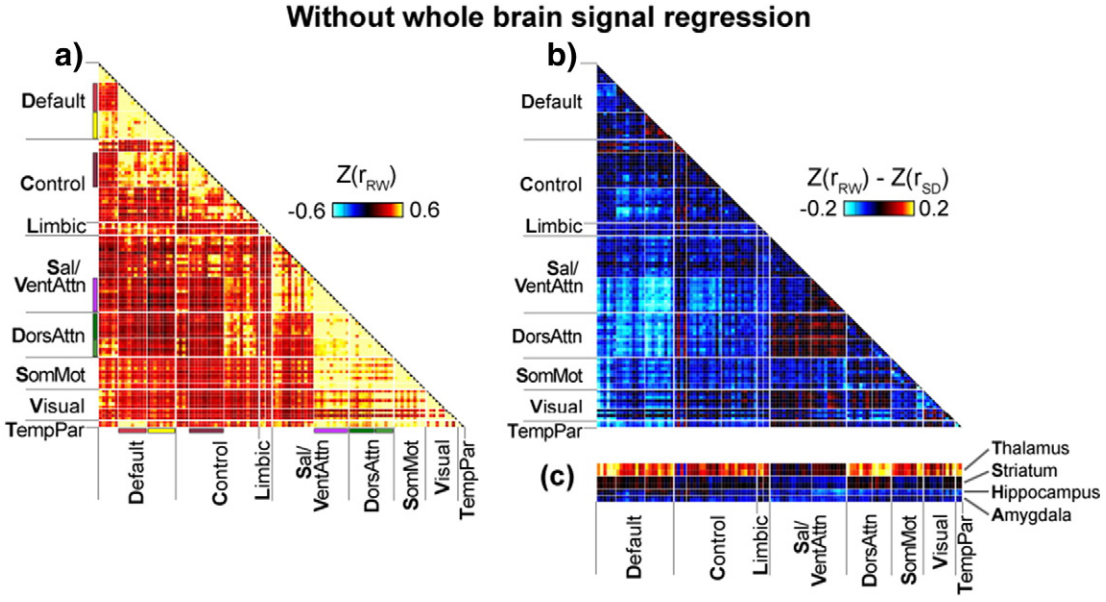

Fig. 5. Analyses of sleep deprivation connectivity changes without whole brain signal regression. (a) Z-transformed pairwise functional connectivity among the 114 cortical ROIs during rested wakefulness. (b) Corticocortical and (c) subcortical–cortical connectivity changes due to sleep deprivation. The increase in functional connectivity with sleep deprivation was (b) evident for almost all pairs of cortical regions, as well as (c) between subcortical and cortical regions, except the thalamus ($p < 0.005$ corrected).

connectivity with sleep deprivation was evident for almost all pairs of cortical regions (Fig. 5b), as well as between subcortical and cortical regions except the thalamus (Fig. 5c).

The decrease in thalamocortical connectivity was very prominent (Fig. 5c) and consistent with previous work (Spoormaker et al., 2010), but was not significant when corrected for multiple comparisons probably because of the (statistical) domination of increased corticocortical connectivity during sleep deprivation.

Functional connectivity differences (without whole brain signal regression) among 122 cortical and subcortical ROIs between resilient and vulnerable subjects during the rested wakefulness state were computed. The more resilient subjects exhibited significantly higher connectivity, although the differentiation was weaker ($p < 0.05$ corrected for only two of the three NBS thresholds) than in the analyses with whole brain signal regression. This increase in functional connectivity held true for almost all pairs of brain regions (not shown).

We emphasize that there is no contradiction despite apparent discrepancies between connectivity changes with and without whole brain signal regression. As previously mentioned, functional connectivity with whole brain signal regression measures fluctuations of fMRI signals relative to the whole brain signal. In contrast, functional connectivity without whole brain signal regression measures fluctuations of total fMRI signals. We will return to this point in the discussion.

Controlling for confounding factors

The analysis of connectivity changes due to sleep deprivation (Figs. 2 and 3) was repeated ($N = 43$) with (1) volumes removed due to wake-up calls, (2) equal number of volumes in the well-rested and sleep-deprived states and (3) comparable motion during both states. For both states, average numbers of volumes were 272.6 per subject. In this subset of subjects, average motion during rested wakefulness and sleep deprivation were both 0.06 mm ($p = 0.98$). The connectivity changes in this subset of subject were very similar to the original analysis ($r = 0.91$ with respect to Figs. 2 and 3).

During the rested state, there were on average 0.2 ± 0.4 and 0.2 ± 0.5 wake-up calls per run for resilient and vulnerable groups respectively ($p = 0.996$). In addition, there was no significant motion difference between resilient (average motion = 0.06 mm) and vulnerable subjects (average motion = 0.06 mm) during rested wakefulness ($p = 0.36$). Therefore differences in motion and the number of wake-up calls were unlikely to account for the more negative correlations in resilient subjects during rested wakefulness.

We also explored the sensitivity of our analyses to the median splitting of each group of subjects into vulnerable and resilient subjects. First, the analysis comparing resilient and vulnerable subjects during rested wakefulness was repeated for each of the three groups separately. The connectivity differences between the more resilient and the more vulnerable subjects within each group were consistent ($r = 0.60$, 0.53 and 0.66 respectively) with the original analysis (Fig. 4a). Second, we replicated the analysis using a ternary split, rather than a median split. There was good agreement between the median and ternary splits ($r = 0.79$). Third, we directly correlated functional connectivity during the well-rested state with the number of lapses during sleep deprivation. The results were again similar to the median split results ($r = -0.72$). However, the above results were not significant when correcting for multiple comparisons.

Finally, CompCor and whole brain signal regression yielded similar pattern of connectivity changes in the sleep-deprived state ($r = 0.87$) and between resilient and vulnerable subjects in the well-rested state ($r = 0.87$). The similarity between CompCor and whole brain signal regression may be due to 62% variance of the whole brain signal (on average across subjects) explained by the CompCor components ($p < 0.001$), suggesting that at least in our data, CompCor strategy might be implicitly removing whole brain signal in addition to physiological noise.

Discussion

When functional connectivity was measured relative to the whole brain signal (i.e., whole brain signal regressed), functionally connected cortical regions in the rested state (e.g., within Default network) evidenced reduced correlation following sleep deprivation, suggesting that highly integrated networks become less integrated during sleep deprivation. In contrast, anti-correlated regions in the rested state (e.g. Default and Attention networks) became less so, suggesting that highly segregated networks become less segregated during sleep-deprivation (Fig. 6a).

Persons more resilient to vigilance decline showed stronger anti-correlations among several networks during rested wakefulness (Fig. 6b). The differences in functional connectivity between the

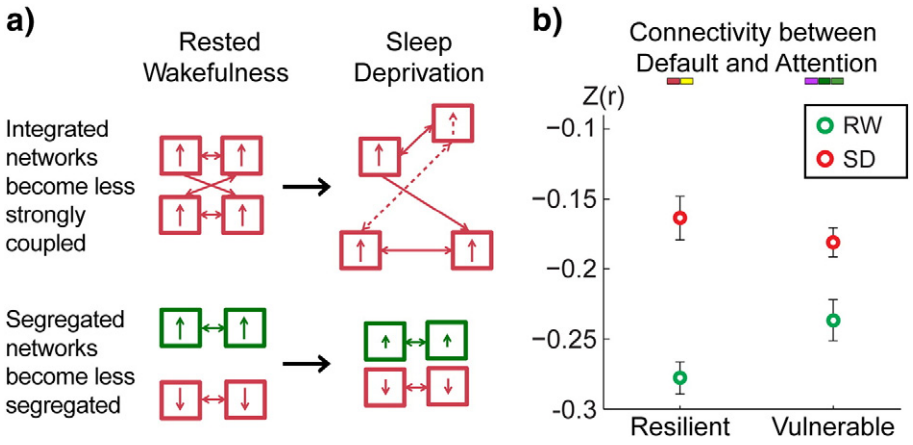

Fig. 6. Illustration of distributed large-scale cortical networks changes following sleep deprivation with whole brain signal regression. (a) Cortical regions that were functionally connected during the rested state (e.g., regions of the Default network) evidenced reduced correlation following sleep deprivation (top panel), suggesting that highly integrated brain regions become less strongly coupled during sleep deprivation. On the other hand, regions that were anti-correlated in the rested state (e.g., Default and Attention networks) became less so (lower panel), suggesting that highly segregated networks become less segregated during sleep-deprivation. (b) Correlation between Default and Attention networks in resilient and vulnerable subjects during the well-rested and sleep-deprived states. Correlation values from 450 ROI pairs between Default networks (A and B) and Attention networks (Dorsal Attention A and B, Salience/Ventral Attention A) were averaged for each subject. These correlation values were then averaged among the resilient and vulnerable subjects during the well-rested and sleep-deprived states. We emphasize that the correlations shown here are for illustration, and not unbiased estimates of differences between resilient and vulnerable subjects (Vul et al., 2009).

resilient and vulnerable subjects only partially overlap with connectivity alterations following sleep deprivation. In contrast to corticocortical connectivity, subcortical–cortical and between-subcortical connectivity were similar across resilient and vulnerable groups despite prominent changes across states.

An unanticipated set of findings concerns the widespread increase in whole brain fMRI signal across the entire brain (except the thalamus) following sleep deprivation. This results in higher correlations of total fMRI signals throughout the brain and reduction in thalamocortical connectivity. The strong increase in whole brain fMRI signal may mask important fluctuations in fMRI signals relative to the whole brain signal. For example, the strong reduction in anti-correlations between Default and Dorsal Attention networks (when whole brain signal is regressed) is masked by significant increase in whole brain fMRI signal in both networks after sleep deprivation (Fig. 7). Together, our results reconcile seemingly discrepant findings regarding state related connectivity shifts (De Havas et al., 2012; Sämann et al., 2010; Spoormaker et al., 2010), suggesting possible value in regressing whole brain signal in contexts where widespread shifts in whole brain signal occur (Thompson et al., 2013).

State-related changes in total fMRI connectivity and whole brain signal

During the transition from wake to sleep (and from light sleep to deep sleep) there is a progressive disengagement from the external environment evident from the higher sensory arousal thresholds associated with deep sleep relative to light sleep (Rechtschaffen et al., 1966). Given that the thalamus relays sensory information to the cerebral cortex, this disconnection from the external environment may result from decreased connectivity between the sensory cortex and the thalamus. Indeed, reduction in thalamic activity precedes cortical deactivation by several minutes (Magnin et al., 2010). Furthermore, there is increased

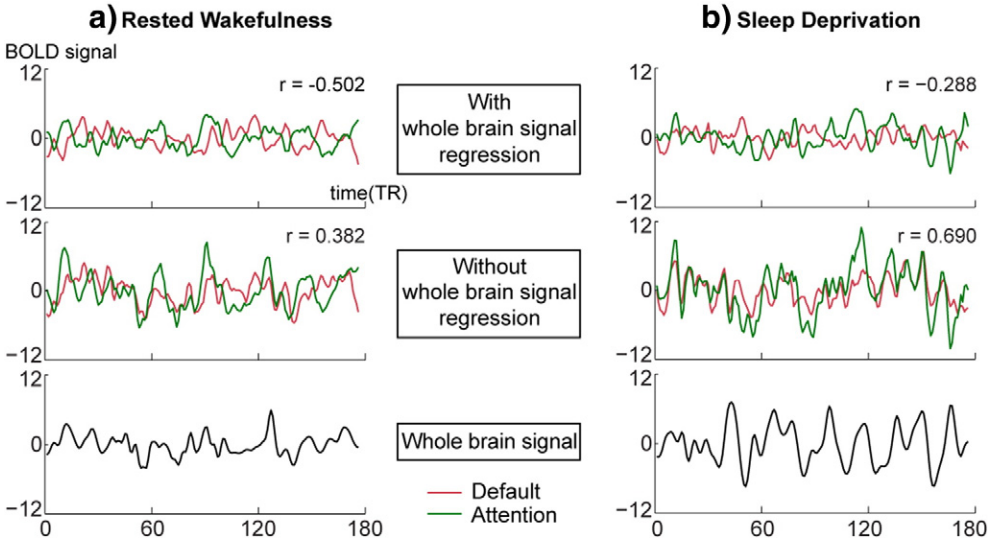

Fig. 7. Signal fluctuations in Default (red) and Attention (green) networks (a) during rested wakefulness and (b) following sleep deprivation. Whole brain signal fluctuations (bottom panel) were significantly stronger following sleep deprivation. Relative fluctuations of Default and Attention network regions (top panel) were dominated by the whole brain signal when whole brain signal regression was omitted (middle panel). This resulted in an increased correlation between Default and Attention networks when whole brain signal was not regressed.

corticocortical connectivity and reduced thalamocortical connectivity when whole brain signal is not regressed (Spoormaker et al., 2010). Our results of increased corticocortical connectivity (Fig. 5b) and reduced thalamocortical connectivity (Fig. 5c) when whole brain signal is not regressed suggest that connectivity changes during sleep deprivation are very similar to connectivity changes in the transition from wake to sleep.

The dissociation of state-related changes in corticocortical and thalamocortical connectivity might be explained by the relative composition of the whole brain signal. The whole brain fMRI signal is known to be strongly present in the thalamus in the well-rested state (Zhang et al., 2008; Fox et al., 2009). In our data, the average correlation between the whole brain signal and all thalamic voxels was 0.12 in both the well-rested and sleep-deprived states. By contrast, the average correlations between the whole brain signal and all cortical regions were 0.13 and 0.18 in the well-rested and sleep-deprived states respectively. Therefore the relative composition of the whole brain signal significantly increases in the cerebral cortex (but not the thalamus) during sleep deprivation ($p < 0.001$), resulting in stronger correlations of total fMRI signals within the cerebral cortex (Fig. 5b) and decreased correlations between the cerebral cortex and the thalamus (Fig. 5c).

Our results are also consistent with previous work reporting a close association between the whole brain fMRI signal and EEG correlates of decreased vigilance (Wong et al., 2013). Indeed, we found that the standard deviation values of the whole brain signals (averaged across all subjects) were 2.3 and 3.2 in the well-rested and sleep-deprived states respectively ($p < 0.001$). The increase in whole brain signal amplitude may be related to an overall increase in cortical excitability with sustained wakefulness reflecting sleep homeostasis (Huber et al., 2013).

State-related changes in relative corticocortical connectivity

The overall increase in whole brain fMRI signal could mask signal fluctuations relative to the whole brain signal, which may be a critical marker of state-related functional changes. When whole brain signal was regressed, there was reduced connectivity within the Default network and weakened anti-correlations between the Default and Attention networks during sleep deprivation (De Havas et al., 2012; Sämann et al., 2010). While state-related changes can be ascribed to entire networks (Horovitz et al., 2009; Larson-Prior et al., 2009), closer scrutiny suggests heterogeneous connectivity shifts across sub-networks (Fig. 2 of Sämann et al., 2011). This is consistent with recent studies highlighting the functional heterogeneity of the Default network (Andrews-Hanna et al., 2010; Laird et al., 2009; Leech et al., 2011; Uddin et al., 2009; Yeo et al., in press).

By exploiting a recently published cortical parcellation (Yeo et al., 2011), we demonstrated finer-grained network changes across the entire brain, refining the findings of previous work (De Havas et al., 2012; Sämann et al., 2010). For example, reduction in intra-network connectivity within the Default network was the strongest within Default network A. Similarly, significant reductions in anti-correlations between Default and Attention networks mostly spare Default network C and Salience/Ventral Attention network B.

The anti-correlations between Default and Attentional networks are thought to be pivotal in segregating internally and externally oriented cognition. The reduced segregation of anti-correlated networks might coincide with the occurrence of hypnagogic hallucinations where vivid and sometimes bizarre multi-sensory experiences can be reported (Rowley et al., 1998). A similar breakdown in the balance of internal and external processing systems has also been linked with psychosis, which is characterized by a loss of touch with reality, delusions and hallucinations (Baker et al., 2014; Buckner, 2013; Whitfield-Gabrieli et al., 2009).

Overall, our results suggest that highly integrated cortical regions become less strongly coupled during sleep deprivation, while highly segregated networks become less segregated during sleep-deprivation.

State-related changes in relative subcortical connectivity

During rested wakefulness, the thalamus was positively correlated with Salience/Ventral Attention network, but anti-correlated with the Dorsal Attention network. We speculate that the positive correlation might arise from the Saliance/Ventral Attention network's role in redirecting attention to salient changes in the external environment (Corbetta and Shulman, 2002; Seeley et al., 2007). By contrast, the anti-correlation might arise from the suppression of reactive allocation of sensory resources to salient environmental stimuli by top-down attention.

Unexpectedly, changes in thalamic connectivity with Dorsal Attention networks (Shao et al., 2013) and Salience/Ventral Attention networks during sleep deprivation do not correlate with vulnerability to vigilance decline. Their functional significances need to be established in future studies.

Predicting vulnerability to sleep deprivation with functional connectivity

Persons more resilient to vigilance decline following sleep deprivation exhibit stronger whole brain signal during the rested-state as evidenced by the higher correlations of total fMRI signals throughout the brain. However, resilient and vulnerable subjects were more strongly differentiated when relative fluctuations about the whole brain signal were considered, i.e., when whole brain signal was regressed.

A novel finding of the present study is that greater anti-correlation among several networks during rested wakefulness were associated with vulnerability to vigilance decline following sleep deprivation (Fig. 6b). Persons with greater segregation between Default networks (A and B) and Ventral/Salience network A might be more resilient on account of their ability to differentiate internally and externally oriented cognition. This reasoning might be extended to nodes within Dorsal Attention network A and Control network B, which include parts of the intraparietal sulcus, putative frontal eye fields and dorsolateral prefrontal cortex that are involved in the control of externally focused attention (Corbetta and Shulman, 2002; Dosenbach et al., 2007; Fedorenko et al., 2013; Yeo et al., in press).

Using a leave-one-out procedure, we were able to achieve a leave-one-out classification accuracy of 60.3%. The modest classification accuracy given this relatively big dataset suggests that there remains significant work to be done in order to establish reliable neuroimaging biomarkers of sleep deprivation vulnerability.

The classification accuracy using functional connectivity is slightly inferior to that of diffusion drift modeling (Patanaik et al., 2014) or heart rate variability (Chua et al., 2012). Therefore the inclusion of measures, such as respiratory and heart rate, can potentially improve the prediction of sleep deprivation vulnerability. Unfortunately, we did not have the interface system necessary to time-lock the physiological information to the scans, so these data were not collected.

Similarity and differences in vulnerability markers and state-related changes in relative fMRI connectivity

The more resilient and the more vulnerable subjects exhibited dissimilar connectivity patterns in the rested state (Fig. 4a). Patterns of functional connectivity modulated by sleep deprivation (Fig. 2) only partially overlapped with those predicting vulnerability to vigilance decline (Fig. 4a). Interestingly, the functional connectivity of resilient and vulnerable subjects became similar following sleep-deprivation (Fig. 4b).

This apparent equalization of differences in connectivity irrespective of vulnerability to SD is puzzling. A possible technical reason is that the smaller amount of data collected in the sleep-deprived state compared to the rested state resulted in reduced statistical power. However, we (De Havas et al., 2012) also did not find a correlation between performance change across state and Default connectivity despite analyzing up to 36 min of task-regressed connectivity data.

While functional connectivity differences between resilient and vulnerable subjects were the strongest during the rested state, task activation differences between resilient and vulnerable subjects were the strongest during the sleep-deprived state (Chee and Tan, 2010; Chuah and Chee, 2008; Chuah et al., 2009). Relatively preserved task-related deactivation may be associated with relatively conserved behavioral performance (Chee and Chuah, 2007).

A possible explanation for the difference between task-related and the present resting-state fMRI results might lie in inter-individual differences in how relevant networks are recruited or deactivated during sleep deprivation during task performance. 'Static' functional connectivity assessed during the 'wake-state' instability of the sleep-deprived state may thus inadequately reflect functional connectivity at critical moments during task performance. As such task-related (Fornito et al., 2012; Krienen et al., 2014; Tomasi et al., 2014) and dynamic (Allen et al., 2012; Hutchison et al., 2013; Zalesky et al., 2014) functional connectivity could potentially yield further insights.

In sum, functional connectivity between the Default and Attention networks in the rested state appears to be a marker for vulnerability to vigilance decline following sleep deprivation. Functional connectivity clearly changes with state as well. However, it appears that the latter may be necessary but insufficient to account for vigilance decline. Differences in the ability to recruit fronto-parietal circuits or deactivate parts of the Default network during task performance might be more important determinants of performance in the sleep-deprived state than static functional connectivity. An integrated study where task-related, static and dynamic functional connectivity are evaluated is necessary to test this hypothesis.

Wake-up calls

Removing volumes associated with wake-up calls did not significantly affect our results. It should be noted that these long episodes (10 s) of eye closures constitute only a minority of the total number of eye closures in the sleep-deprived state, so the robust results may not be surprising. These longer eye closures, which may represent microsleeps, are a critical feature of sleep deprivation, so it would not make sense to remove all periods of eye closures. Long periods of eye closures are removed because otherwise, we would simply be studying the neuroimaging signatures of sleep. Indeed, a critical motivation of our study is to include periods of "wake-state instability" in the analysis.

Conclusion

This study discovered functional connectivity between brain regions that were predictive of sleep deprivation vulnerability. Our results suggest that more resilient individuals may be better able to maintain segregation of highly segregated networks when well-rested. While we gained some insight into the potential mechanism underlying resiliency to sleep deprivation, the modest classification accuracy suggests that there remains significant work to be done in order to establish reliable neuroimaging biomarkers of sleep deprivation vulnerability. The most appropriate spatial scale for characterizing state-related changes would also benefit from further clarification.

Acknowledgments

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