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Resting Spontaneous Activity in the Default Mode Network Predicts Performance Decline during Prolonged Attention Workload

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Abstract

After continuous and prolonged cognitive workload, people typically show reduced behavioral performance and increased feelings of fatigue, which are known as “time-on-task (TOT) effects”. Although TOT effects are pervasive in modern life, their underlying neural mechanisms remain elusive. In this study, we induced TOT effects by administering a 20-minute continuous psychomotor vigilance test (PVT) to a group of 16 healthy adults and used resting-state blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) to examine spontaneous brain activity changes associated with fatigue and performance. Behaviorally, subjects displayed robust TOT effects, as reflected by increasingly slower reaction times as the test progressed and higher self-reported mental fatigue ratings after the 20-minute PVT. Compared to pre-test measurements, subjects exhibited reduced amplitudes of low-frequency fluctuation (ALFF) in the default mode network (DMN) and increased ALFF in the thalamus after the test.

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Subjects also exhibited reduced anti-correlations between the posterior cingulate cortex (PCC) and right middle prefrontal cortex after the test. Moreover, pre-test resting ALFF in the PCC and medial prefrontal cortex (MePFC) predicted subjects' subsequent performance decline; individuals with higher ALFF in these regions exhibited more stable reaction times throughout the 20-minute PVT. These results support the important role of both task-positive and task-negative networks in mediating TOT effects and suggest that spontaneous activity measured by resting-state BOLD fMRI may be a marker of mental fatigue.

Keywords

Time-on-task (TOT) effects; fatigue; default mode network (DMN); amplitudes of low-frequency fluctuation (ALFF); functional connectivity

Introduction

Maintaining a steady level of attention and performance is an important and essential requirement for many daily jobs. However, people typically display slower response times, more errors (of omission and commission), and increased feeling of fatigue while engaging in a task over prolonged periods of time, which is known as “vigilance decrement” or “time-on-task (TOT) effects” (Langner & Eickhoff, 2013; Mackworth, 1948; Mackworth, 1968; Pattyn et al., 2008; See et al., 1995).

Fatigue due to prolonged workload and/or sleep loss is pervasive in contemporary society and can lead to serious consequences, such as accidents while driving or administering medical care (Arnedt et al., 2005; Dinges, 1995; Dubal and Jouvent, 2004). However, not all individuals show the same extent of vulnerability to fatigue and there are large inter-individual differences in responses to sleep loss and cognitive workload (Lim et al., 2010; Parasuraman et al., 2009). Individual differences in TOT effects have been associated with dopaminergic polymorphisms, which suggested that increased availability of dopamine may promote activity in striatal and prefrontal regions associated with attention (Lim et al., 2012a).

Previous studies have used multiple neuroimaging techniques to examine the neural correlates of TOT effects, including positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and electroencephalography (EEG). Paus et al. (1997) examined time-related brain function changes during continuous performance on a 60-min auditory vigilance task and found decreased regional cerebral blood flow (CBF, measured using PET) in the thalamus, frontal, parietal, and temporal cortices in the right hemisphere as a function of TOT. Coull et al. (1998) also used PET and measured CBF changes in frontal and parietal cortices during non-selective and selective attention tasks. They observed decreases in performance as TOT increased during the non-selective attention task but not during the selective attention task. Furthermore, performance decrement during the non-selective task was accompanied by reduced CBF in the right fronto-parietal network. Lim et al. (2010) used arterial spin labeling (ASL) perfusion fMRI and measured CBF changes during continuous performance of a 20-min psychomotor vigilance test (PVT) and observed reduced CBF in the frontal, cingulate, and parietal regions after the task. CBF

changes from pre-test to post-test in the fronto-parietal network correlated with performance decline. Collectively, these studies consistently illustrate the important role of the fronto-parietal attention network in TOT effects.

Recently, fMRI has been increasingly used to assess intrinsic spontaneous brain activity during task-independent resting states and has consistently revealed various resting-state brain networks, including the default mode network (DMN) and the fronto-parietal attention network (FAN) (e.g., Damoiseaux et al., 2006; Zhu et al., 2013). The DMN is a task-negative network consisting of the posterior cingulate cortex/precuneus (PCC/PCu), medial prefrontal cortex (MePFC), and the lateral parietal cortex (Fox et al., 2005; Zhang and Raichle, 2010; Zhu et al., 2013) and is thought to be involved in intrinsic and stimulus-independent thoughts (Mason et al., 2007). Brain activity in the DMN is usually higher at rest and lower during performing goal-directed cognitive tasks. In contrast, the FAN is a task-positive network and activity in this network is usually higher during performing cognitive tasks and lower when in the resting state. Significant anti-correlations between spontaneous activity in the DMN and FAN have been consistently reported in normal healthy subjects (Fox et al., 2005; Gao and Lin, 2012; Kelly et al., 2008).

A few recent studies have used resting-state fMRI and examined changes in spontaneous brain activity patterns associated with TOT effects. Breckel et al. (2013) used resting-state fMRI and compared the topological and spatial properties of brain networks before and after an attentional task and found increased connectivity strength and clustering, decreased connection distance, and less efficiency in brain networks immediately after the task. In addition, individuals who were more resilient to TOT effects showed faster recovery of brain networks after prolonged attentional effort. Giessing et al. (2013) examined the effects of nicotine during a prolonged go/no-go attention task, and found robust TOT effects that were associated with decreased connection distance and increased clustering of brain networks. However, none of these studies have examined the influences of TOT effects on DMN function and it remains unknown whether TOT impairs spontaneous resting activity in the DMN and the balance between the task-positive and task-negative networks.

In this study, we used resting-state blood oxygen level dependent (BOLD) fMRI to examine intrinsic and spontaneous neural activity and connectivity changes in resting brain networks, particularly in the DMN, after prolonged attention workload. Consistent with previous studies (Lim et al., 2010; Sun et al., 2014a, 2014b), we used a continuous 20-min PVT to induce TOT effects. The PVT is a simple, reliable and highly sensitive reaction time task and free of aptitude and leaning effects (Dinges et al., 1997; Lim and Dinges, 2008).

The amplitude of low-frequency fluctuation (ALFF) was used as the metric for assessing spontaneous neural activity changes in this study. The ALFF measures the power or intensity of low frequency (<0.08 HZ) oscillations of the BOLD time courses, which is considered to be physiologically meaningful and reflective of regional spontaneous neural activity (Yang et al., 2007; Zang et al., 2007; Zou et al., 2008; Duff et al., 2008; Jiang et al., 2011; Xu et al., 2014). Previous studies have shown that ALFF has high test-retest reliability and is closely related to CBF (Zuo et al., 2010; Li et al., 2012a; 2012b), suggesting that ALFF may be an useful index to examine state-dependent resting brain function changes

associated with TOT effects. We hypothesized that TOT would alter ALFF in the DMN. In addition, we used seed-based functional connectivity (FC) analysis to examine DMN connectivity changes after prolonged attention workload. Functional connectivity reflects the temporal correlation of low-frequency fluctuation between distinct brain regions and provides another index of functional integration of resting brain function. We hypothesized that TOT would impair the balance between the DMN and the FAN. Finally, although the aim of this study is to examine resting brain function changes after TOT effects, we also performed a conventional event-related fMRI analysis to examine task-related activation changes during the 20-min PVT.

Materials and Methods

Participants

Sixteen healthy undergraduate and graduate students (11 females, 21.3 ± 1.3 years) participated in this study. Two subjects were excluded due to excessive head motion in the scanner. All participants were right-handed, normal vision (with or without correction), reported no history of affective disorders, neurological diseases and no regular use of medication. Participants who qualified for enrollment were instructed to obtain 7-9 hours sleep per night during the two nights prior to the experiment and not to consume caffeine, alcohol, or any other psychoactive substances during the 24h before the experiment. In addition, subjects completed the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) to assess their recent sleep quality and history. Subjects were compensated for their effort and time after participating in the study. All participants provided written informed consent according to the guidelines of the Department of Psychology at Sun Yat-sen University and the School of Psychology at Southwest University in China.

Psychomotor Vigilance Test (PVT)

A Matlab and Psychtoolbox-based version of the PVT was used in the study. The PVT is a simple reaction time test with varying and random inter-stimulus intervals ranging from 2 to 10 s (Dinges et al., 1997; Lim and Dinges, 2008). Before entering the scanner, subjects were given a brief 1-min opportunity to practice the PVT. During the PVT, participants were instructed to maintain their attention on a red-outlined rectangle in the center of a black screen. A millisecond counter, which acts as the target, appears within the red-outlined rectangle in yellow font. When subjects respond to the target, the millisecond counter freezes and the rectangle becomes outlined in yellow rather than red; thus, subjects are able to see their reaction time. The rectangle then returns to red and the subject must fixate until the next target (the millisecond counter) appears. Participants were instructed to respond as quickly as possible without making errors of commission ("false alarms"). False alarms occur if subjects hit the button before a target is presented. When this occurs, the words "False Alarm" appear on the screen. If subjects do not respond to the target within 500 msec, it is considered an error of omission ("Lapse"). However, subjects are not given any feedback when their reaction time exceeds 500 msec. The millisecond counter continues counting up to 30,000 msec or the subject's response, whichever comes first. If subjects do not respond within 30,000 msec, the rectangle resets for the next target. The length of PVT was 20 minutes in order to elicit the TOT effects and to increase between-subject variance in

performance. All participants rated their subjective fatigue level on a 9-point scale before and after the PVT.

Similar to previous study (Lim et al., 2010), the following variables were extracted as a measure of overall level of PVT performance: median reaction time (RT), standard deviation of RT, and number of lapses (RT > 500 ms). To assess the TOT effects, the 20-min PVT was divided into 4-min quintiles and the median RT was obtained for each quintile. The percentage changes in median RT from the first to the last quintile (ratio = (Last Quintile – First Quintile) / First Quintile * 100%) were calculated as the index for performance declines.

Data acquisition

Functional imaging was acquired using a Siemens TRIO 3T MRI scanner in the key Laboratory of Cognition and Personality at the Southwest University in China. Two 8-min resting state scans were obtained immediately before and after the PVT. Participants were instructed to lie down in the scanner quietly and keep eyes open during the resting scans. Functional scanning used a standard echo planar imaging (EPI) sequence (TR=2000ms; TE=30ms; flip angle: 90 degree; field of view: 220mm; in-plane resolution: 64 × 64; voxel size = 3.44mm × 3.44mm × 4mm) with prospective acquisition correction (PACE), which helps reduce head motion during data acquisition. Thirty-two axial slices were acquired to cover the whole brain with no gap. High-resolution (1mm × 1mm × 1mm) anatomical images were obtained by T1-weighted 3D magnetization prepared rapid gradient echo (MPRAGE) sequence (inversion time=900ms; TR=2600ms; TE=3.02ms; flip angle=8 degree; field of view=256mm × 256mm). In order to reduce potential interference from time-of-day variations, all subjects were scanned in the afternoon between 1-5pm.

Data analysis

Statistical Parametric Mapping software (SPM8, Wellcome Department of cognitive Neurology, UK) and the REST 1.7 toolbox (Song et al., 2011) (<http://resting-fmri.sourceforge.net/>) implemented in Matlab 2008a (Math Works, Natick, MA) were used to analyze image data.

For image preprocessing, resting images of each subject were first realigned to correct for head motion, co-registered with the anatomical image and smoothed in space using a three-dimensional 4-mm full width at half maximum (FWHM) Gaussian kernel. Images were then normalized to standard Montreal Neurological Institute (MNI) space and re-sampled with isotropic 3 × 3 × 3 mm³ voxel size. Linear band pass filter at 0.01Hz ~ 0.08Hz to reduce low-frequency drift and physiological high-frequency respiratory and cardiac noise. Nuisance covariates including the six head motion parameters, global mean signal, white matter signal and CSF signal were regressed out from the data (Fair et al., 2008). Each voxel's BOLD time series was transformed into the frequency domain and the mean amplitude of the spectrum over the frequency range of 0.01-0.08Hz was calculated as the ALFF (Yang et al., 2007; Zou et al., 2008). Group-level whole brain paired *t*-test was then performed to examine the ALFF differences before and after the 20 minutes PVT. Activation clusters were identified at a significance level of voxel-wise uncorrected $p <$

0.005 and cluster level whole brain FWE corrected $p < 0.05$. For region of interest (ROI) analysis, spherical ROIs (radius = 6 mm) were defined using coordinates of the each peak voxels identified as significantly different between pre- and post-task resting-states. Furthermore, in order to investigate ALFF changes in brain networks rather than specific brain regions, an independently network of interest (NOI) analysis was conducted by extracting and comparing mean ALFF values from 12 resting-state networks identified from previous literature (Zhu et al., 2013) at resting baselines before and after the PVT.

For the functional connectivity analysis, the posterior cingulate cortex cluster detected from the ALFF analysis was used as the seed region. For each subject, the mean BOLD fMRI signal time series was extracted from the seed and used as the regressor in the FC analysis. The correlation coefficients between the time series of the seed region and other brain areas were grouped into an individual FC map and transformed into z-score through a Fisher's r-to-z transformation to improve the normality of the correlation coefficients. These z-transformed individual FC maps were then entered into the second level group analysis using paired t-tests to compare functional connectivity between pre- and post-task resting scans. Threshold was defined at a significance level of voxel-wise uncorrected $p < 0.005$ and cluster level whole brain FWE corrected $p < 0.05$.

For the PVT task activation analysis, task images of each subject were realigned to correct for head motion, co-registered with the anatomical image, and smoothed in space using a three-dimensional 8-mm FWHM Gaussian kernel. A general linear modeling (GLM) with event-related design was used to model the preprocessed PVT task images and detect brain activations in response to the onset of each stimulus. Consistent with a previous study (Lim et al., 2010), a contrast was defined to compare the last 4-min quintile of PVT with the first 4-min quintile of PVT (PVTq5 vs. PVTq1). Threshold was defined as follows: voxel-wise uncorrected $p < 0.001$ and cluster level whole brain FWE corrected $p < 0.05$.

Results

PVT performance and ratings of fatigue

Subjects exhibited TOT effects during the 20-minute PVT. Median reaction time (RT) (repeated-measures ANOVA, $F(4,52) = 9.15$, $p < 0.001$; Fig.1a) and the number of lapses (errors of omission) increased across task time quintiles ($F(4,52) = 3.12$, $p = 0.02$). Post-hoc comparisons revealed that both median RT and number of lapses increased significantly from the first to last quintile ($p < 0.05$). However, the standard deviation (variability) of RT did not vary significantly across quintiles ($p > 0.3$). After the PVT, participants reported significantly higher mental fatigue ratings compared to pre-PVT ratings ($p = 0.023$, Fig.1b). There was no correlation between changes in median RT and changes in self-reported mental fatigue ($r = 0.22$, $p > 0.4$, Fig.1c). There was also no correlation between PSQI scores and changes in RT or self-reported mental fatigue ratings (all $p > 0.05$).

There were robust inter-individual differences in the change in performance across quintiles. The percentage changes in median RT from the first to last quintile (ratio = (Last Quintile – First Quintile) / First Quintile * 100%) ranged from –7.07% (improved performance) to 20.71%. Figure 1d shows the median RT of four subjects (two representatives as

“vulnerable” to TOT effects and two representatives as “resistant” to TOT effects) during each quintile.

Changes in ALFF

Consistent with our hypothesis, we found significant ALFF changes in DMN regions after the 20-min PVT. Specifically, ALFF was decreased in the posterior cingulate cortex (PCC) and right inferior parietal lobule (IPL)/angular, and was increased in the thalamus. Using a more liberal threshold of uncorrected $p < 0.005$, additional ALFF decreases were found in the medial prefrontal cortex (MePFC), left IPL/angular, left inferior frontal gyrus (IFG)/anterior insula, and left superior frontal gyrus (SFG), while additional ALFF increases were found in bilateral occipital lobe, left posterior insula, and left precentral gyrus (Table 1, Fig. 2a). Results from an independent resting-state network analysis are illustrated in Figure 3. This analysis showed significantly decreased ALFF in the DMN ($p = 0.008$) and increased ALFF in the visual network ($p = 0.034$) after the PVT, which partially confirm the findings from whole brain voxel-wise analysis.

We did not find observe significant correlations between ALFF changes in the DMN regions and changes in PVT performance (all $p > 0.05$). However, there was a trend for a positive correlation between changes of ALFF in the PCC and increases in RT ($r = 0.51$, $p = 0.063$, Fig.2c). Moreover, resting ALFF values assessed before the PVT in two regions of the DMN predicted subsequent PVT performance decline. Specifically, pre-PVT resting ALFF values in the PCC ($r = -0.57$, $p = 0.016$; Fig. 2b) and MePFC ($r = -0.67$, $p = 0.005$; Fig. 2b) negatively correlated with median RT changes from the first to last quintiles. That is, individuals with lower pre-PVT ALFF in the PCC and MePFC exhibited greater performance decline from the beginning to the end of the PVT.

There were no correlations between PSQI scores and PVT performance or ALFF changes (all $p > 0.05$). Pre-test ALFF values in the PCC and MePFC still significantly correlated with RT increases after covarying PSQI score (PCC: $r = -0.57$, $p = 0.022$; MePFC: $r = -0.67$, $p = 0.006$) or the first quintile RT (PCC: $r = -0.47$, $p = 0.049$; MePFC: $r = -0.67$, $p = 0.006$).

Changes in resting state functional connectivity

Compared to the pre-PVT test resting-state, functional connectivity was significantly higher between the PCC (the seed) and the right middle frontal gyrus (MFG) and left occipital lobe and was significantly lower between the PCC (the seed) and the left superior temporal gyrus (STG) during the post-PVT test resting-state (Fig.4a, Table 2). ROI analysis showed that increased connectivity between the PCC and the right MFG was due to reduced anti-correlations between these two regions (Fig.4b).

Changes in PVT task activation

Multiple brain regions showed activation increases during the last quintile compared to the first quintile of the PVT, including bilateral MFG, MePFC, supplementary motor area (SMA), right thalamus/caudate, left occipital cortex, and left precentral cortex (Table 3, Fig 5a). No brain regions showed decreases in activation during the last quintile compared to the

first quintile of the PVT. There was a trend for a negative correlation between changes in MFG activation and RT increases ($r = -0.48$, $p = 0.079$, Fig 5b).

Discussion

Using resting-state BOLD fMRI, the present study aimed to examine resting brain function changes associated with TOT effects. Consistent with previous studies (Lim et al., 2012b; Lim et al., 2010; Sun et al., 2014b), subjects exhibited slower reaction times and more lapses at the end of the PVT than at the beginning, and reported greater mental fatigue ratings after completing the task. After the PVT, significantly decreased ALFF was found in several core regions of the DMN, including the PCC, IPL/angular, and the MePFC, supporting our hypothesis that TOT effects impair resting spontaneous activity in the DMN.

These findings differ from the previous study (Lim et al., 2010) which used ASL perfusion fMRI but did not observe CBF changes in the DMN regions after a 20-min PVT. This inconsistency may due to the different signal measured by CBF and ALFF. Although CBF and ALFF are highly correlated and both related to regional neural activity (Li et al., 2012a; Zhu et al., 2013), CBF reflects a quantitative and absolute rate at which blood flows through the microvasculature of a region of tissue, whereas ALFF reflects a relative power (amplitude) of low-frequency oscillation of the BOLD signal during resting scans. These findings suggest that TOT may affect fluctuations in the DMN spontaneous activity but not its absolute level.

Pre-test resting baseline ALFF values in two core DMN regions (the PCC and the MePFC) negatively correlated with subsequent performance decline (reaction time slowing). These findings suggest that subjects with greater resting-state ALFF values in these DMN regions prior the sustained attention test (PVT) were more resistant to TOT effects. Because the DMN is a task-negative network with reduced activity during task performance, one possible explanation is that individuals with higher resting DMN ALFF may have greater flexibility and more brain resources to reallocate from the task-negative network to the task positive network when performing a mental demanding task. Failure to reallocate resources from the DMN may contribute to performance decrement, as indicated by the trend for a positive correlation between change in PCC ALFF and reaction time. This explanation is further supported by the trend for a negative correlation between MFG activation increases and reaction time increases during the sustained attention task, which indicates that subjects with greater brain activation increases in the task-positive network were more resistant to the TOT effects. Increased brain activations from the first to last quintile of the PVT are also consistent with previous studies showing that enhanced brain activation or recruitment of additional neural resources may provide a compensatory mechanism to help people maintain normal cognition (Elman et al., 2014; Witiuk et al., 2014).

In addition to ALFF and task activation changes, we also observed significant functional connectivity changes after the 20-min PVT. Functional connectivity was increased between the PCC and MFG and occipital lobe, but was decreased between the PCC to temporal cortex after prolonged sustained attention workload. Since the MFG is one core region of the fronto-parietal attention network that is anti-correlated with the DMN, the increased PCC-

MFG connectivity reflects a reduced negative correlation between these two regions, which was confirmed by the ROI analysis. This finding supports our hypothesis that TOT effects affect the balance between the task-negative DMN and task-positive attention network. Previous studies have suggested that these two networks comprise a competing brain system that regulates and sustains essential brain functions (Fox et al., 2005; Vincent et al., 2008). Greater anti-correlation between the DMN and the task-positive attention network has been associated with more reliable behavioral performance (Kelly et al., 2008), while failure to suppress DMN activity during tasks has been associated with attention lapses (Weissman et al., 2006). Our findings are consistent with these studies and support the important role of both task-positive and task-negative networks in TOT effects. Our results also add to the increasing literature showing that resting brain functions are linked to individual differences in cognitive function and behavioral performance, including visual cognition and attention (Cellini et al., 2013; Zhang et al., 2009; Zhu et al., 2011; Wang et al., 2013), memory recall (Cao et al., 2014; Zou et al., 2013), language processing (Li et al., 2013a; Wei et al., 2012), and decision-making (Li et al., 2013b).

The finding that impaired resting-state DMN spontaneous activity and connectivity are associated with TOT effects and mental fatigue may have clinical implications. Fatigue is a universal experience in both normal and clinical populations and a common symptom of multiple diseases (Carter et al., 1993; Bonner et al., 2013; Fabbri et al., 2013; Ghajarzadeh et al., 2013). Recent studies have identified DMN dysfunction in some clinical populations in which fatigue symptoms are pervasive. For example, mental fatigue (e.g., difficulty concentrating) is a common symptom in major depressive disorder, and these patients show dysfunction in the DMN (Orosz et al., 2012; Stahl et al., 2003). Tiredness and fatigue are also frequently reported in Alzheimer's disease (Roepke et al., 2009; Teel and Press, 1999), and these patients exhibit reduced spontaneous activity in the DMN (Buckner et al., 2005). However, future studies are needed to further determine the association between fatigue symptoms and DMN dysfunction in these clinical populations.

ALFF in the thalamus and visual cortex was increased after the 20-min PVT. The thalamus is tightly connected to the visual cortex and plays a key role in regulating arousal and awareness level (Thomas et al., 2000). Increased thalamic activity may reflect a compensatory effort to maintain normal brain function and alertness after prolonged task demand and fatigue, which is consistent with findings from previous sleep deprivation studies (Portas et al., 1998; Tomasi et al., 2009). Greater thalamic activation has been consistently reported in sleep-deprived subjects after sleep deprivation compared to those after normal sleep (Ma et al., 2015). Thalamic activation was inversely correlated with parietal and prefrontal activation after sleep deprivation; suggesting that increased thalamic activation is needed to compensate for decreased parietal activation in order to complete tasks (Tomasi et al., 2009). In addition, a recent study comparing the deleterious effects of sleep deprivation and TOT on sustained attention found that sleep deprivation and TOT may have shared neural and psychological causes (Asplund and Chee, 2013).

There are several limitations of this study. First, the study did not include a control condition in which subjects would be scanned during the same protocol without a prolonged attention task. Thus we cannot completely exclude the possibility that other factors, such as staying in

an fMRI scanner and/or habituation to the experimental environment, may contribute to the observed ALFF and connectivity changes in the current study. However, previous studies (for a review, see Zuo and Xing, 2014) showed no significant changes in ALFF or connectivity during repeated resting-state fMRI scans within a scan session and demonstrated high test-retest reliability of ALFF and connectivity, suggesting that significant DMN function changes observed in this study are likely due to engaging in the sustained attention task rather than staying in the fMRI scanner and/or habituation to the experimental environment. Second, in order to minimize the potential interference from time-of-day variations, we scanned all subjects in the afternoon between 1-5pm. Although this is a strength of the study, the current findings may not be generalized to other times of the day such as on the morning and evening, since previous studies have demonstrated significant circadian effects on brain activity and showed differential brain activations during the afternoon compared to other times of the day (Baehr et al., 2000; Goel et al., 2013; Kerkhof and Van Dongen, 1996). Future studies are needed to validate these findings on other times of the day and further examine how time-of-day may interact with prolonged cognitive workload to impact performance. Finally, our sample is a cohort of healthy young adults with a small age range. Therefore the current findings cannot be generalized to older adults and patients with clinical diseases. Future studies are needed to examine the neural correlates of cognitive fatigue and performance decline in older adults as well as clinical populations.

In summary, this study used resting-state fMRI and revealed significant changes in default mode network spontaneous activity and connectivity after a 20-minute continuous psychomotor vigilance test. In addition, pre-test resting-state activity in two core regions of the DMN predicted subsequent performance decline during the test. These findings support the important role of the DMN in mediating time-on-task effects and suggest that resting brain function may be a marker of performance potential and susceptibility to mental fatigue. Impaired DMN spontaneous activity and connectivity also provides a plausible mechanism for understanding fatigue symptoms in multiple brain diseases and mental disorders like depression and Alzheimer's disease.

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Highlights

- A continuous sustained attention task induces significant Time-on-task (TOT) effects.
- TOT effects reduce resting spontaneous activity in the default mode network (DMN).
- TOT effects impair the balance between the DMN and attention network.
- Pre-test DMN spontaneous activity predicts performance decline during the task.
- Impaired DMN function may be associated with fatigue symptom in multiple diseases.

Figure 1.

Time-on-task effects during a 20-minute psychomotor vigilance test. (a) Median reaction time (RT, msec) increased as the task progressed and subjects exhibited significantly slower reaction times during the last quintile compared to the first. (b) Mental fatigue ratings (on a 9-point scale) increased significantly after the PVT. (c) Changes in median RT did not correlate with changes in self-reported mental fatigue. There were individual differences in the response to prolonged workload; the change in median RT (ratio = (Last Quintile – First Quintile) / First Quintile * 100%) ranged from –7.07% to 20.71%; four representative subjects are shown in (d), two who were vulnerable to the TOT effects of the PVT and two who were resistant to the TOT effects of the PVT. Error bar represents standard error. * $p < 0.05$.

Figure 2.

(a) Comparison between post- and pre-PVT resting states revealed significant ALFF changes in multiple brain regions. Blue-green colors indicate regions that exhibited resting-state ALFF decreases after the PVT and red-yellow colors indicate regions that exhibited resting-state ALFF increases after the PVT. The display threshold was set as uncorrected $p < 0.005$. (b) Pre-PVT resting-state ALFF in the posterior cingulate cortex (PCC) and medial prefrontal cortex (MePFC) were negatively correlated with the change in median RT on the PVT (ratio = (Last Quintile – First Quintile) / First Quintile * 100%). (c) There was a trend for a positive correlation between the change in ALFF in the PCC and the change in median RT on the PVT (ratio = (Last Quintile – First Quintile) / First Quintile * 100%).

Figure 3.

Resting-state ALFF values in 12 resting-state networks before and after the 20-min PVT. ALFF was decreased in the DMN and increased in the visual network after the PVT. Error bar represents standard error. * $p < 0.05$.

Figure 4.

(a) Comparison between post- and pre-PVT resting states revealed significant functional connectivity changes between the PCC and multiple brain regions. Blue-green colors indicate regions that exhibited resting connectivity decreases after the PVT and red-yellow colors indicate regions that exhibited resting connectivity increases after the PVT. The display threshold was set as uncorrected $p < 0.005$. (b) Region-of-interest analysis showed reduced anti-correlations between the PCC and the right MFG during the post-PVT resting state compared to pre-PVT resting state.

Figure 5.

(a) Comparison between the last and first quintile of the PVT revealed significant activation increases in multiple brain regions. Red-yellow colors indicate regions that exhibited activation increases during the last quintile. The display threshold was set as uncorrected $p < 0.001$. (b) There was a trend for a negative correlation between the change in MFG activation and the change in median RT on the PVT (ratio = (Last Quintile – First Quintile) / First Quintile * 100%).

Table 1

Brain areas showing significant ALFF changes at resting-state after a 20-min PVT compared to the resting-state before the PVT. L., left; R., right; B., bilateral.

Region	Cluster Size	MNI Coordinates			Peak <i>p</i> uncorrected	Peak <i>Z</i>	<i>T</i>
		<i>x</i>	<i>y</i>	<i>z</i>			
ALFF decreases							
B. PCC, Precuneus	347	12	-69	48	<0.001 [*]	4.14	-6.16
R. IPL/Angular	65	57	-54	27	<0.001 [*]	3.57	-4.78
B. MePFC	20	3	51	21	<0.001	4.04	-5.89
L. IPL/Angular	50	-57	-33	30	<0.001	3.89	-5.52
L. IFG/ Insula	39	-30	6	15	<0.001	3.97	-5.70
L. SFG	22	-6	24	57	<0.001	3.49	-4.61
ALFF increases							
B. Thalamus	138	6	-3	9	<0.001 [*]	4.20	6.33
R. Occipital	25	6	-96	-6	<0.001	3.50	4.63
L. Occipital	30	-42	-81	-18	<0.001	3.58	4.81
L. Insula	25	-39	-30	15	<0.001	3.22	4.08
L. Precentral	20	33	-24	66	<0.001	3.06	3.79
L. Precentral	27	-36	-3	57	<0.001	3.97	5.70

* These clusters survived the whole brain FWE corrected $p < 0.05$.

Table 2

Brain areas showing significant resting-state functional connectivity (RSFC) (PCC as a seed ROI) changes at resting-state after a 20-min PVT compared to the resting-state before the PVT. L., left; R., right; B., bilateral.

Region	Cluster Size	MNI Coordinates			Peak <i>p</i> uncorrected	Peak <i>Z</i>	<i>T</i>
		<i>x</i>	<i>y</i>	<i>z</i>			
RSFC increases							
R. MFG	85	33	54	36	<0.001 [*]	3.99	5.75
L. Occipital	117	−39	−90	9	<0.001 [*]	4.12	6.11
RSFC decreases							
R. Temporal	130	57	−12	6	<0.001 [*]	3.98	−5.73

* These clusters survived the whole brain FWE corrected $p < 0.05$.

Table 3

Brain areas showing significantly increased activation during the last quintile compared to the first quintile in PVT task. L., left; R., right; B., bilateral.

Region	Cluster Size	MNI Coordinates			Peak <i>p</i> uncorrected	Peak <i>Z</i>	<i>T</i>
		<i>x</i>	<i>y</i>	<i>z</i>			
R. MFG	94	39	48	36	<0.001 [*]	4.42	6.95
L. MFG	74	-39	45	33	<0.001 [*]	4.12	6.11
L. Occipital	63	-36	72	12	<0.001 [*]	4.56	7.40
R. SMA	216	0	6	66	<0.001 [*]	4.54	7.33
R. Thalamus	176	15	-21	15	<0.001 [*]	4.50	7.20
L. Precentral	66	-36	-6	51	<0.001 [*]	4.09	6.02
R. SFG	64	0	27	42	<0.001 [*]	4.01	5.80

* These clusters survived the whole brain FWE corrected $p < 0.05$.