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Functional cortical connectivity analysis of mental fatigue unmasks hemispheric asymmetry and changes in small-world networks

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ABSTRACT

Changes in functional connectivity across mental states can provide richer information about human cognition than simpler univariate approaches. Here, we applied a graph theoretical approach to analyze such changes in the lower alpha (8–10 Hz) band of EEG data from 26 subjects undergoing a mentally-demanding test of sustained attention: the Psychomotor Vigilance Test. Behavior and connectivity maps were compared between the first and last 5 min of the task. Reaction times were significantly slower in the final minutes of the task, showing a clear time-on-task effect. A significant increase was observed in weighted characteristic path length, a measure of the efficiency of information transfer within the cortical network. This increase was correlated with reaction time change. Functional connectivity patterns were also estimated on the cortical surface via source localization of cortical activities in 26 predefined regions of interest. Increased characteristic path length was revealed, providing further support for the presence of a reshaped global topology in cortical connectivity networks under fatigue state. Additional analysis showed an asymmetrical pattern of connectivity (right > left) in fronto-parietal regions associated with sustained attention, supporting the right-lateralization of this function. Interestingly, in the fatigue state, significance decreases were observed in left, but not right fronto-parietal connectivity. Our results indicate that functional network organization can change over relatively short time scales with mental fatigue, and that decreased connectivity has a meaningful relationship with individual difference in behavior and performance.

1. Introduction

Working a long day at the office or studying hours for an exam are everyday experiences that can induce high levels of mental fatigue. Just as physical fatigue may involve the over-taxation of the muscular or cardiovascular system, mental fatigue has been associated with excessive demands on cognitive systems (Grier et al., 2003), leading to a putative strain on finite neural resources (Helton & Russell, 2011; Warm, Parasuraman, & Matthews, 2008). This fatigue is, of course, experienced subjectively, but is also often accompanied by worsening performance on cognitive tasks, seen in an increased propensity for errors and slowed reaction times (Davies & Parasuraman, 1982). Collectively, these objective declines are known as the effects of time-on-task (TOT). TOT-related effects have been implicated in on-the-job lapses in industries where workers are required to work long periods without rest (Tucker, Folkard, & Macdonald, 2003), leading to lowered productivity and increased safety risks. Because of these undesirable consequences, efforts have been made to understand the psychological and neural correlates of those vulnerable to TOT effects, with the ultimate aim of reducing human error in real-world situations (Lal & Craig, 2001).

In the laboratory, tests of sustained attention have been particularly amenable to studies of the TOT effect because of their reliability and validity. Moreover, the neural mechanisms associated with sustained attention are fairly well understood. Previous neuroimaging studies of sustained attention have uncovered a network of regions associated with arousal and attention, including a top-down right-lateralized network of fronto-parietal regions (Cohen et al., 1988; Corbetta & Shulman, 2002; Coull, Frackowiak, & Frith, 1998), and areas providing bottom-up input such as the thalamus and basal forebrain (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Kinomura, Larsson, Gulyas, & Roland, 1996; Portas et al., 1998). As TOT increases, cerebral blood flow in the former (top-down) network of areas tends to decrease (Lim, Wu, et al., 2010; Paus et al., 1997), possibly reflecting a

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depletion of neural resources, or an inability to retrieve these resources (Langner, Willmes, Chatterjee, Eickhoff, & Sturm, 2010).

TOT-related changes have also been detected via the use of EEG, with a large number of studies reporting increases in lower alpha and theta band power with increasing levels of fatigue (Boksem, Meijman, & Lorist, 2005; Craig, Tran, Wijesuriya, & Nguyen, 2012; Paus et al., 1997). Progressive increases in the 6–10 Hz band have specifically been implicated with decreasing arousal and alertness during periods when the attentional system is challenged (for reviews, see (Klimesch, 1999; Oken & Salinsky, 1992)). Event-related desynchronization in the lower alpha band also reflects alerting and expectancy in tasks with high demands on attention (Klimesch, Doppelmayr, Russegger, Pachinger, & Schwaiger, 1998).

While the studies summarized above have been useful in identifying neural markers of cognitive fatigue, they have not addressed the issue of whether the integrity of the cortical network as a whole is preserved, due to the fact that analyses are usually carried out in a univariate fashion. For example, little is known about whether the connectivity of brain networks changes with increasing TOT, or if its effects are confined to circumscribed areas of the brain. To date, most EEG and fMRI studies of cortical connectivity associated with mental fatigue have used approaches such as psychophysiological interaction (PPI) (Friston et al., 1997) or dynamic causal modeling (Friston, Harrison, & Penny, 2003) to generate testable hypotheses about communication within neural networks. Such approaches typically depend on *a priori* knowledge of the function of relevant brain areas in order to select seed regions and time courses. As a result, only a subset of the available data is typically used, and the richness of information in a whole-brain dataset is not exploited. Moreover, hypothesis-driven methods may also discard interesting information about phase and directionality when assessing network coupling.

One particular question that has not been adequately addressed using multivariate approaches is whether connectivity changes are associated with individual differences in performance under conditions of fatigue. This is important as previous studies have reported substantial between-subject variability in susceptibility to TOT (Parasuraman & Jiang, 2012), as well as moderate stability in one's individual level of vulnerability to these effects (Lim et al., 2012). Fatigue detection algorithms have not yet taken advantage of connectivity information to measure this brain state, making this a potentially rich area of exploration for developers of these tools.

In the current experiment, we utilized a relatively novel method of studying cortex-wide connectivity known as complex network analysis (Bullmore & Sporns, 2009), a powerful set of techniques based on graph theory that captures the features of brain networks using a small number of valid and reliable measures (Deuker et al., 2009; Giessing, Thiel, Alexander-Bloch, Patel, & Bullmore, 2013). One such key feature of the brain connectome is that it displays small-world characteristics (Watts & Strogatz, 1998); that is to say, most of its nodes maintain a small number of direct connections while remaining linked to all other nodes by a relatively short path length. Importantly, this approach allows one to assess the robustness of topological features of the brain after undergoing trait- or state-like changes. It is also believed that the small-worldness reflects the brain's ability to efficiently integrate information and select appropriate responses when confronted with the complex demands of the external environment, as evidenced by the fact that its loss occurs under conditions of reduced consciousness (Uehara et al., 2013) or neuropathology (Micheloyannis et al., 2006; Stam, Jones, Nolte, Breakspear, & Scheltens, 2007; Stam et al., 2009). In a couple of recent experiments, this approach has also been applied to fMRI data of TOT and attentional declines (Breckel et al., 2013; Giessing et al., 2013), with these studies reporting decreases in network clustering and efficiency over time.

Our objective in the present work was thus to use complex network analysis to investigate the changes in brain connectivity associated with TOT declines. We applied this method to event-related potentials time-locked to stimuli in the Psychomotor Vigilance Test (PVT), a challenging test of sustained attention (Dinges et al., 1997; Dorrian, Rogers, & Dinges, 2005). Data analysis, presented in this study, is restricted to EEG activity in the 8–10 Hz band, due to the known association of this bandwidth with sustained attention (Klimesch, Doppelmayr, et al., 1998; Klimesch, Russegger, Doppelmayr, & Pachinger, 1998). To obtain information on the spatial extent of connectivity changes, we also performed source localization on the high-resolution EEG data and created cortical connectivity maps in the fatigued and non-fatigued state. Based on prior imaging research on sustained attention (Lim, Wu, et al., 2010), we developed the following hypotheses: (i) that mental fatigue would be associated with a breakdown of the small-world organization of the brain (as seen in lower clustering and longer path lengths), (ii) that these network differences would be correlated with declines in task performance, and (iii) that mental fatigue would specifically be associated with a decoupling of frontal from posterior cortical regions, signifying a decay in top-down control, and that these differences would show hemispheric asymmetry owing to the lateralization of processes associated with sustained attention.

2. Methods and materials

2.1. Subjects

Participants for this study were 32 right-handed students and staff members (15 males) recruited from the National University of Singapore. All subjects reported normal or corrected-to-normal vision and were aged between 20 and 25 years (mean age 22.2 ± 1.5 years). These subjects were recruited from a pool of participants who had previously performed the Psychomotor Vigilance Test (PVT) as part of a genetic study (Lim et al., 2012). All subjects were pre-screened via a short telephone interview to ensure that they met all inclusion criteria in the present study. We excluded subjects who admitted to chronic physical or mental illness, had been diagnosed with a sleep disorder or childhood history of ADHD, or who were taking long-term medication. Subjects were required to obtain a full night (>7 h) of sleep for the 2 nights prior to the study to refrain from consuming caffeine or alcohol and not undertake strenuous exercise for the 6 h preceding the study. The investigation was approved by the Institutional Review Board of the National University of Singapore. Participants gave informed consent prior to the start of the experiment and were reimbursed $20 for their participation.

2.2. PVT paradigm and procedure

The details of the experiment have been described previously (Lim et al., 2012). Upon arriving at the lab, subjects were required to provide self-reports of their sleep history and alcohol/medication use over the previous 48 h. Those who did not fulfill these requirements were either rejected from the experiment or rescheduled. Subjects were then prepared to undergo EEG recording before performing a single bout of the PVT in a sound-attenuated room. The PVT is a simple reaction time test that is mentally demanding because of its high stimulus-load (Fig. 1). During the test, subjects were required to monitor a small box subtending approximately 4.1 (width) $\times$ 1.2° (height) of visual angle for the appearance of a millisecond counter, whereupon they responded with a button press on the keyboard (space bar) as quickly as possible. The