The Fatigued Brain: Fatigue and Cognitive Functions in Young Adults

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2015

document version
Publisher's PDF, also known as Version of record

CHAPTER FOUR

The Fatigued Brain: Associations of Chronic Fatigue and Acute Mental Fatigue on Resting-State Functional Connectivity

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ABSTRACT

Fatigue is common among medical students and it is associated with impaired cognitive functions. In the present study we used fMRI to investigate intrinsic brain function associated with fatigue in medical students. We compared medical students with and without chronic fatigue (*N* = 25 per group, all females, mean age = 22 years). In addition, we manipulated acute fatigue and compared the groups on effects of a fatigue inducing session and a non-fatiguing control session. We investigated whole brain functional connectivity and targeted the default mode network (DMN) and all networks that covered areas specifically associated with executive function and attention. Our results showed that chronically fatigued students were characterized by reduced resting state functional connectivity in the DMN, ventral stream network and dorsal attention network. Moreover, the anterior and posterior DMN were less widespread in chronically fatigued students (as indicated by a significantly lower number of supra-threshold voxels). The DMN and ventral stream network also showed functional connectivity changes in response to the fatigue manipulation. This manipulation affected the groups differently on functional connectivity in the right frontoparietal network. Based on these results, we conclude that fatigue in medical students involves functional organization changes that are possibly linked to reductions in a broad range of cognitive control functions. Further research should provide more insight into the nature of this link.

INTRODUCTION

In medical student populations, fatigue is a common phenomenon (Plukaard, Van Batenburg-Eddes, Vos, Croiset, & Jolles, submitted; Tanaka, Fukuda, Mizuno, Kuratsune, & Watanabe, 2009; Tanaka, Mizuno, Fukuda, Shigihara, & Watanabe, 2008). Eventually, fatigue can adversely affect academic development, since it is associated with reduced academic performance (Nagane, 2004). Also, associations between fatigue and burnout (Galán, Sanmartín, Polo, & Giner, 2011; Guthrie et al., 1998) or depression (e.g., Bozoky & Corwin, 1994; Lavidor, Weller, & Babkoff, 2002; ter Wolbeek, van Doornen, Kavelaars, & Heijnen, 2006) indicate that fatigued students may be at risk for more severe mental health problems. There are several indications for compromised cognitive processes associated with fatigue (see DeLuca, 2005). However, research into the neural basis of fatigue is scarce, especially in healthy, young and intelligent individuals such as medical students. The current study investigated fatigue-related differences in intrinsic brain function in medical students by comparing students with and without chronic fatigue ("chronic" in this study refers to persisting for at least 2 months). Spontaneous brain activity was examined after a cognitively demanding manipulation and after a non-demanding control manipulation. The goal of this manipulation was to investigate whether chronically fatigued and non-fatigued students would respond differently to cognitively challenging situations that increase acute fatigue.

The Multiple Sclerosis (MS) Council defined fatigue as a perceived lack of mental or physical energy that interferes with desired activities (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998). In general, fatigue has been attributed to a variety of causes, such as disease, lack of sleep, unhealthy lifestyle and stress, which renders it a non-specific phenomenon (Leavitt & DeLuca, 2010). Neuroimaging studies have related fatigue to increased neural effort (DeLuca, Genova, Capili, & Wylie, 2009). Excessive effort may disrupt the balance between invested energy demands and reward benefits, which is suggested to underlie the experience of fatigue (Boksem & Tops, 2008; Chaudhuri & Behan, 2000; Dobryakova, DeLuca, Genova, & Wylie, 2013). Neural changes associated with fatigue have been attributed to inefficient processing or compensatory

increases in neural effort. Because such changes were not always accompanied by behavioral changes (Deluca, Genova, Hillary, & Wylie, 2008; Kohl, Wylie, Genova, Hillary, & Deluca, 2009), neuroimaging proved to be a valuable instrument to measure fatigue-related differences.

The vast majority of neuroimaging research into fatigue focused on specific task-related brain processes. However, fatigue commonly persists over time (e.g., Mizuno, Tanaka, Fukuda, Imai-Matsumura, & Watanabe, 2011; Viner et al., 2008) and can be transferred from one task to another (van der Linden & Eling, 2006; van der Linden, Frese, & Meijman, 2003; van der Linden, Frese, & Sonnentag, 2003). This suggests that effects of fatigue are not necessarily task-related. In a review, Fox & Raichle (2007) point out that spontaneous neuronal activity "consumes most of the brain's energy" (p. 700). It is thus conceivable that fatigue, which commonly refers to a lack of perceived energy (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998), is accompanied by changes in spontaneous activity of the brain.

Intrinsic brain function is typically studied by evaluating spontaneous fluctuations in the blood oxygenation level-dependent (BOLD) signal during resting-state functional magnetic resonance imaging (RS fMRI). When the BOLD signal in different areas of the brain fluctuates simultaneously, it is assumed that these areas are functionally connected (Horwitz, 2003). As such, higher correlations of BOLD signal fluctuations between areas indicate stronger functional connectivity (FC). The most commonly studied resting-state network (RSN; i.e., a network comprised of areas with strong FC) is the default mode network (DMN). The DMN is thought to represent internally driven thought processes such as mind wandering and considered important for maintaining a resting state (Fox et al., 2005; Greicius, Krasnow, Reiss, & Menon, 2003; Raichle et al., 2001). The DMN is typically deactivated during task performance and therefore also referred to as a task-negative RSN. Networks that are usually activated during task performance, and anti-correlated with the DMN, are so-called task-positive RSNs (e.g., Damoiseaux et al., 2006).

Changes in FC within RSNs have been related to fatigue in different contexts. For instance, reduced connectivity within the DMN is observed in patients suffering from mild traumatic brain injury (mTBI; Mayer, Mannell, Ling, Gasparovic, & Yeo, 2011) as well as MS (Bonavita et al., 2011). Both conditions are characterized by fatigue. Sämann et al., (2010) observed reduced FC in sleep deprived healthy volunteers in the DMN as well as its anti-correlated network, which was proposed to underlie behavioral effects of sleep deprivation. Fatigue may thus relate to reduced FC in both task-positive and task-negative RSNs. Such differences in intrinsic brain function could underlie cognitive impairments (Baldassarre, Lewis, Committeri, & Snyder, 2012; Broyd et al., 2009) that have also been associated with fatigue. Yet, it is unclear whether healthy participants with long-term fatigue compared to those without are characterized by RSN alterations. Therefore our first research question relates to differences in intrinsic brain activity between students with and without chronic fatigue complaints.

Sustained cognitive activity is commonly found to increase or induce feelings of fatigue (Boksem, Meijman, & Lorist, 2005; Evers, Klaassen, Rombouts, Backes, & Jolles, 2012; Klaassen et al., 2014; van der Linden, Frese, & Sonnentag, 2003). Previous studies have reported changes in RSNs due to preceding task performance (see Northoff, Qin, & Nakao, 2010 for a review). The second question in the current study therefore pertains to whether fatigue induced by a period of performance on challenging cognitive tasks alters subsequent RSN connectivity. A study by Pyka et al., (2009) reported increased DMN activity after a challenging working memory task. Although this might represent a neural correlate of cognitive fatigue, fatigue was not assessed in this study. In a study investigating effects of muscle fatigue, Peltier and colleagues (2005) observed reduced FC between the left and right motor cortex after 20 minutes of repetitive hand grips. According to the authors, these results indicate a "temporary disrupted state" in the motor cortices as a result of muscle fatigue. It is not yet clear whether a cognitive fatigue induction in medical students would lead to comparable alterations in networks that cover relevant domains, such as attention or executive control. Evers et al., (2012) investigated effects of a 1.5-hour sustained cognitive load intervention that increased

perceived levels of fatigue. They found that the intervention increased FC between several task-positive networks and areas outside of these networks. This study also showed that the effect of such an intervention on subsequent FC can differ between individuals; young participants showed increased FC and middle-aged participants showed decreased FC between a superior temporal area and the executive network. Similarly, it is plausible that students with and without fatigue would respond differently to a cognitively demanding manipulation, aimed at increasing cognitive fatigue. In this study we expected that students with chronic fatigue would be more vulnerable to effects of a fatigue induction, because their level of fatigue is more likely to exceed a certain threshold.

In the current study, we investigated a group of medical students with chronic fatigue and a group without fatigue. The groups were compared after a cognitively demanding manipulation, aimed at inducing (additional) fatigue, and after a non-demanding control manipulation (adopted from Evers et al., 2012). We selected seven RSNs that were considered functionally relevant based on earlier fatigue research and examined both the strength of FC and the distribution of these networks. Strength of FC was investigated within RSNs as well as between the RSNs and the rest of the brain. We hypothesized that the DMN and networks that play a role in attentional control are affected in fatigue. Based on the literature described above, we specifically expected that fatigue would be represented by reduced connectivity.

METHOD

Participants

A total of 50 female students took part in this study. Participants consisted of 25 chronically fatigued females (age range 19.0 – 30.6 years, *M* = 21.8, *SD* = 2.3) and 25 non-fatigued females (age range 18.8 – 28.2 years, *M* = 21.6, *SD* = 1.9). Two other participants, one from each group, were excluded due to equipment failure. All participants were right-handed and reported no history of medical, neurological or psychiatric disorder.

Participants were recruited from the medical student population of the VU University Medical Center Amsterdam. A survey was distributed among all students in the first three years of Medical College. Students who scored above 76 on the Checklist Individual Strength (CIS; Vercoulen et al., 1999) and reported fatigue complaints for longer than 2 months were selected for the *fatigue group*. The cutoff point of >76 indicates a fatigue level at which individuals are at risk of subsequent sickness absence (Bültmann et al., 2000). Students who scored below 65 on the CIS (i.e., the mean score of all survey respondents; *N* = 701) and reported no fatigue complaints were selected for the *control group*.

All participants gave written informed consent prior participation and received financial compensation. The study was approved by the Medical Ethics Committee of the VU University Medical Center Amsterdam.

Procedure

All participants visited the lab on three occasions: a 1.5 h. training-session on one day and two 3 h. test-sessions on two other days. The training session was scheduled within a week before the first test session and included administration of the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977), the CIS (once more), several neuropsychological tests that served to compare the groups on basic cognitive abilities, and practice versions of three MRI tasks that are not discussed in this paper. The test battery consisted of the 20-minute version of the Raven Advanced Progressive Matrices Test (RAPM; Raven et al., 1993; Hamel & Schmitmann, 2006) to assess non-verbal intelligence, the fourth version of the Peabody Picture Vocabulary Test (PPVT-IV; Dunn & Dunn, 2005) to assess verbal intelligence, the Letter Digit Substitution Task (LDST; Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006[a]) to assess information processing speed, the Concept Shifting Task (CST; Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006[b]) and the Stroop Color-Word Test (Stroop, 1935) to assess general cognitive flexibility.

The test sessions took place on weekend days with one or two weeks apart, and started at 14:00 or at 15:30 h. The test sessions commenced outside the scanner with a cognitively demanding fatigue manipulation in one session (i.e., *fatigue session*) and a non-demanding control manipulation in the other session (i.e., *control session*; the order of the sessions was counterbalanced). Apart from the manipulation, both test sessions were identical. The fatigue manipulation consisted of 20 minutes of mental arithmetic, followed by 20 minutes of brainteaser puzzles (such as arithmetic sequences and syllogisms), 20 minutes of a computerized Stroop task (Stroop, 1935) adopted from Evers and colleagues (Evers, Van der Veen, Jolles, Deutz & Schmitt, 2009) with extra auditory interference, and an N-back computer task (2- and 3-back) for 30 minutes (see also Klaassen et al., 2013 for details). The control manipulation consisted of reading magazines or watching documentaries for 1.5 h. (a collection of magazines and documentary style DVD's was provided). After the manipulation, the participants were transferred to the scanner as quickly as possible. The scan session started with a 6-minute RS scan during which the participants were instructed to lie still with their eyes closed, but to try not to fall asleep. The RS scan was followed by an anatomical scan and three tasks, results of which are described elsewhere.

Fatigue questionnaires

The CIS consists of 20 statements that measure different aspects of fatigue: fatigue severity (8 items, e.g., "I feel tired"); concentration (5 items, e.g., "my thoughts easily wander off"); motivation (4 items, e.g., "I'm looking forward to many fun things to do"); and physical activity (3 items, e.g., "I don't do much during the day"). Respondents rated how they felt during the previous two weeks. Responses were scored on a 7-point Likert scale, ranging from 1 "Yes, that is true", to 7 "No, that is not true". The sum of all items yields a fatigue score ranging from 20 to 140.

The fatigue scale of the Profile of Mood States (POMS; Wald & Mellenbergh, 1990; short version in Dutch) and the Rating Scale Mental Effort (RSME; Zijlstra, 1993) were administered to assess the effect of the manipulation. The scales were completed before

(T0) and after the manipulation (T1). The POMS contains five mood scales (fatigue, depression, vigor, tension and anger) that each consist of several adjectives to describe momentary mood states. Participants indicated their current mood on a 5-point Likert scale. Scores on the fatigue scale range from 6 to 30. The RSME contains seven visual analog scales (range: 0 – 150) that measure different aspects of fatigue, including required effort for focusing of attention, tiredness and boredom (e.g., "How much effort does it take to suppress feelings of boredom?"). The mean of the seven scales resulted in the total RSME score that ranged from 0 to 150.

fMRI data acquisition

Imaging data were collected on a GE Signa HDxt 3.0-Tesla MRI-scanner with an 8-channel head coil (General Electric, Milwaukee, Wisconsin) at the VU University Medical Center. Functional images were acquired with 34 slices in ascending order using a T2*-weighted echo planar imaging (EPI) sequence (repetition time (TR) = 1800 ms, echo time (TE) = 35 ms, flip angle (FA) = 80°, field of view (FOV) = 21.1 x 21.1 cm, voxel size = 3.3 x 3.3 x 3.3 mm). A T1-weigthed anatomical scan with 172 slices was acquired for co-registration and normalization (TR = 8.2 ms, TE = 3.2 ms, FA = 12°, FOV = 25.6 x 25.6 cm, voxel size = 1 x 1 x 1 mm).

fMRI data analysis

Imaging data were preprocessed with Statistical Parametric Mapping (SPM8; www.fil.ion.ucl.ac.uk/spm). Preprocessing comprised reorienting, followed by realignment and unwarping, slice time correction, coregistration, normalization into MNI standard space, reslicing to voxels of 3 x 3 x 3 mm, and spatial smoothing with an 8 mm full width at half maximum (FWHM) isotropic Gaussian kernel. The data were subsequently band pass filtered (between 0.01 and 0.08) with the 'Resting-State fMRI Data Analysis Toolkit' (REST version 1.3, by Song Xiaowei, http://restfmri.net/forum/?q=rest).

Next, independent component analysis (ICA) was performed on all data (groups and sessions collapsed) with the 'Group ICA Of fMRI Toolbox' (GIFT, v1.3i: http://icatb.sourceforge.net) using the Infomax algorithm. The number of components was restricted to 20. Out of the 20 components, we selected functionally relevant components that showed spatial similarities to functional networks described in earlier resting-state studies (Damoiseaux et al., 2006; Jolles et al., 2011). Based on earlier fatigue research, we considered the default mode network functionally relevant, as well as all networks that covered areas specifically associated with executive function and attention. Our selection (see Figure 2: A-G) comprised A: anterior default-mode network (aDMN); B: posterior default-mode network (pDMN); C: right frontoparietal network (rFPN); D: left frontoparietal network (lFPN); E: executive control network (ECN); F: ventral stream network (VSN); G: dorsal attention network (DAN); H: superior parietal network (SPN). The other 12 networks that were not selected included two visual networks, the auditory network, motor and sensorimotor networks, occipitoparietal network and networks related to cerebral spinal fluid, motion and other non-neuronal noise.

Subsequently, the components were back-reconstructed into subject and session specific component maps. Back-reconstruction involved extraction of individual time series for each component (based on spatial regression), which were then entered in a temporal regression to obtain the component maps per subject and session.

To investigate fatigue differences in the size of the functional networks, we calculated per component for each participant the number of activated voxels (i.e., voxels with $z > 1$; derived from the individual component maps). These numbers were analyzed in SPSS using mixed ANOVAs with session (fatigue and control) as dependent factor and group (fatigue and control) as independent factor.

Fatigue differences in strength of FC were examined in SPM8; for each network, the individual component maps were entered in mixed ANOVAs. Higher correlation values were interpreted as increased FC, since these correspond to stronger involvement of

these areas within the network. Differences were considered significant at $p < .05$, false-discovery rate (FDR) corrected and first investigated with whole brain (WB) analysis and second, with a small volume correction (SVC) based on the size of the respective network (i.e., voxels that survived the threshold of $p < .05$, FWE corrected for multiple comparisons across the whole brain across session and group).

RESULTS

Sample Characteristics

Table 1 displays the characteristics of the sample. The fatigue group scored significantly higher on all subscales of the CIS and reported higher levels of depression. Both groups scored similarly on all neuropsychological tests. The fatigue group showed more interference on the STROOP color word test, but this difference was not significant after a Bonferroni correction for multiple comparisons (the corrected alpha for 13 tests with a mean correlation coefficient of $\rho = .26$ was .0074929; http://www.quantitativeskills.com/sisa/calculations/bonfer.htm).

Table 1

Sample Characteristics

		Fatigue	Control	*p*
N		25	25	
Age		21.8 (2.4)	21.6 (1.9)	.985
CIS score	total*	84.8 (15.7)	39.7 (9.3)	<.001
	fatigue severity*	38.2 (7.2)	16.8 (5.2)	<.001
	concentration*	19.8 (6.2)	10.3 (3.9)	<.001
	motivation*	12.8 (4.2)	6.4 (1.7)	<.001
	physical activity*	14.1 (4.3)	6.3 (3.7)	<.001
CES-D*		13.6 (7.4) [a]	4.4 (3.5)	<.001
Hb (nmol/l)		8.4 (1.0) [b]	8.5 (0.7) [a]	.543
RAVEN		23.4 (3.1)	22.7 (3.7)	.390
PPVT		109.3 (7.3)	110.0 (6.9)	.977
LDST		45.4 (4.5)	46.5 (4.9)	.284
CST		6.1 (4.7) [a]	3.9 (3.5)	.139
STROOP interference		28.8 (9.3) [a]	23.1 (7.6)	.009

Note. * Indicates significant group difference with $p < .0038$ (Bonferroni correction).

[a] Data of 1 person is missing (N=24); [b] Data of 2 persons is missing (N=23).

Manipulation check

The effect of the manipulation on fatigue ratings is illustrated in Figure 1. We conducted a mixed repeated-measures ANOVA to analyze the RSME scores with *time of assessment* (T0, T1, T2) and *session* (fatigue, control) as within-subjects factors, and *group* (fatigue, control) as between-subjects factor. A significant interaction between time of assessment and session ($F(2,96) = 19.87$, $p < .001$) indicated that fatigue ratings increased more in the fatigue session compared to the control session. Post hoc *t*-tests confirmed that fatigue ratings differed significantly between sessions at T1 (i.e., higher fatigue ratings after the fatigue manipulation compared to the control manipulation; $t(49) = 6.51$, $p < .001$, $r = .34$) and not at T0 and T2 ($t(49) < 0.94$, $p > .351$, $r < .14$). Other significant

effects showed that overall, fatigue increased from T0 to T2 ($F(2,96) = 78.09$, $p < .001$, $r = .67$), fatigue ratings were higher in the fatigue session compared to the control session ($F(1,48) = 13.44$, $p < .001$, $r = .47$), and the fatigue group had higher subjective fatigue compared to the control group ($F(1,48) = 8.48$, $p = .005$, $r = .39$). A significant interaction between group and time of assessment ($F(2,96) = 5.89$, $p = .004$) indicated that across both sessions, the fatigue group showed a steeper increase in fatigue ratings from T0 to T2 compared to the control group. No other significant effects were observed ($F < 0.71$, $p > .492$).

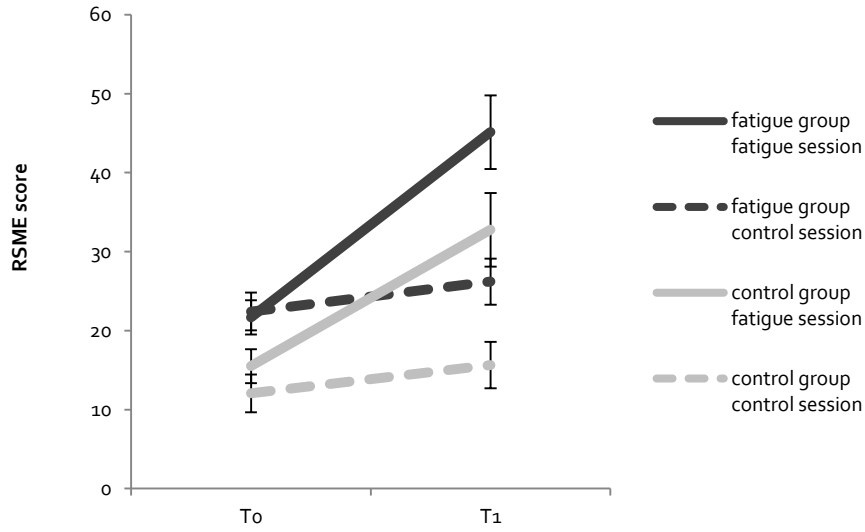

Figure 1. Fatigue scores assessed with the RSME at baseline (T0) and after the manipulation (T1). Dark gray represents the fatigue group and light gray represents the control group with solid lines for the fatigue session and dashed lines for the control session. For both scales, the scores differed significantly between sessions only at T1. Error bars show standard error of the mean (SEM).

Functional connectivity

Figure 2A-H displays the selected networks that were examined. First, we investigated differences in the size of the networks. The average number of voxels per group per session is depicted in Figure 3. Group x session ANOVAs showed that the aDMN and pDMN were significantly larger in the control group compared to the fatigue group (aDMN: $F(1,48) = 6.28$, $p < .05$, $r = .34$; pDMN: $F(1,48) = 5.31$, $p < .05$, $r = .32$). There were no effects of session, or interactions between group and session on the size of the RSN's.

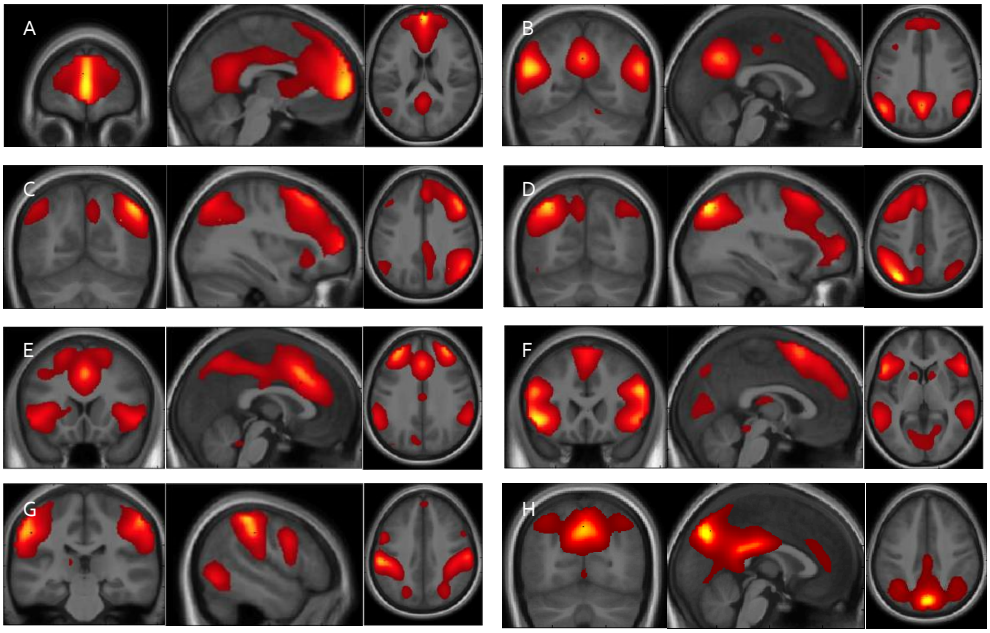

Figure 2. ICA group maps of the networks of interest. A: anterior default-mode network; B: posterior default-mode network; C: right frontoparietal network; D: left frontoparietal network; E: executive control network; F: ventral stream network; G: dorsal attention network; H superior parietal network.

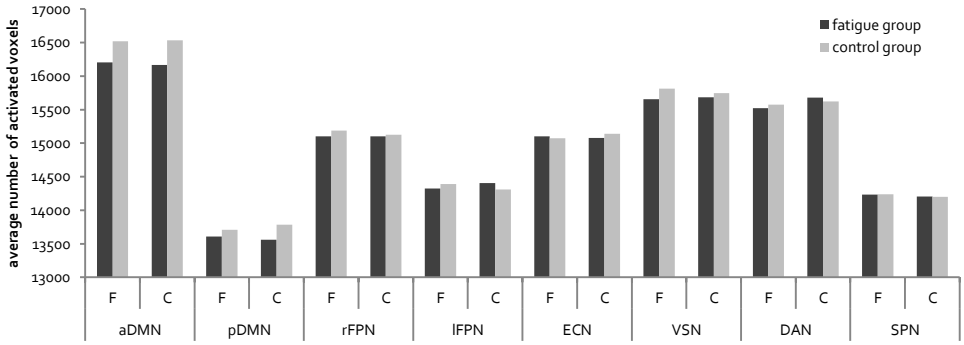

Figure 3. Average number of voxels for the fatigue group (dark gray) and the control group (light gray) for each of the selected resting-state networks in the fatigue (F) and control (C) session. aDMN = anterior default mode network; pDMN = posterior default mode network; rFPN = right frontoparietal network; lFPN = left frontoparietal network; ECN = executive control network; VSN = ventral stream network; DAN = dorsal attention network. The aDMN and pDMN were significantly larger in the control group compared to the fatigue group.

Next, we investigated differences in strength of FC for each of the RSNs. Group comparisons revealed decreased FC in the fatigue group compared to the control group in the pDMN, aDMN, VSN and DAN. Areas that were less involved in these networks in the fatigue group included the right superior temporal gyrus (STG), left anterior cingulate (ACC), left and right inferior parietal lobule (IPL), left middle frontal gyrus (MFG) and right middle temporal gyrus (MTG; Table 2).

Across the groups, increased FC within the aDMN (right insula) as well as between the VSN and left MFG was observed in the fatigue session compared to the control session.

An interaction between group and session was observed in the right precuneus as part of the right FPN. The control group showed increased connectivity, whereas the fatigue group revealed decreased connectivity within this area in the fatigue session compared to the control session (Figure 4).

Table 2

Fatigue-related differences in functional connectivity for the networks of interest

Network	Area	BA	x	y	z	*z*	k
Group main effect: control > fatigue							
pDMN	Superior Temporal Gyrus (SVC)	13	50	-44	28	4.16	47
	Inferior Parietal Lobule (SVC)	39	-42	-64	46	3.80	13
aDMN	Anterior Cingulate (SVC)	32	2	48	4	4.32	118
VSN	Inferior Parietal Lobule (SVC)	40	-62	-44	25	4.09	26
	Inferior Parietal Lobule (SVC)	40	62	-40	28	4.02	30
DAN	Inferior Parietal Lobule (SVC)	40	-54	-24	31	4.49	33
	Middle Frontal Gyrus (SVC)	6	-54	8	40	4.44	22
	Middle Temporal Gyrus (SVC)	37	58	-56	-8	3.75	36
Session main effect: fatigue > control							
aDMN	Insula (SVC)	13	50	-12	4	4.81	64
VSN	Middle Frontal Gyrus (WB)	6	-18	-12	52	4.70	27
Group x session interaction							
rFPN	Precuneus (SVC)	7	22	-72	43	4.05	24

Note. Coordinates are in MNI space. BA = Brodmann Area. pDMN = posterior default-mode network; aDMN = anterior default-mode network; VSN = ventral stream network; DAN = dorsal attentional network; rFPN = right frontoparietal network. All effects are significant at $p < .05$, FDR corrected. SVC = Small volume corrected, representing areas inside the RSN. WB = Whole brain analysis, representing areas outside of the RSN.

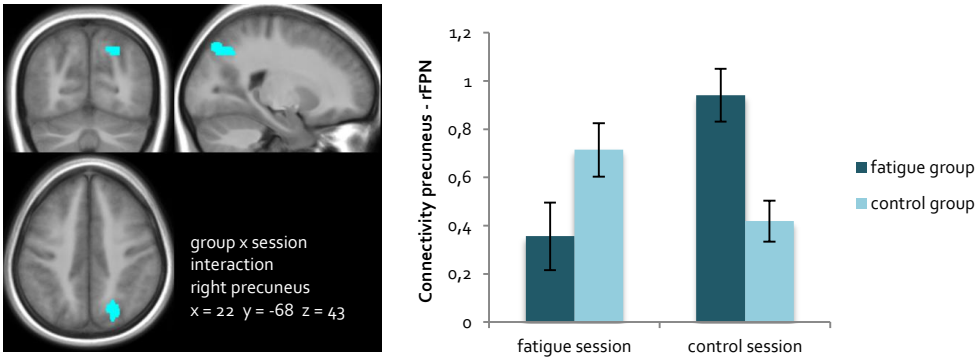

Figure 4. An interaction was observed in the right precuneus of the right frontoparietal network. Control participants increased functional connectivity after the fatigue manipulation within this area, whereas chronically fatigued participants decreased functional connectivity in response to the fatigue manipulation.

DISCUSSION

The goal of the present study was to investigate differences in RS FC between medical students with and without chronic fatigue. In addition, we evaluated effects of a cognitive fatigue inducing manipulation on subsequent RS FC in both groups. The principle finding of this study is that RS FC in chronically fatigued students deviates significantly from non-fatigued students. In line with our hypothesis, chronic fatigue was associated with reduced RS FC in several areas of the DMN, VSN and DAN. Moreover, the anterior and posterior DMN were less widespread in chronically fatigued students (as indicated by a significantly lower number of supra-threshold voxels). The cognitive fatigue manipulation resulted in stronger anterior DMN and VSN FC. An interaction between fatigue group and session was observed in the precuneus as part of the right FPN; chronically fatigued students showed reduced FC whereas non-fatigued students showed increased FC in this area in response to the cognitive fatigue manipulation.

Compared to their non-fatigued peers, chronically fatigued medical students showed decreased connectivity in multiple networks. Similar observations have resulted from studies related to the subject of fatigue, in which muscle fatigue (Peltier et al., 2005), medical conditions with excessive fatigue as main complaint such as mTBI (Mayer et al., 2011) or MS (Bonavita et al., 2011), and sleep deprivation (Sämann et al., 2010) all corresponded to reduced RS FC in functionally relevant neural networks. Previous work has revealed positive correlations between resting-state FC and subsequent task performance (Baldassarre et al., 2012). Moreover, reduced FC in nodes of the DMN is often associated with conditions that are characterized by cognitive dysfunction (Broyd et al., 2009). Therefore, weaker resting-state FC in DMN, VSN and DAN may reflect deficits in attention, executive control and internally driven thought processes. In other words, reduced FC in chronically fatigued students could indicate less effective cognitive functioning compared to non-fatigued students.

Differences in the size of the networks between the groups were only found in the anterior and posterior DMN; the DMN in non-fatigued students was more widely

distributed. In developmental studies, more diffuse patterns of brain activity or FC have been interpreted as less efficiently organized or less specialized brain function (Durston et al., 2006; Fair et al., 2009; Jolles, van Buchem, Crone, & Rombouts, 2011). Particularly in combination with weaker FC within these networks, more widely distributed networks would be a strong indication of less efficient and specialized brain organization in fatigue. Clearly, our results did not support this notion of more diffused functional organization. We therefore propose that the smaller size of the DMN in chronically fatigued students is a representation of the general reduction in FC. The fact that we only found a difference in size of the DMN and not in other RSNs indicates that FC reductions in chronic fatigue are most pronounced within this network.

The areas in which chronically fatigued students showed reduced FC (i.e., STG, ACC, IPL, MFG and MTG) have previously been associated with fatigue (Chaudhuri & Behan, 2004; Cook, O'Connor, Lange, & Steffener, 2007; Dobryakova et al., 2013; Lim, Wu, Wang, Detre, & Dinges, 2009). For instance, Calabrese et al., (2010) observed atrophy in the IPL and other regions in fatigued MS patients relative to non-fatigued patients. In the current study, the IPL appeared to play an important role, as this area showed reduced FC within multiple networks. This area is thought to underlie several cognitive functions such as multimodal integration and attention maintenance (see Singh-Curry & Husain, 2009). The IPL collaborates with DLPFC in attentional set-shifting, which is found to be affected by fatigue (Boksem et al., 2005; Plukaard, Huizinga, Krabbendam, & Jolles, 2015; Van der Linden, Frese, & Meijman, 2003). Reduced IPL, STG and ACC cerebral blood flow during rest have been observed after a fatiguing vigilance task (Lim, Wu, Wang, Detre, & Dinges, 2009). Over the last decade, ACC proved to be one of the key neural areas in fatigue (Chaudhuri & Behan, 2000; Chaudhuri & Behan, 2004; Cook, O'Connor, Lange, & Steffener, 2007; Dobryakova et al., 2013; Lorist, Boksem, & Ridderinkhof, 2005). ACC alterations in fatigue are commonly thought to represent differences in neural effort, suggesting a disrupted balance between invested effort and reward outcomes (Boksem & Tops, 2008; Chaudhuri & Behan, 2000; Dobryakova et al., 2013). The currently observed reduced ACC FC is another indication of deficient functionality of this region in fatigue.

The fatigue manipulation resulted in stronger FC in the aDMN and between the VSN and a cluster in the middle frontal gyrus (MFG). Altered RS FC following task performance has often been observed and generally attributed to learning effects (Albert, Robertson, & Miall, 2009; Lewis, Baldassarre, Committeri, Romani, & Corbetta, 2009; Stevens, Buckner, & Schacter, 2010; Tambini, Ketz, & Davachi, 2010; Waites, Stanislavsky, Abbott, & Jackson, 2005). The present result is in line with Pyka et. al., (2009), who also observed increased DMN FC following task performance. They attributed this increase either to evaluation of the preceding task or to a representation of recovery from preceding high cognitive demands. The current manipulation was adopted from Evers et al. (2013), who studied its effects in young and middle aged schoolteachers. Their results demonstrated increased FC between task positive networks and areas outside of these networks. Possibly, these areas were recruited during the demanding tasks of the manipulation, which resulted in additional functional connections to this network (as suggested by Fox & Raichle, 2007). Similarly, increased FC between the VSN and left premotor cortex in the present study may have resulted from recruitment of additional brain regions during the fatigue manipulation. In the computerized n-back and Stroop tasks, participants had to respond adequately based on fast evaluation of visual stimulus characteristics. We reason that such tasks may well have increased the coupling between premotor cortex and the VSN.

An interaction in the right FPN reflected increased FC in the precuneus in non-fatigued students in response to the fatigue manipulation, whereas the chronically fatigued students showed decreased precuneus FC. Increased FC within a task-positive network is in line with the aforementioned memory or learning effect following task performance. Chronically fatigued students showed the opposite effect; FC within the precuneus decreased after the fatigue manipulation. Possibly, the group of fatigued students differently engaged this area or employed other, less consistent, strategies during the fatigue manipulation, which resulted in decreased subsequent connectivity within the fronto-parietal circuit. The rFPN is typically engaged in sustained mental workload (Cabeza & Nyberg, 2000) and activation of areas in this network are positively correlated

with behavioral performance (Lawrence, Ross, Hoffmann, Garavan, & Stein, 2003). The present result indicated reduced connectivity within this network in chronically fatigued students in response to a period of demanding task performance, suggesting that sustained attentional control may be more easily affected in this group.

Conclusion

The results of the present study demonstrated functional differences at rest (i.e., while no specific cognitive task was performed) between chronically fatigued and non-fatigued students, between a demanding cognitive fatigue manipulation and a control manipulation, and it showed differential responses to this manipulation by students with and without chronic fatigue. While an fMRI task may indicate neural correlates of functions necessary for that particular task, these RS FC results indicate intrinsic organizational differences that may underlie a broader range of tasks. Future studies could focus on the potential link and perhaps directional effects between these network differences and cognitive performance.

In the present study, we analyzed between and within group differences in a total of eight networks. To minimize the risk of false positives, we used a conservative statistical threshold within each network (Bennett, Wolford, & Miller, 2009). Another limitation in this study refers to our study sample. We deliberately recruited a homogeneous sample of participants in terms of age, sex and educational background. This minimized potential noise due to these factors, but it also limited generalizability of the results. However, the results may be generalizable to others with comparable levels of educational background and who are encountered with high (environmental) demands.

Acknowledgments

The authors would like to thank Arnout de Groot and Gertjan M.J.J. Jong for their great assistance during the preparation and data collection of this study. This research was supported by a grant from The Netherlands Organization of Scientific Research (NWO 433-08-205).