The Fatigued Brain: Fatigue and Cognitive Functions in Young Adults

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CHAPTER FIVE

fMRI Correlates of Fatigue in Female Medical Students: Effects on Task Switching

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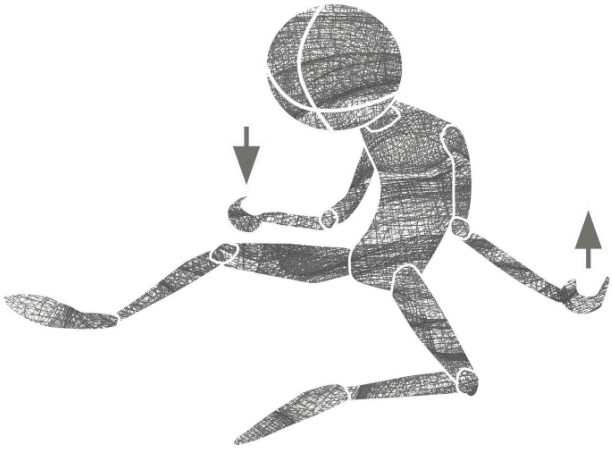
(submitted)



ABSTRACT

Fatigue is common among medical students and associated with impaired cognitive functions. In the present study we used fMRI to investigate underlying neural mechanisms of fatigue in medical students. We compared medical students with and without chronic fatigue (N = 26 and 25 resp., all females, mean age = 22 years) on behavioral performance and brain activation during task switching. In addition, we investigated effects of an acute fatigue manipulation. The groups were compared on effects of a fatigue inducing manipulation and a non-fatiguing control manipulation. The neuroimaging data showed that fatigued students were characterized by greater anterior cingulate cortex activation compared to their non-fatigued counterparts. This is taken to indicate that chronically fatigued students engage more evaluative monitoring and need more brain resources. No behavioral differences in task switching were found. A moderate positive correlation between ACC activation and RT switch cost indicated that performance decline was related to higher ACC monitoring. As to the fatigue manipulation, non-fatigued students showed elevated activity in the left dorsolateral prefrontal cortex, the left premotor cortex and precuneus after the fatigue manipulation. In contrast, fatigued students showed elevated activity in the same areas after the control manipulation, which decreased after the fatigue manipulation. These findings may have important implications as they suggest that fatigued students exert more attentional effort at baseline. As such, fatigued students perform at their capacity limits and fail to invest more effort in the demanding conditions of additional fatigue.

INTRODUCTION

Fatigue is a common complaint in medical students (Plukaard, Van Batenburg-Eddes, Vos, Croiset, & Jolles, submitted; Tanaka, Fukuda, Mizuno, Kuratsune, & Watanabe, 2009; Tanaka, Mizuno, Fukuda, Shigihara, & Watanabe, 2008) and may lead to more severe conditions such as burnout (Galán, Sanmartín, Polo, & Giner, 2011; Guthrie et al., 1998). Studies that investigated effects of fatigue on cognition show inconsistent results (e.g., Bryant, Chiaravalloti, & DeLuca, 2004; Claros-Salinas et al., 2013; DeLuca, Genova, Capili, & Wylie, 2009). Yet, many studies are compatible with the notion that fatigued subjects experience reduced cognitive control (Lorist, 2008). The present study examined differences in cognitive flexibility between medical students with and without fatigue. We defined fatigue as a multidimensional concept, including both physical and mental fatigue, persisting over a period of time (i.e., longer than 2 months; from now on referred to as 'chronic fatigue'). In addition, we subjected the students to an experimental manipulation to evaluate effects of an acute fatigue induction in both groups.

Fatigue in general refers to a perceived lack of energy (mental and/or physical) that interferes with desired activities (e.g., Multiple Sclerosis Council, 1998). Subjective fatigue states are common in people's daily lives and are usually ameliorated by a period of rest. In some individuals however, fatigue is not alleviated with rest and persists for a period of weeks or even months. This is typical in fatigue-related disease, such as multiple sclerosis (MS), traumatic brain injury, or chronic fatigue syndrome (CFS; e.g., DeLuca, Genova, Capili, & Wylie, 2009), but such complaints are also common in healthy populations (Bultmann et al., 2000; Plukaard et al., submitted; Tanaka et al., 2009; Tanaka et al., 2008; ter Wolbeek, van Doornen, Kavelaars, & Heijnen, 2006). Severe or persistent fatigue may hamper subjective well-being, engagement in social and leisure activities, work commitment and productivity, or academic performance (e.g., Breslin, 1998; Nagane, 2004; Ricci, Chee, Lorandeau, & Berger, 2007). As such, fatigue can have serious impact on the students' social and academic development, as well as their future careers.

Compromised cognitive performance is frequently reported as one of the most disabling symptoms of fatigue. However, subjective fatigue ratings and objective cognitive measures, such as task performance, do not correlate well (e.g., Bryant, Chiaravalloti, & DeLuca, 2004; Claros-Salinas et al., 2013; DeLuca, Genova, Capili, & Wylie, 2009). Other measures such as functional magnetic resonance imaging (fMRI), are sometimes more sensitive than behavioral performance to detect differences between groups (e.g., Dibbets, Bakker, & Jolles, 2006; Dibbets, Evers, Hurks, Bakker, & Jolles, 2010). Neuroimaging may therefore offer further insight into underlying cognitive mechanisms of fatigue. In fact, recent studies in patient populations associated fatigue with changes in terms of brain structure (Pardini, Capello, Krueger, Mancardi, & Uccelli, 2013; Pardini, Krueger, Raymont, & Grafman, 2010) as well as function (Cook, O'Connor, Lange, & Steffener, 2007; DeLuca, Genova, Hillary, & Wylie, 2008; Klaassen et al., 2013; Kohl, Wylie, Genova, Hillary, & Deluca, 2009). Fatigue-related differences in neural activity have been found even in the absence of (accuracy) performance differences (DeLuca et al., 2008; Kohl et al., 2009). To date, it is unclear whether fatigue in individuals from the general population is based on neural mechanisms similar to those found in patients. To address this issue, the current study used fMRI to investigate whether fatigue in medical students is accompanied by alterations in neural activation.

Typically, fatigued individuals experience much higher effort while performing mental or physical tasks (Chaudhuri & Behan, 2000). This is in line with evidence from clinical neuroimaging studies that related fatigue to increased mental effort. For instance, Cook et al. (2007) found enhanced neural activation in CFS patients compared to healthy controls in a wide range of areas during a challenging working memory task. These areas included the hippocampus, superior temporal and inferior frontal cortex. Similar findings were obtained in MS patients, who showed increased activation of the orbitofrontal cortex, superior parietal cortex and basal ganglia in response to a sustained attention task (DeLuca et al., 2008). Fatigue has been associated with impairments in cortico-striatal circuitry, in particular between the basal ganglia and prefrontal areas, including the dorsolateral PFC (DLPFC), the ventromedial PFC (VMPFC) and the anterior cingulate

cortex (ACC; Boksem & Tops, 2008; Chaudhuri & Behan, 2000; Chaudhuri & Behan, 2004; for a review see Dobryakova et al., 2013). According to this model, fatigue relates to abnormalities within this network, representing a disrupted balance between perceived energy demands (e.g., effort requirements) and outcome benefits (e.g., performance benefits or rewards; see also Boksem & Tops, 2008).

In non-clinical populations, there is likewise evidence for an association between fatigue and PFC functioning. In healthy individuals, fatigue can be induced by prolonged performance on a variety of tasks. Prolonged task performance may result in attenuation of the error related negativity (ERN) as well as the N2 event-related potential (ERP) components (Boksem, Meijman, & Lorist, 2006; Lorist, Boksem, & Ridderinkhof, 2005). Both ERP components are thought to originate from the ACC or at least rely on intact ACC functioning (Dehaene, Posner, & Tucker, 1994; Lange, Wijers, Mulder, & Mulder, 1998).

Cognitive decline associated with fatigue mainly involves processes with high demands on cognitive control. For instance, manipulation of fatigue state resulted in reductions in planning ability, cognitive flexibility (van der Linden, Frese, & Meijman, 2003; van der Linden, Frese, & Sonnentag, 2003), attention (Boksem et al., 2005; van der Linden & Eling, 2006) and error monitoring (Boksem, Meijman, & Lorist, 2006; Lorist et al., 2005). In contrast, automatic processes generally remain unaffected (Schellekens, Sijtsma, Vegter, & Meijman, 2000; van der Linden & Eling, 2006). An explanation for this dissociation is that cognitive control requires effort while automatic processes occur reflexively without effortful demands (Schneider & Shiffrin, 1977).

One of the processes that have been associated with fatigue is cognitive flexibility (Lorist et al., 2000; van der Linden, Frese, & Meijman, 2003). Cognitive flexibility refers to the ability to adaptively switch between changing environmental demands (Monsell, 2003). This ability relies mainly on cognitive control and is crucial for learning and the acquisition of new skills. A typical task to investigate this ability is the task switching paradigm, in

which participants are required to switch between two or more simple task sets (Monsell, 2003). Lorist and colleagues (2000; 2009) showed that overall performance on a switch task decreased with time on task. However, a direct relation between fatigue and the actual task switches was not always established; only in the Lorist et al. study (2009), fatigue-related performance declines depended on trial type. Effects of fatigue did not differentiate between switch and repetition trials in the Lorist et al. (2000) study. We argue that with increased effort, fatigued individuals can maintain performance, which could be detected with neuroimaging methods, such as fMRI.

In sum, fatigue is common in medical students and can have strong adverse effects on academic achievements or their future careers. Neuroimaging may be more sensitive than behavioral measures to detect differences between students with and without fatigue. Insights from previous imaging research suggest that fatigue may relate to increased neural effort to keep up performance.

Current study

The goal of the present fMRI study was to better understand neural mechanisms underlying fatigue in medical students. We focused on medical students because individuals from this population are often characterized by fatigue (Plukaard, Van Batenburg-Eddes, Vos, Croiset, & Jolles, submitted; Tanaka, Fukuda, Mizuno, Kuratsune, & Watanabe, 2009; Tanaka, Mizuno, Fukuda, Shigihara, & Watanabe, 2008) and burnout (Galán et al., 2011; Guthrie et al., 1998). This population thus appears to be vulnerable to fatigue. Furthermore, medical students are relatively homogeneous in terms of intelligence and educational background, and for the current study we only included females. This reduces noise, which increases the probability of detecting fatigue-related differences that are possibly subtler than differences in intelligence or sex.

Fatigue in this study was operationalized in two ways; first, we investigated differences in the neural bases of task switching between medical students with chronic fatigue (i.e., high fatigue for longer than two months) and students without fatigue. Second, we

studied the effect of an acute fatigue manipulation. The rationale behind this double approach is that acute fatigue and chronic fatigue possibly act upon a common mechanism, such as changes in neural effort (see for example Boksem & Tops, 2008 and Dobryakova, DeLuca, Genova, & Wylie, 2013). To this end, we experimentally manipulated fatigue in both groups by comparing effects of a fatigue inducing session (i.e., 90 minutes of performance on cognitively challenging tasks) to effects of a control session (i.e., 90 minutes of non-challenging activity). Based on previous findings, we hypothesized that both chronic and acute fatigue would coincide with increased neural effort in terms of higher or more widespread PFC activation during task switching. This is not yet studied and of obvious relevance for medical students, who are often cognitively challenged.

METHOD

Participants

Twenty-six fatigued females (age range 19.0 – 30.6 years, *M* = 21.8, *SD* = 2.3) and twenty-five non-fatigued females (age range 18.8 – 28.2 years, *M* = 21.6, *SD* = 1.9) were included in the analyses. Data from one participant (a non-fatigued female) were excluded due to excessive movement in the scanner. All participants were right-handed, had normal or corrected-to-normal vision and no hearing problems. All reported no history of medical, neurological or psychiatric disorder, and no use of medication (apart from contraceptive drugs).

Participants were recruited via a survey distributed among all first, second and third year medical students (i.e., the pre-clinical stage of medical school) at the VU University Medical Center Amsterdam. Out of 1050 eligible students, 701 students returned the completed questionnaire (67% response rate). We selected students who reported fatigue complaints for longer than 2 months and who scored above 76 on the Checklist Individual Strength (CIS; Vercoulen et al., 1994) for the *fatigue group*. The cutoff point of >76 was determined by Bültmann and colleagues (Bültmann et al., 2000), and indicates a fatigue level at which individuals are at risk of subsequent sickness absence. Of the 701

survey respondents, 31% scored above this threshold. For the *control group*, we selected students who reported no fatigue complaints and who scored below 65 on the CIS (i.e., the mean score of all respondents; SD = 21). Although the students were recruited during the pre-clinical stage of medical school, five participants from the fatigue group and four from the control group started their clinical internships by the time they participated in the study.

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

Procedure

The participants completed a 1.5 h. training session and two 3 h. test sessions on three separate days. The training session was scheduled within a week before the first test session. During the training session, participants completed a self-report depression scale (CES-D Scale; Radloff, 1977), the CIS (once more) and several neuropsychological tests that served to compare the groups on basic cognitive abilities. The tests included the 20-minute version of the Raven Advanced Progressive Matrices Test (RAPM; Raven et al., 1993; Hamel & Schmitmann, 2006) and the fourth version of the Peabody Picture Vocabulary Test (PPVT-IV; Dunn & Dunn, 2005) as measures of non-verbal and verbal intelligence, the Letter Digit Substitution Task (LDST; Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006[a]) as a measure of 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) as measures of cognitive flexibility. The training session ended with a practice version of the fMRI tasks.

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 fatigue manipulation in one session (i.e., fatigue session) and a control manipulation in the other session (i.e., control session; the order of the sessions was randomized). 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) with extra auditory interference, adopted from Evers and colleagues (Evers, Van der Veen, Jolles, Deutz & Schmitt, 2009) and an N-back computer task (2- and 3-back) for 30 minutes (see also Klaassen et al., 2013 for details). During the control manipulation, the participants spent 1.5 h. reading magazines or watching documentaries (a collection of magazines and documentary style DVD's was provided). Subsequently, the participants were as quickly as possible transferred to the scanner in which they performed the switch task and two other tasks that are described elsewhere.

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 scales yields a fatigue score ranging from 20 to 140. An additional question required the participants to indicate whether they suffered from fatigue complaints for longer than two weeks. If they answered this question with yes, they were asked to specify how long they experienced fatigue by choosing one of the following options: "from two weeks to one month", "from one to two months", "from two to three months", "from three to four months" or "longer than four months".

The fatigue Rating Scale Mental Effort (RSME; Zijlstra, 1993) was administered to assess the effect of the manipulation on subjective levels of fatigue and mental effort. The scale was completed before (T0) and after the manipulation (T1), as well as after scanning (T2). 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?"). Total RSME scores are based on the mean of all seven scales and range from 0 to 150.

Switch Paradigm

The switch task was programmed in Eprime version 1.2, running under windows XP on a HP Compaq Desktop PC (Intel Core 2 processor, 17 inch 60 Hz monitor). Stimuli were back-projected onto a screen located behind the scanner. Participants viewed the screen through an angled mirror attached to the head coil.

Each trial of the task started with a white fixation cross, which remained on the screen for 500-750 ms (pseudorandomly varied in steps of 10 ms), followed by a target stimulus (500 ms), and a black screen (inter trial interval (ITI); 500 ms). All stimuli were presented centrally on a black background. The target stimuli were arrows that varied in color (blue or red) and direction (pointing up or down), and yellow circles (as baseline condition). Participants were instructed to respond to the arrows by following two rules: blue arrows indicated that the participant should press the response button in the direction of the arrows (e.g., press "up" for a blue arrow pointing up). For red arrows, the rule was to press the response button in the opposite direction (e.g., press "up" for a red arrow pointing down). For yellow circles, participants were instructed to press one of the two response buttons. The response window lasted from the start of the target presentation until the end of the ITI (i.e., 1000 ms). Responses did not affect duration of target presentation or ITI, and no feedback was given. The response box was placed vertically on the participant's body with their index finger and middle finger on two buttons. The button closest to the head represented "up" or "down" depending on the participant's personal representation of up and down. All participants responded with their right hand and were instructed to respond as fast and accurate as possible.

When an arrow was preceded by an arrow of the same color (regardless of the direction of the arrow), this trial was considered a *task repetition trial* (on these trials, the rule did not change). When an arrow was preceded by an arrow of a different color, this trial was

considered a *task switch trial,* as the participant had to switch from one rule to the other rule. Repetition sequences ranged from three to six repetitions.

The task consisted 235 blue arrows, 235 red arrows and 90 yellow circles, presented in 560 trials. Of these trials, 380 were task repetition trials and 90 were task switch trials. The yellow circles were presented in ten sequences of on average nine repetitions throughout the task. Task duration was approximately 15 minutes.

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 40 slices in ascending order using a T2*-weighted echo planar imaging (EPI) sequence (repetition time (TR) = 2100 ms, echo time (TE) = 30 ms, flip angle (FA) = 80°, field of view (FOV) = 22.4 x 22.4 cm, voxel size = 3.5 x 3.5 x 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).

Behavioral Data Analysis

Accuracy and reaction times (RT) were recorded during the switch task. The first 5 trials were considered as "warm-up" trials and therefore excluded from the analyses. Likewise, we excluded trials with responses faster than 120 ms and extreme outliers (i.e., responses slower than 2.5 standard deviations above the mean). For the RT analyses, we excluded all error trials. Average accuracy scores (i.e., fractions correct) and RTs on repetition and switch trials were compared in separate *trial type* (repetition, switch) x *manipulation* (fatigue, control) x *group* (fatigue, control) mixed repeated measures ANOVAs. Behavioral switch costs were determined by calculating the difference between the average RT's and accuracy scores on switch and repetition trials. The switch costs were compared in manipulation x group mixed repeated measures ANOVAs.

fMRI Data Analysis

Imaging data were analyzed 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.

At first level, an event-related approach was used to model task repetition trials, task switch trials and baseline trials. The events were convolved with a hemodynamic response function. A high-pass filter of 128 s cutoff was applied to remove low frequency noise. In case of motion artifacts (i.e., > 0.5 mm movement between scans), additional regressors were computed and added to the model as regressors of no interest. For each participant in each session, contrasts were computed by subtracting the response to repetition trials from the response to switch trials.

The first level contrasts were entered into a second level mixed ANOVA with *group* (2 levels) as between-subjects factor and *manipulation* (2 levels) as within-subjects factor. For the main effect of condition, significance level was thresholded at $p < .05$ following a Family Wise Error rate (FWE) correction for multiple comparisons. For group and manipulation differences, the FWE correction was considered too conservative and we therefore used a Monte Carlo simulation of brain volume (Slotnick et al., 2003) to obtain appropriately corrected results. Assuming an individual voxel type I error of $p < .005$, a cluster extent of 30 contiguous resampled voxels (3 x 3 x 3 mm) was required to correct for multiple comparison at $p < .05$. The mean activity within the region showing a group effect was extracted using the data extraction tool available in MarsBaR (http://marsbar.sourcefourge.net) and correlated with behavioral switch costs using Pearson's product-moment correlations.

RESULTS

Sample Characteristics

Sample characteristics are summarized in Table 1. Independent t-tests were carried out to compare the groups on descriptive variables, questionnaire scores and neuropsychological tests. The CES-D and PPVT showed skewed distributions, which violated the assumption of normality. Therefore, we applied non-parametric Mann-Whitney *U* tests to compare the groups on these variables. The fatigue group scored significantly higher on all subscales of the CIS and reported higher levels of depression. Both groups scored equally 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 ρ = .26 corresponded to .0038462; http://www.quantitativeskills.com/sisa/calculations/bonfer.htm).

Table 1

Sample Characteristics

		Fatigue group	Control group	*p*
N		26	25	
Age		21.8 (2.3)	21.6 (1.9)	.746
CIS score	total	85.1 (15.5)	38.9 (9.8)	<.001
	fatigue severity	38.4 (7.2)	16.4 (5.3)	<.001
	concentration	20.2 (6.5)	10.0 (4.0)	<.001
	motivation	12.8 (4.1)	6.2 (1.7)	<.001
	physical activity	13.8 (4.4)	6.2 (3.7)	<.001
CES-D Scale		14.0 (7.5) [a]	3.9 (3.2)	<.001
Hb (nmol/l)		8.4 (1.0) [b]	8.5 (0.7) [a]	.660
RAVEN		23.3 (3.1)	22.8 (3.8)	.549
PPVT		108.9 (7.4)	109.4 (6.6)	.910
LDST		45.4 (4.4)	46.5 (4.9)	.404
CST		6.4 (4.8) [a]	4.0 (3.6)	.057
STROOP interference		29.1 (9.2) [a]	22.7 (7.8)	.012

Note. [a] Data of 1 person is missing (fatigue group: *N*=25; control group: *N*=24); [b] Data of 2 persons is missing (*N*=24).

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 *manipulation* (fatigue, control) as within-subjects factors, and *group* (fatigue, control) as between-subjects factor. A significant interaction between time of assessment and manipulation ($F(2,98) = 21.22$, $p < .001$) indicated that fatigue ratings increased more in the fatigue session compared to the control session.

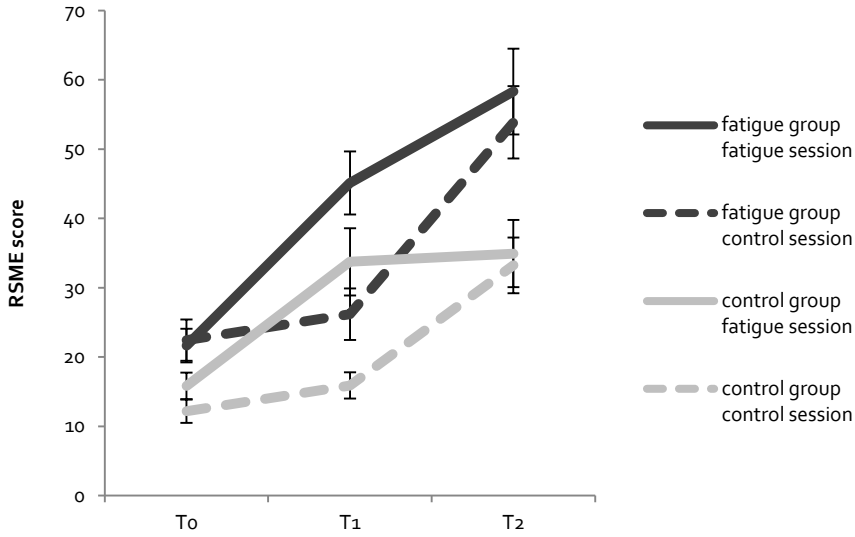


Figure 1. Fatigue scores measured by the Rating Scale of Mental Effort (RSME) at baseline (T0), after the manipulation (T1) and after scanning (T2). Dark gray represents the fatigue group and light gray represents the control group with solid lines for the fatigue session and dashed lines for the control session. Error bars show standard error of the mean (SEM). The scores differed significantly between sessions only at T1.

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; $t(50) = 6.73$, $p < .001$, $r = .34$) and not at T0 and T2 ($t < 0.98$, $p > .330$, $r < .14$). Other significant effects showed that overall, fatigue increased from T0 to T2 ($F(2,98) = 81.38$, $p < .001$), fatigue ratings were higher in the fatigue session compared to

the control session ($F(1,49) = 14.83$, $p < .001$), and the fatigue group had higher subjective fatigue compared to the control group ($F(1,49) = 9.85$, $p = .003$). A significant interaction between group and time of assessment ($F(2,98) = 6.05$, $p = .003$) 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 ($F < 0.85$, $p > .428$).

Behavioral Results

Results of the repeated measures ANOVAs are summarized in Table 2. For both the accuracy and the RT data we observed a main effect of trial type, with decreased accuracy and increased latencies on switch trials compared to repetition trials. This indicates that the switch cost in terms of accuracy as well as RT for this task was significant. There were no effects of group or manipulation.

Table 2

ANOVA table: Behavioral results of the switch task

	Accuracy data			**RT data**		
	F(1,49)	*r*	*p*	*F*(1,49)	*r*	*p*
Main effects						
Trial type	121.63	.84	< .001	761.82	.97	<.001
Manipulation	0.84	.13	.36	0.58	.11	.45
Group	0.25	.07	.62	1.894	.19	.18
Interactions						
Trial type x Group x Manipulation	0.35	.08	.56	1.39	.17	.24
Trial type x Manipulation	2.26	.21	.14	0.85	.13	.36
Trial type x Group	0.64	.11	.43	2.70	.23	.11
Manipulation x Group	3.42	.26	.07	0.75	.12	.39

Behavioral switch costs (illustrated in Figure 2) were analyzed separately because they are directly comparable to the contrasts used in the fMRI analyses. Also for these measures, we observed no effects of group or manipulation ($F(1,49) < 2.71$; $p > .15$; $r < .24$ for all comparisons).

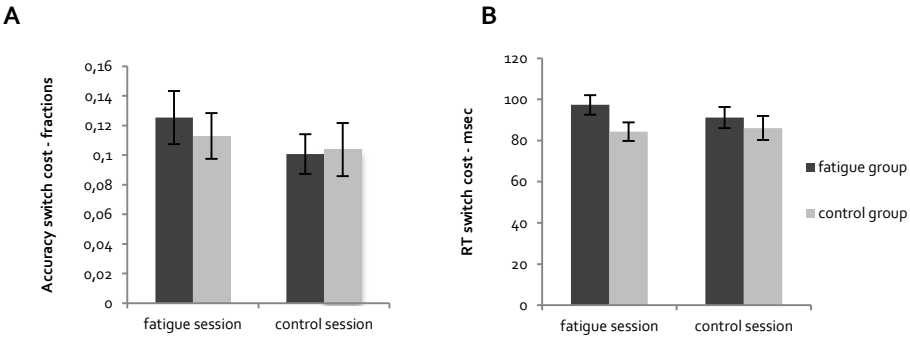


Figure 2. Behavioral switch costs. This figure displays the switch costs (i.e., the mean difference between responses to switch trials and repetition trials) in terms of accuracy (**A**) and RT (**B**) after the fatigue and the control manipulation. Dark gray bars represent the fatigue group and light gray bars represent the control group. Error bars show SEM.

fMRI Results

Effects of task switching. The switch minus repetition contrast represents additional processing related to task switching. The results across groups and sessions are summarized in Table 3. The most prominent switch related activated clusters were the left premotor and supplementary motor area (SMA), the left dorsolateral prefrontal cortex (DLPFC), and the left and right posterior cingulate cortex (PCC).

Table 3

Brain regions showing greater activation on switch trials compared to repetition trials

Peak activation area	BA	x	y	z	*z*	k
Precentral Gyrus	6	-54	-1	34	> 8	6570
Inferior Parietal Lobule	40	-42	-40	46	> 8	same cluster
Middle Frontal Gyrus	6	-24	-7	55	> 8	same cluster
Culmen		-36	-52	-26	> 8	876
Fusiform Gyrus	37	-42	-67	-11	7.54	same cluster
Middle Temporal Gyrus	37	-45	-61	1	7.21	same cluster
Middle Frontal Gyrus	9	-42	32	28	6.74	128
Thalamus		-12	-19	7	6.23	55
Putamen		-21	8	4	5.59	58
Claustrum		-27	20	7	5.51	same cluster
Thalamus		12	-16	7	5.52	28
Posterior Cingulate	23	6	-28	25	5.34	37
Posterior Cingulate	23	-6	-28	25	4.95	same cluster
Superior Temporal Gyrus	13	63	-40	19	5.31	24

Note. Activations are thresholded at $p < .05$, FWE corrected. Coordinates are in MNI space. BA = Brodmann Area.

Effects of fatigue group. Areas associated with fatigue are summarized in Table 4. Across sessions, the contrast *control group* > *fatigue group* revealed no significantly activated clusters. The reversed contrast (*fatigue group* > *control group*) revealed one cluster in the left anterior cingulate cortex (ACC; MNI = -6 14 37, Z = 3.35). This area was more activated in the fatigue group compared to the control group during task switching (Figure 3A).

Regression analyses of the relationship between activity within the ACC cluster and behavioral switch costs across sessions (i.e., the mean of the fatigue and control session) revealed a near-significant positive correlation with switch cost accuracy ($r = .26$, $p = .07$) and a significant positive correlation with switch cost RT ($r = .33$, $p < .05$; Figure 3B). The same analyses for the groups separately showed no significant correlations (switch cost

accuracy for the fatigue group: r = .25, p = .23, control group: r = .29, p = .17; RT switch cost for the fatigue group: r = .19, p = .36, control group: r = .34, p = .10).

To test whether the correlations between RT switch costs and ACC activation differed significantly between the groups, the Fisher transformed (Fisher, 1921) correlation coefficients and the slopes were compared between groups. These analyses revealed that neither the coefficients (z = 0.53, p = .30) nor the slopes (t = 0.71, p = .24) differed significantly between the groups. This indicates that the relation between ACC activation and behavioral response of both groups was comparable.

Table 4

Brain regions associated with fatigue in the switch > repetition contrast

Peak activation area	BA	x	y	z	*z*	k
Group main effect: fatigue > control						
Anterior Cingulate	32	-6	14	37	3.35	40
Manipulation main effect: control > fatigue						
Culmen		27	-34	-23	3.23	54
Culmen		21	-40	-26	3.07	same cluster
Culmen		24	-46	-20	2.98	same cluster
Declive		-24	-70	-14	3.22	46
Uvula		-18	-73	-23	2.65	same cluster
Group x manipulation interaction						
Middle Frontal Gyrus	9	-27	41	22	3.86	51
Precuneus	7	0	-55	40	3.73	118
	31	27	-49	34	3.43	same cluster
	7	18	-49	43	3.20	same cluster
Precentral Gyrus	6	-33	11	22	3.44	31

Note. Activations are thresholded at p < .005, corrected for magnitude of k = 30. Coordinates are in MNI space. BA = Brodmann Area.

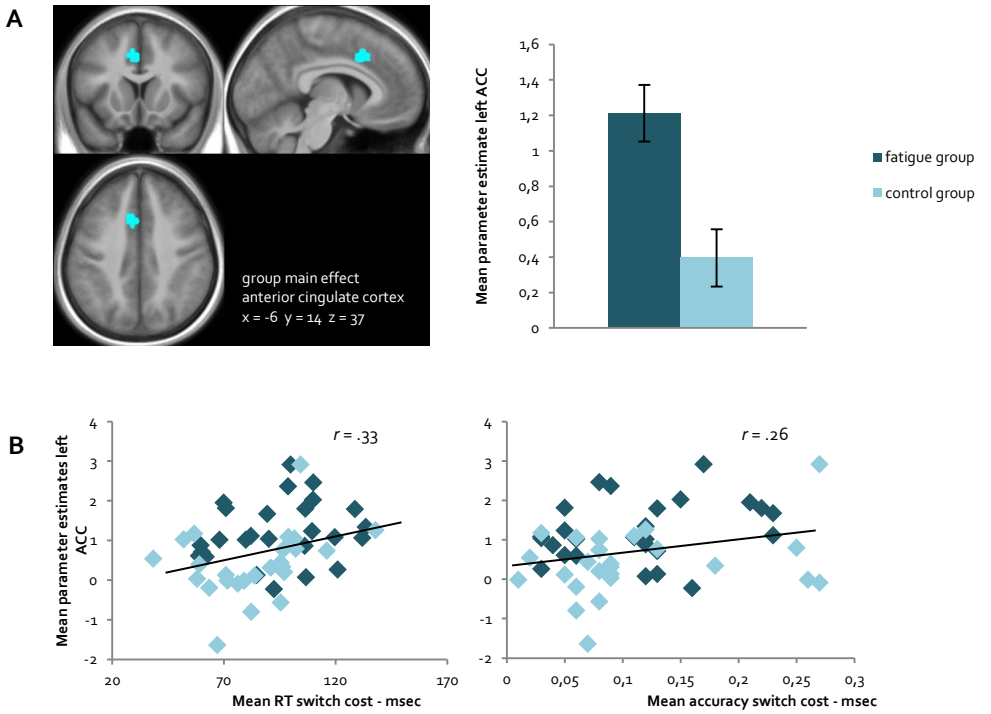


Figure 3. (**A**) Main effect of group (fatigue group > control group) across sessions overlayed on a mean anatomical image of all participants (left). A cluster in the anterior cingulate cortex (ACC) was activated more by the fatigue group across both sessions. The right side of the image shows the mean parameter estimates within the activated ACC cluster with error bars showing SEM. (**B**) Scatterplots illustrating the relation between activity within the ACC and switch cost in terms of RT (left) and accuracy (right), collapsed over sessions. Pearson's correlation across the two groups showed a moderate positive relation that was significant for the RT data ($p < .05$) and a weak and non-significant positive correlation for the accuracy data ($p = .73$). Dark turquoise represents the fatigue group and light turquoise represents the control group.

Effects of fatigue manipulation. Main effects of manipulation were found in the cerebellum: across the groups, two clusters were more activated after the control manipulation compared to the fatigue manipulation. There were no clusters showing stronger activation after the fatigue manipulation compared to the control manipulation. No main effects of manipulation were found in frontal or parietal areas.

Group and manipulation interactions. Group x manipulation interactions were observed in the left DLPFC (MNI = -27 41 22, $z = 3.86$), precuneus (including the somatosensory

association area (SAS) and PCC; MNI = 0 -55 40, z = 3.73) and left premotor area (MNI = -33 11 22, z = 3.44; Table 4). These results indicate that the two groups responded differently to the fatigue manipulation. When comparing the fatigue manipulation to the control manipulation, the control group showed increased activation in these areas after the fatigue manipulation, whereas the fatigue group showed a reversed effect (Figure 4). Post hoc t-tests were performed to compare neural response in these areas between the fatigue and control manipulation within each group. These analyses confirmed that the control group showed significantly increased activity in the premotor cortex and precuneus (t > 2.49, p < .05 for both comparisons) after the fatigue manipulation. Conversely, the fatigue group revealed significantly increased activity in the DLPFC, premotor cortex and precuneus (t < -2.86, p < .01 for all comparisons) after the control manipulation.

To evaluate whether the observed effects were associated with switches and not with repetition trials, we extracted data associated with the *repetition* > *baseline* contrast from the activated clusters (ACC, DLPFC, premotor area and precuneus). Mixed repeated measures ANOVAs on these data revealed no significant group effect on the ACC (F(1,49) = 0.48, p = .49) and no significant interactions (DLPFC: F(1,49) = 0.39, p = .54, premotor area: F(1,49) = 2.52, p = .12, precuneus: F(1,49) = 3.53, p = .07). This confirms that the fatigue effects from the *switch* > *repetition* contrast are based on additional processes related to switching and not on processes associated with repetition trials.

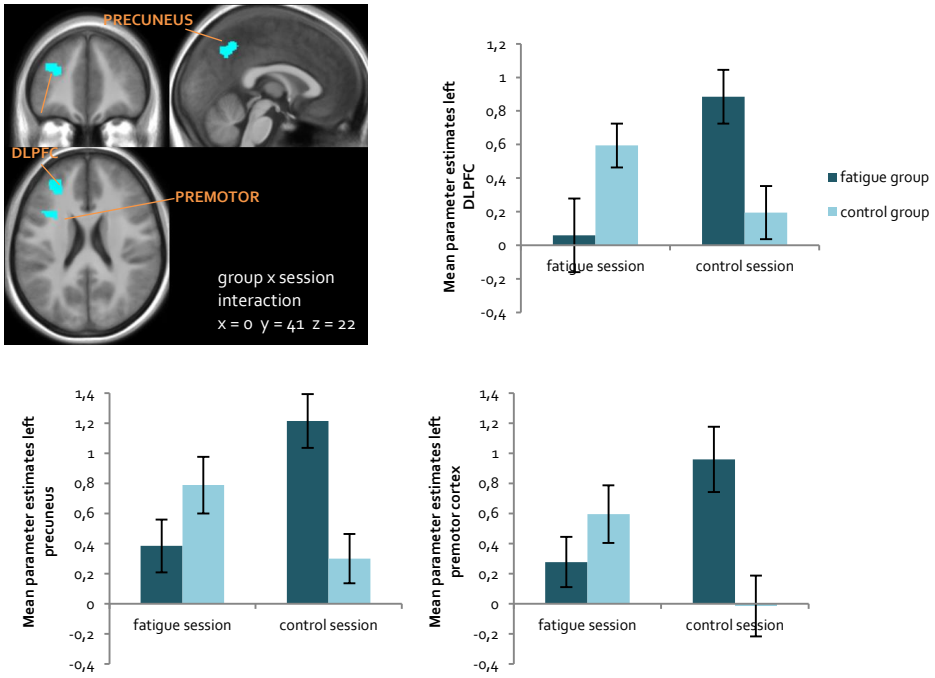


Figure 4. Group x session interactions. After the fatigue manipulation, the control group increased switch-related activation in the dorsolateral prefrontal cortex (DLPFC), the precuneus and the premotor cortex, whereas the fatigue group decreased activation in these areas compared to the control manipulation.

DISCUSSION

The present study set out to investigate underlying neural mechanisms of fatigue in healthy medical students by means of fMRI. We anticipated that fMRI would be more sensitive than behavioral measures to detect effects of fatigue, which currently appeared to be the case. Our research questions pertained to whether fatigue in medical students shared commonalities with insights from clinical neuroimaging research. Furthermore, we aimed to investigate whether a common mechanism underlies chronic and acute fatigue. We expected that effects would involve higher or more widespread PFC activation (Chaudhuri & Behan, 2000; Dobryakova et al., 2013), representing an increase in neural effort (Boksem & Tops, 2008). To this end, medical students with and without chronic fatigue were compared. In addition, we experimentally manipulated acute fatigue by a cognitive fatigue inducing manipulation in one session and a control

manipulation in the other session. We targeted task switching because of its high demands on cognitive control. Based on fatigue research in patients and healthy participants, we expected the switch task to be sensitive to fatigue (e.g., Cook et al., 2007; Deluca et al., 2004; Lorist et al., 2000; van der Linden, Frese, & Meijman, 2003).

The findings confirmed that fMRI is a sensitive tool to assess fatigue in medical students; effects of fatigue were observed while there were no differences in behavioral performance. Effects of fatigue were found in areas that are regarded as part of the cortico-striatal circuit: A main effect of group showed that fatigued students increased activation in the dorsal ACC compared to non-fatigued students, independent of manipulation. An interaction between group and manipulation was observed in the left DLPFC, precuneus and left premotor area. In response to the fatigue manipulation, the non-fatigued control group increased activation, whereas the group of fatigued students decreased activation in these areas. Moreover, we found a main effect of manipulation in the cerebellum; independent of group, activation of several cerebellar areas increased in response to the fatigue manipulation.

Increased ACC activation in fatigued students is in line with a mechanism proposed by Chaudhuri and Behan (2000) as well as previous clinical neuroimaging findings (Cook et al., 2007; Dobryakova et al., 2013). A relation, although indirectly, between ACC activation and fatigue has also been established in healthy participants as result of prolonged task performance using EEG (Lorist et al., 2005) and arterial spin labeling fMRI (Lim, Wu, Wang, Detre, & Dinges, 2009). The mechanism suggested by Chaudhuri and Behan (2000) associates fatigue with abnormalities in one or more areas of cortico-striatal circuitry (see also: Dobryakova et al., 2013). Correspondingly, Boksem and Tops (2008) explained fatigue in terms of a disrupted balance between effort and reward processing; fatigue arises when the amount of invested effort (e.g., indicated by PFC activation) outweighs the outcome benefits (processed in e.g., basal ganglia areas). Within this framework, increased ACC activation in fatigued students could reflect an increase in effort processing. The observed effect specifically involved the dorsal portion

of the ACC. This area is considered to be accountable for top-down cognitive evaluation processes, such as performance monitoring (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004), conflict monitoring (Botvinick, Cohen, & Carter, 2004), decision making (Kennerley, Walton, Behrens, Buckley, & Rushworth, 2006), and effort calculation (Dehaene, Kerszberg, & Changeux, 1998; Kerns et al., 2004; MacDonald, 2000). Notably, ACC activity may constitute a common process underlying many different cognitive demands (Duncan & Owen, 2000). Cook et al. (2007) found a positive correlation between subjective fatigue and activation in the ACC and other areas during a working memory task. They attributed increased cingulate activation to enhanced attentional monitoring of feelings of fatigue, since their participants were asked to attend to those feelings. Elevated ACC activity in fatigued students in the present study could therefore indicate an increase in effortful evaluative processing (e.g., performance monitoring or evaluating whether top-down control processes should be more strongly engaged: Kerns et al., 2004; MacDonald, 2000) or effort calculation (e.g., estimating the amount of invested effort or feelings of fatigue). In both cases, fatigued students in the current study seem to rely more on evaluative monitoring while switching between tasks.

Across sessions, activation in the ACC was moderately correlated with behavioral switch cost; increased activation was associated with larger differences between switch and repetition trials. In other words, participants with higher activation of the ACC, and therefore relying more on evaluative monitoring, took longer to switch between tasks. This relationship is consistent with current perspectives on the role of the ACC in relation to behavioral performance. For instance, increases in ACC activation accounts for more behavioral adjustment (i.e., slower RT after an error) when adjustment of attentional control is required to counteract performance declines (Kerns et al., 2004). Our current observations included a stronger positive correlation for the control group compared to the fatigue group, but this difference was not significant. A difference between the groups would suggest less efficient or less effective involvement of the ACC in fatigued individuals, which would also be in line with previous research showing fatigue-related

ACC instability (Lim et al., 2009). Nonetheless, this was not clearly supported by our findings.

The present findings also demonstrated that the groups responded differently to the experimental fatigue induction. The control group showed increased activation in the left DLPFC, left premotor and right inferior parietal areas in response to induced mental fatigue. These frontal and parietal areas are generally associated with top-down cognitive control processes such as working memory application (Curtis & D'Esposito, 2003) or the maintenance of sustained attention (Cabeza & Nyberg, 2000). There were no performance declines. Therefore, such increases may represent an enhancement of cognitive effort to compensate for reduced cognitive control. This notion implies that the fatigue manipulation affected cognition by taking up valuable working memory or attentional resources, at least in individuals who are not chronically fatigued. Remarkably, the chronic fatigue group displayed an opposite pattern: activation in these fronto-parietal areas was elevated compared to non-fatigued students in the control session, but decreased after the fatigue induction. This finding implicates that at baseline (i.e., in the control condition in which there was no fatigue induction), fatigued students used compensatory strategies. This is indicated by enhanced use of cognitive resources (or: increased effort) to obtain a level of performance comparable to that of non-fatigued students. The reduction in activity after the fatigue manipulation is of major relevance because it attracts attention to the possibility that chronically fatigued subjects already perform to the best of their potencies in regular conditions. Interestingly, previous imaging research showed increases in activity in response to fatigue (e.g., Cook et al., 2007). We propose two possible explanations for the present result: Neural effort may decrease when it exceeds resource limits. This corresponds to the theory that the capacity for cognitive control resources is limited (Schneider & Shiffrin, 1977). However, one would expect a decrease in neural effort to be accompanied by performance declines, which was currently not the case. Another explanation refers to a possible shift towards automaticity. Perhaps the fatigued students shifted towards more efficient strategies that required less attentional effort, but were still sufficiently adequate to

maintain performance. This might be due to fatigued individuals being more used to adapt to high demands. The latter explanation may be less plausible, since in the long run, fatigue is associated with reduced work or academic performance (Nagane, 2004; Ricci et al., 2007). Moreover, the current behavioral data showed the largest switch costs for the fatigued students in the fatigue session, which indicates that switch cost did not improve, but likely increased even further. This effect however, was not supported by statistical significance. The current task was possibly not sensitive enough to detect performance declines associated with declines in neural effort.

Regardless of group, the fatigue manipulation resulted in increases in several cerebellar areas. Even though its specific role in cognition is yet unclear, the cerebellum has been implicated in various functions, including memory, attention executive function and motor learning and initiation (Cabeza & Nyberg, 2000; Strick, Dum, & Fiez, 2009). Increased activation thus suggests that certain aspects of these functions might be altered by the mental fatigue induction. The results are consistent with findings by Cook et al. (2007), who observed positive correlations between fatigue and activity in several cerebellar areas during a working memory task.

Limitations

We deliberately investigated medical students, given the high prevalence of fatigue and the relation between fatigue and academic attainment. The current sample consisted of participants that were similar in terms of age, educational level and intelligence, and all were female. We consider this an advantage, because we expected effects of fatigue to be subtle. Further research is necessary to investigate whether the present findings also apply to other populations. For example, it would be useful to investigate whether mechanisms of fatigue are similar for males and females, or for individuals with different educational backgrounds.

A relevant point to consider is that the present operationalization of fatigue may not have been sufficient. A fatigue induction of 1.5 h. of cognitively demanding tasks may not

be fatiguing enough or the time it takes to be transferred into the scanner may have diminished the effects. This could explain why we failed to find an effect of manipulation on PFC activation or, perhaps, the lack of a behavioral effect of induced fatigue in the group of fatigued students. On the other hand, we consider this relatively short period of fatigue induction as strength. It translates well to everyday life, which often consists of periods of cognitive engagement in different tasks separated by short breaks. Moreover, the fatigue induction took place in the afternoon, when many people experience a cognitive dip after more than half-a-day of activities. In that sense, the current design is rather realistic.

To conclude, the present study showed a relation between fatigue (both chronic and acute) and increased neural activation, which we interpreted in terms of enhanced effortful control to keep up performance. A decrease in fronto-parietal activation in fatigued students after the fatigue induction is possibly the result of a breakdown in invested neural effort, even though this was not accompanied by a breakdown in performance. More research is necessary to further elucidate this effect. Clearly, fatigue is a complex concept, which renders it likely that effects are not always straightforward. Nonetheless, the present neuroimaging data revealed fatigue-related differences in cognitive control that were not detected behaviorally and could underscore the problems that many chronically fatigued people experience in daily life. Investigating neural mechanisms using imaging methods evidently provides additional insights into the field of fatigue research that may provide a guide towards interventions.

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