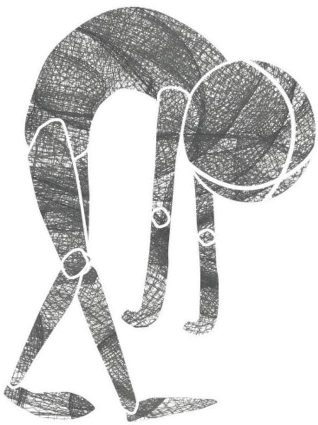
The Fatigued Brain: Fatigue and Cognitive Functions in Young Adults

Plukaard, S.C.

2015

CHAPTER ONE

General Introduction



Fatigue plays a common role in our daily lives. It emerges naturally by the end of the day, or after a period of hard work, and typically goes away during a good night's sleep or some other type of rest. We all know how obstructive this feeling can be; fatigue hinders us with getting on with our desired activities, it coincides with negative mood and the feeling itself is perceived as unpleasant.

University students are potentially vulnerable to fatigue as they are challenged in many ways by personal, social, cognitive and environmental changes. For instance, the transition from secondary to higher education requires the students to adjust to a new academic setting with different learning procedures, materials, demands and responsibilities. They also run into a new social and personal environment in which they develop new friendships, leave their parents' home, reach financial independence, and gain more autonomy (Arnett, 2004). Along with these environmental changes, students encounter cognitive changes as the brain continues to develop between the ages of 18 to 25 years, both structurally (Giedd & Rapoport, 2010; Lebel & Beaulieu, 2011; Tamnes et al., 2010) and functionally (Veroude, Jolles, Croiset, & Krabbendam, 2013).

According to the national students union, 23% of all students in The Netherlands report mental health problems (e.g., fatigue, anxiety, depression; Schmidt & Simons, 2013). Fatigue was one of the most predominant complaints in this evaluation. Given the abovementioned challenges as well as the typical lifestyle of students, i.e., various social activities that often comprise alcohol and lack of sleep, it is not surprising that many of them suffer from fatigue. To a certain extent, fatigue is possibly a natural part of student life. For most students it is likely a temporary phenomenon that will solve itself after they enroll in a more structured lifestyle, whether a new work environment imposes this after graduation or whether a student consciously chooses to engage in fewer extracurricular or leisure activities. However, this does not alter the fact that fatigue can have major impact on their quality of life (DeLuca, 2005) as well as their academic success (e.g., Nagane, 2004), or their success in life after graduation (e.g., work productivity: Ricci, Chee, Lorandeau, & Berger, 2007). Moreover, in the long run, fatigue can lead to more severe conditions such as burnout (Galán, Sanmartín, Polo, & Giner, 2011; Guthrie et al., 1998) and depression (Bozoky & Corwin, 1994).

Still, little is known about the cognitive differences between students who are prone to fatigue and students who do not suffer from fatigue. Improving our understanding of fatigue can help tackle the problems described above; it may provide a basis for optimizing life success and enjoyment at a professional and personal level. In this thesis, it is hypothesized that fatigue is for a large part connected to less effective and efficient cognitive control. The main objective of this thesis is to examine fatigue and associated brain mechanisms in university students. To this end, we set out to (1) describe the issue of fatigue among students, (2) evaluate the added value of functional neuroimaging in fatigue research and (3) investigate effects of acute cognitive fatigue as well as differences between students with and without chronic fatigue in the context of several cognitive control functions. The objectives and approach will be explained in more detail after a short overview of our current knowledge on fatigue and the potential link to cognition.

The concept of fatigue

Fatigue is as elusive as it is universal. It is elusive because it entangles divergent aspects that are variable between and within individuals (see DeLuca, 2005). These aspects involve underlying causes (e.g., sleep deficiencies, stress, mental workload, physical or mental disease), duration (e.g., acute fatigue, which is easily restored, or chronic fatigue, in which recovery does not occur easily) and affected domain (e.g., mental fatigue or physical fatigue). Fatigue is at the same time universal because it is a natural part of everyday life in all of us. It is only natural to feel fatigued by the end of a busy week, or after intensive physical or mental exercise. Usually, this feeling can be alleviated by a period of rest, of which the duration and type depends on the nature of fatigue. Also, fatigue is possibly the most commonly reported symptom of all kinds of disease (Aaronson et al., 1999). In fact, there are several medical conditions, e.g., multiple sclerosis, traumatic brain injury and chronic fatigue syndrome, in which fatigue is the most prominent complaint.

The Multiple Sclerosis Council for Clinical Practice Guidelines (MS Council, 1998) has constructed a definition of fatigue that is applicable regardless of the cause, duration or domain. The council described fatigue as "a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities". With this definition in mind, the research that is presented here targeted the entire construct of fatigue, while delineating the concept based on severity, duration and domain. Accordingly, the present thesis distinguishes between *chronic fatigue*, *persistent fatigue*, and *acute mental fatigue*. With chronic fatigue we refer to high levels of fatigue (i.e., a combination of mental, physical, and motivational components), persisting for at least two months. Persistent fatigue refers to general feelings of fatigue that are built up and lasting for a period of several days. Acute mental fatigue refers to the cognitive domain and results directly from a period of cognitively demanding activity. Of note, in clinical terms fatigue is referred to as *chronic* when it persists for at least six months. For practical purposes, the studies in this thesis recruited participants who reported at least two months of fatigue complaints as chronically fatigued students. The period between recruitment and actual scanning varied between two to six months. Consequently, not all, but most of the fatigued students (i.e., 92%) in the end met this critical period of six months.

Fatigue and cognition

There are several indications for a relation between fatigue and functions that rely on cognitive control. First of all, declines in concentration and sustained attention are generally viewed as a subcomponent of fatigue (Vercoulen et al., 1994), and are consistently reported by fatigued individuals (Park, Kim, Chung, & Hisanaga, 2001). Second, when fatigue arises during or after a period of mental workload, we tend to respond slower to stimuli (e.g., Lorist, Boksem, & Ridderinkhof, 2005). We also become less adequate at adjusting our responses when we make a mistake (Boksem, Meijman, &

Lorist, 2006), less flexible at changing between strategies (van der Linden, Frese, & Meijman, 2003; van der Linden, Frese, & Sonnentag, 2003), and less efficient at planning and preparation (Lorist, 2008; van der Linden, Frese, & Meijman, 2003). Third, comparable findings are documented for chronic fatigue in patient populations (Bryant, Chiaravalloti, & DeLuca, 2004; Krupp & Elkins, 2000; Schwid et al., 2003) and fatigue due to sleep deprivation (Jacques, Lynch, & Samkoff, 1990).

In contrast to cognitive control, automatic processes appear to remain unaffected by fatigue (Schellekens, Sijtsma, Vegter, & Meijman, 2000; van der Linden & Eling, 2006). These findings are in line with the distinction between automatic and controlled processes, which was put forward by Schneider and Shiffrin (1977). According to their description, automatic processes require no additional effort, and occur reflexively and in parallel. Conversely, controlled processes are effortful, occur sequentially and depend on limited resource capacity (Schneider & Shiffrin, 1977; Schneider, 2003). These controlled processes are essential for adequate adaptive and goal-directed behavior, which also underlies abilities in higher education, such as the acquisition of new skills, evaluation of feedback and academic proficiency (e.g., Best, Miller, & Naglieri, 2011; Latzman, Elkovitch, Young, & Clark, 2010; Miller & Cohen, 2001; Miller, 2000; Zelazo, Müller, Frye, & Marcovitch, 2003). This underlines the relevance of examining fatigue in the context of cognitive mechanisms in students.

Research into fatigue and cognition is mainly limited to mental fatigue induced in healthy individuals, or to chronic or prolonged fatigue in clinical populations. To date, associations between prolonged fatigue in healthy populations and cognitive processing have received little to no attention. The literature outlined above generates an important question regarding fatigue in university students: To what extent can differences between students with and without fatigue be explained by differences in cognitive processing? Also without clinical conditions or neural injuries, there appear to be individual differences in fatigability. Perhaps more general features, such as cognitive capacity or efficiency of information processing, may underlie these differences.

Neuroimaging of fatigue

One of the most prominent issues in fatigue research relates to the fact that fatigue is a subjective experience. The measurement of fatigue is thus generally based upon self-report. Self-report measures, such as questionnaires, do not seem to correlate well with cognitive performance (e.g., Bryant et al., 2004; Krupp & Elkins, 2000; Paul, Cohen, & Gilchrist, 2002). More recently, cognitive performance research has been complemented by insights from functional neuroimaging. Fatigue-related differences in neural activity have been found in the absence of (accuracy) performance differences (DeLuca et al., 2008; Kohl et al., 2009). This illustrates that neuroimaging can be more sensitive than behavioral measures to detect differences related to the experience of fatigue. Moreover, clinical neuroimaging studies have indicated a relation between fatigue and increased mental effort (Cook, O'Connor, Lange, & Steffener, 2007; DeLuca, Genova, Hillary, & Wylie, 2008; Kohl, Wylie, Genova, Hillary, & Deluca, 2009). Individuals can increase their level of effort, for instance by recruiting additional brain areas, to prevent performance declines. This suggests that neuroimaging can be an invaluable tool to examine fatigue in the context of cognitive capacity and efficiency.

Thesis aims

The research presented in this thesis addressed the issue of fatigue among healthy young students in relation to cognition. The main goals were (1) to describe the prevalence and correlates of fatigue in medical students, (2) to evaluate the added value of functional neuroimaging in fatigue research, and (3) to investigate effects of acute cognitive fatigue as well as differences between students with and without chronic fatigue in the context of cognitive control.

Approach

This thesis describes behavioral, survey and neuroimaging data. In the behavioral study, acute mental fatigue was experimentally induced. In the survey study, the prevalence of fatigue was investigated amongst all medical bachelor students of the VU Medical Centre Amsterdam. The largest part of this thesis is based on an extensive fMRI experiment in which students with and without chronic fatigue were compared. In addition, mental fatigue was manipulated by subjecting both groups to a cognitive fatigue inducing session and a control session. Effects of fatigue were investigated on resting-state functional connectivity, task switching, working memory load and emotion processing.

Chapter overview

Chapter 2 describes an experimental study that investigated effects of a cognitive fatigue manipulation as well as individual differences in prolonged fatigue on cognitive flexibility. First year psychology students who received a fatigue inducing session were compared to peers who received a non-demanding control session. The students in both groups performed a switch task in which they were required to switch between task-rules of unequal difficulty.

Chapter 3 evaluates the prevalence of fatigue in medical bachelor students and explores correlations with relevant lifestyle factors as well as self-reported executive abilities.

The next four chapters are based on the abovementioned fMRI experiment.

Chapter 4 examines fatigue-related alterations in resting-state functional connectivity following a data-driven approach by means of independent component analysis. At whole brain level, we compared the groups and sessions on the size of eight relevant functional networks as well as on the strength of functional connectivity within these networks.

Chapter 5 investigates effects of fatigue on the neural bases of task switching. Participants performed an adjusted version of the switch task described in chapter 2 of this thesis. Both behavioral and fMRI data are examined.

Chapter 6 describes effects of fatigue on working memory under different load conditions. The task constituted a block design in which working memory load increased in a stepwise fashion. Groups and sessions were compared on brain activation that increased in correspondence with working memory load. In addition, the relation between brain activation and working memory performance was evaluated.

Chapter 7 reports effects of fatigue on emotion processing using an emotion regulation paradigm. This paradigm aimed to distinguish between the processing of negative emotional stimuli and the regulation of these processes.

Chapter 8 provides an overview of the main results with implications and suggestions for future research.