The Fatigued Brain: Fatigue and Cognitive Functions in Young Adults

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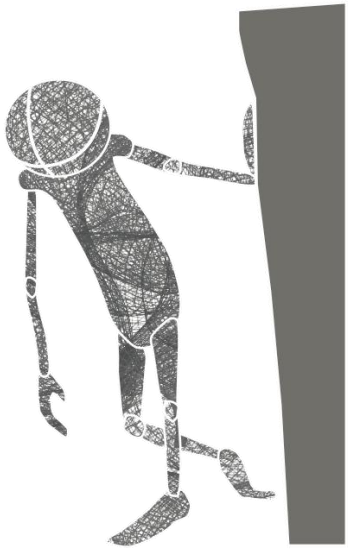
Chapter eight

Concluding Remarks



OBJECTIVE AND KEY FINDINGS

Bearing in mind the prominent role that fatigue can play in our daily lives, this thesis investigated its cognitive aspects. The main objective was to improve our understanding of the relation between fatigue and cognitive functioning in healthy young individuals. This thesis targeted university students, because they are considered vulnerable to fatigue given their lifestyle and the cognitive challenges they face, as outlined in Chapter 1. One way to address our main objective was to describe cognitive differences between students with and without chronic fatigue, helping us understand why some students are troubled by fatigue, whereas others are not. Another way was to explore possible effects of a period of challenging cognitive task performance – which induced acute cognitive fatigue – on the performance and neural processing of other cognitive tasks. As such, the studies in this thesis evaluated several of the so-called *cognitive control functions* by collecting behavioral, questionnaire and neuroimaging data.

On fatigue and neuroimaging findings

The findings described in the various chapters of this thesis indicated that fatigue is a relevant issue in university (medical) students. Indeed, one third of our survey respondents experienced severe fatigue (Chapter 3). Students with higher fatigue reported more sleeping problems, medical conditions, and less engagement in sports as well as lower self-reported executive abilities (i.e., planning and self-monitoring). This suggested that, as expected, a close link exists between fatigue and cognitive control functions. This link was confirmed by our experimental studies that showed behavioral changes in task switching (Chapter 2) and working memory (Chapter 6) as well as alterations in neural correlates of task switching (Chapter 5), working memory (Chapter 6) and emotion regulation (Chapter 7).

Neuroimaging appeared to be an invaluable tool to investigate fatigue in this homogeneous sample of young and intelligent individuals (Chapters 4-7). Our functional neuroimaging data showed profound changes in brain activation: Fatigued students exhibited alterations in intrinsic functional networks as well as task-related neural

activations (Chapters 4-7). In contrast, behavioral changes were less prominent, e.g., in Chapters 5 and 7 we detected no behavioral changes while there were obvious alterations in neural activation. With respect to chronic fatigue, we consistently found differences in neurocognitive processing. These differences suggested that the neural basis in chronically fatigued students is slightly reduced compared to that of their non-fatigued peers in terms of efficiency (Chapter 5), capacity (Chapter 6) and robustness (Chapter 4). Chapter 7 showed differential processing of emotional stimuli, rendering chronically fatigued students also more vulnerable to negative emotional stimulation.

As to acute fatigue, our main findings suggested that the cognitive fatigue manipulation resulted in changes in effortful control (Chapter 5 and 7), visual attention (Chapter 7), and in resting-state functional networks (Chapter 4). In some cases these acute fatigue effects differentiated between students with and without chronic fatigue. To give an example, non-fatigued students displayed higher effortful control during task switching whereas chronically fatigued students appeared to break down in effortful control (Chapter 5).

What now remains is to put these results into a broader perspective. This final chapter therefore evaluates our key findings in light of the current scientific knowledge and views on the relation between fatigue and cognition. It also provides methodological considerations, implications and suggestions for future research.

FATIGUE AND COGNITION: BRAIN MECHANISMS

It has become clear that the subjective experience of fatigue and functional neural mechanisms are closely related. In each chapter we zoomed in on specific cognitive aspects, i.e., task switching, working memory, emotion regulation, or functional networks in the absence of task performance. The question that now arises is: Are these fatigue-related activation changes task-specific or could they represent a common cognitive mechanism?

The perception of fatigue as manifestation of increased neural effort

The fact that fatigue generally affects *effortful* cognitive control functions while *effortless* automatic functions remain unaffected (Schellekens, Sijtsma, Vegter, & Meijman, 2000; van der Linden & Eling, 2006) constitutes a link between fatigue and cognitive effort. This corresponds to the commonly reported increase in required effort to maintain performance by fatigued individuals (e.g., Chaudhuri & Behan, 2000). Neuroimaging studies on fatigue in patient populations ascribed cognitive effort to neural activation increases during task performance (Cook, O'Connor, Lange, & Steffener, 2007; DeLuca, Genova, Capili, & Wylie, 2009; Dobryakova, DeLuca, Genova, & Wylie, 2013).

In line with the above, we saw in Chapter 2 that one hour of mental arithmetic, brainteaser puzzles and other cognitively demanding tasks drastically increased the experience of fatigue in terms of mental effort. In contrast, the increase in fatigued mood was much less pronounced. Students who received this manipulation reported that they had to make greater effort to suppress feelings of fatigue, to sustain attention, and to keep up performance. They were also characterized by slower responses, suggesting that the increase in experienced effort was accompanied by a change in cognitive processing that takes more time. This notion was supported by our neuroimaging experiment in which we observed neural activation increase after a similar cognitive fatigue manipulation in medical students during task switching (Chapter 5) and also during emotion regulation (Chapter 7). Explicit reappraisal of negative pictures required enhanced activation of the dorsolateral prefrontal cortex (Chapter 7). Task switching required increased neural activation of the left-lateralized frontoparietal network (FPN) in students who were not fatigued at baseline. In Chapter 4 we reasoned that these students engaged the right FPN during the demanding cognitive manipulation by showing increased functional connectivity within this network. One interpretation is that the right FPN got depleted during the manipulation, and the left-lateralized FPN as a reserve resource was called upon to keep up performance. Compare this to muscle fatigue: when you lift objects with one hand, after a while your arm loses power (i.e., muscle fatigue) and you can compensate for this by using both hands. Similarly, you can

recruit corresponding brain areas in the opposite hemisphere. This neural compensation is more commonly observed, for instance in aging (Cabeza & Dennis, 2012; Park & Reuter-Lorenz, 2009).

All in all, a period of cognitively challenging activities caused students to expend more neural 'effort' by recruiting cognitive reserve resources, as represented by increase activation of cognitive control areas of the brain. Apparently, their 'baseline' cognitive resources were no longer sufficient to maintain the same level of performance. These findings therefore provide evidence for enhancement of neural effort as a common mechanism to cope with effects of fatigue, as caused by a period of hard cognitive work.

When it comes to chronic fatigue, there were also indications for increased neural effort. Abnormal use of the anterior cingulate cortex (ACC) is previously related to persistent fatigue in patient populations (e.g., Dobryakova et al., 2013). Here, we found that chronically fatigued students additionally recruited the ACC when switching between tasks (Chapter 5). Given the absence of performance differences between the groups, and on top of that, the small negative relation between ACC activation and task performance in the two groups together, this was taken to indicate use of less efficient strategies. Compatibly, even without an explicit task to perform, chronically fatigued individuals showed weaker functional organization, as shown by resting-state fMRI (Chapter 4). This is another indication of reduced neural efficiency in terms of a less effective cognitive basis or less consistent strategy usage, which is discussed more in depth in Chapter 4. On the other hand, recruitment of additional brain areas may also – as argued above – represent neural compensation. That is, we observed that chronically fatigued students who increased neural activation also showed more accurate working memory performance (Chapter 6). Taken together, our findings suggest that not only acute cognitive fatigue, but also chronic fatigue can be associated with enhanced neural effort.

Chronic fatigue: a cognitive capacity problem?

A broad range of studies suggest that cognitive control functions rely on resources with limited capacity (e.g., Ilkowska & Engle, 2010; Inzlicht, Schmeichel, & Macrae, 2014; Schneider, 2003). The extent of this capacity represents the degree to which an individual can call upon their cognitive resources. The idea is that individuals can increasingly employ cognitive resources in order to keep up performance until their capacity limits are reached (Callicott et al., 1999; Curtis & D'Esposito, 2003). Keeping this in mind, our findings related to task switching (Chapter 5) suggest that chronically fatigued students operate at the limits of their cognitive capacity. This is indicated by elevated neural activation at baseline, and a breakdown of these activation levels after additional cognitive fatigue. Our working memory study (Chapter 6) extended this notion by demonstrating that chronically fatigued students responded slower compared to their non-fatigued peers at higher levels of working memory load. This was accompanied by attenuation of the typical load-dependent increase in activation of working memory related brain areas. From these findings we inferred that chronically fatigued students had less available working memory capacity at their disposal compared to their non-fatigued peers.

The abovementioned findings suggest that chronic fatigue is associated with reduced cognitive capacity. Subsequently, the question arises as to what underlies this capacity reduction. Do chronically fatigued students simply possess less cognitive capacity? Or is part of their cognitive capacity preoccupied by other cognitive processes? One way in which the cognitive capacity in chronically fatigued students might be preoccupied refers to emotional sensitivity. In Chapter 7 we demonstrated a relation between chronic fatigue and elevated emotional brain response to pictures with negative emotional content. Prior research showed that emotional salience could in some cases hinder working memory performance (e.g., (Kensinger & Corkin, 2003). This indicates that emotional stimuli can in fact occupy part of cognitive resources, reducing the resources available for other cognitive control processes. Moreover, chronically fatigued students were less likely to engage in reappraisal strategies (Chapter 7). Even though the following

conclusion cannot be drawn from our emotion regulation data, chronically fatigued students may be more likely to use other, cognitively costly strategies such as suppression (Gross, 2002) to deal with their ongoing emotions.

METHODOLOGICAL CONSIDERATIONS

The larger part of this thesis (Chapters 4-7) was based on a mixed-design fMRI experiment in which students with and without chronic fatigue were compared. On top of that, acute cognitive fatigue was manipulated within participants by a cognitive fatigue induction in one session, and a control manipulation in another session. The experimental manipulation allowed us to draw causal inferences regarding effects of a cognitive fatigue induction. This was not possible with effects of chronic fatigue as the group differences only revealed associations between fatigue and neural activations. Thus, with respect to chronic fatigue, it remains unclear whether and to what extent the differences in brain activation are a cause or a consequence of fatigue. However, the fact that we employed a mixed design allowed us to investigate how both groups differed in their response to a cognitive fatigue induction, which provided us with indications for possible underlying mechanisms of chronic fatigue. For instance, our observations in Chapter 5 allowed us to suggest that chronically fatigued students are under normal circumstances able to tap into their cognitive reserve, but they fail to do so with additional cognitive fatigue.

Based on our observations on chronic fatigue, what we do know now is that there are substantial differences related to chronic fatigue in terms of neural processing and, more importantly, these differences appeared to be rather robust: Whether or not additional cognitive fatigue was induced, prominent neural activation differences between students with and without chronic fatigue were present. In addition, neural activation differences were observed in association with different cognitive functions and were thus not restricted to one specific task.

This thesis attempted to demarcate a multidimensional concept by evaluating chronic fatigue in its multifaceted form and by manipulating a more specific subcomponent, i.e.,

cognitive fatigue. As explained in Chapter 1, the term *chronic* was applied as the majority of the fatigued students experienced high levels of fatigue for at least six months by the time they were scanned. The term *control* for the group of non-chronically fatigued students is arguable because, even though recruitment of control participants was based on the average fatigue score of all students together (i.e., lower than the average of all survey respondents), the control group scored well below this mean. Another prerequisite for this group was a 'no' answer to the question whether they suffered from fatigue for longer than two weeks. The combination of these criteria and our general inclusion criteria resulted in a group who scored very low on fatigue. Our 'control group' may thus be slightly more exceptional than the average medical bachelor student. On the other hand, using these criteria, we ensured that the groups differed considerably on fatigue, and not on other criteria, allowing us to draw strong conclusions from our group differences in the context of fatigue.

IMPLICATIONS

Obviously, we do not know whether fatigue is a cause or a consequence of the observed differences in brain mechanisms. But our observations certainly provide us with information that can help students who are troubled by fatigue. Our survey study (Chapter 3) suggested a link between higher levels of fatigue and less planning and self-control skills. These students may thus particularly benefit from additional guidance in keeping up with their schedules and preparing for exams. Given our neuroimaging findings, fatigued students may also benefit from interventions aimed at improving cognitive control, which is found to have positive effects on behavior (Hofmann, Schmeichel, & Baddeley, 2012).

It also appeared that chronically fatigued students were more sensitive to negative emotional stimulation, which we linked to reduced cognitive control over emotions (Chapter 7). Emotional control may thus be another target for improvement in fatigued students. Particularly since chronically fatigued students were less likely to engage in cognitive reappraisal strategies, which are considered as the more effective strategies to

cope with negative emotional events (Goldin, McRae, Ramel, & Gross, 2008; Gross, 1998; Gross & John, 2003). Of course, we do not know whether this would reduce fatigue in these students, but since fatigued students seem more vulnerable to negative emotions, better emotion regulation could reduce the impact of negative stimuli in these students, making them more emotionally resilient.

FUTURE DIRECTIONS

To date, most neuroimaging research in the field of fatigue targets populations with medical conditions, such as chronic fatigue syndrome, multiple sclerosis or traumatic brain injury (e.g., DeLuca et al., 2009). Here we presented neuroimaging research into fatigue in a healthy population, i.e., female medical students. The fact that we found clear effects of fatigue is of practical importance for this particular group of individuals. Whether the findings can be generalized to a broader population depends on future research. For instance, future studies could evaluate whether our findings also hold for males, other age groups, individuals with permanent jobs or individuals with different educational backgrounds.

A second suggestion for future research pertains to the issue of causality. In some cases, fatigue is a clear outcome of changes in the brain – for instance in TBI, complaints of fatigue result from damage to the brain (e.g., Stulemeijer et al., 2006) – but more often it is not exactly clear what causes the experience of fatigue. In this thesis we observed robust alterations in brain activation in chronically fatigued students, but we are not able to decipher whether fatigue is caused by shortcomings of the brain, or whether altered brain function is an outcome of fatigue. To be able to draw causal inferences we need to learn more about the origins of fatigue and its changes over time. In other words, one of the aspects of fatigue that warrants more attention from future research is its course of development in the generally healthy population. Longitudinal research is a key method to unravel the progress of fatigue in relation to cognitive function. In the medical educational context it would be highly informative to investigate how fatigue develops during the residency programs, which is a stage of medical training in which a recent

study showed that high fatigue was most common (Dyrbye et al., 2014). It would be of great value to be able to protect students from high fatigue later on in their training or in their careers.

Third, future intervention studies could elucidate whether fatigue can be reduced or whether fatigued individuals could profit from improving cognitive control or increasing working memory capacity. Prior research has indicated that this can be accomplished by training (Hofmann, Schmeichel & Baddeley, 2012; Jha, Stanley, Kiyonaga, Wong, & Gelfand, 2010; Olesen, Westerberg, & Klingberg, 2004).

A last suggestion for future research builds on our findings in Chapter 7 that demonstrated that chronically fatigued students were more responsive to emotional stimulation. In a world dominated by information flow through television, email and social media, it is most relevant to investigate how such stimuli contribute to the incidence of fatigue in the general population. As late adolescents appear to spend most of their time using these media, with profound influence on their behaviors and achievements (Coyne, Padilla-Walker, & Howard, 2013), this issue is of prominent relevance. Future studies should aim at integrating the impact of such stimuli on neural processing and fatigue. Perhaps particular cognitive mechanisms increase or decrease our risk of becoming fatigued in response overstimulation. Or the other way around: perhaps fatigue increases or decreases our ability to process and cope with the overwhelming amount of stimuli that we currently encounter on a daily basis.

CONCLUSION

Collectively, the studies in this thesis increased our understanding of the complex interplay between fatigue and cognitive processing. Both chronic fatigue and acute cognitive fatigue in generally healthy individuals were associated with substantial changes in cognitive control. The findings provide potential mechanisms of fatigue that involve variations in neural effort and restrictions to cognitive capacity. The results also highlighted the importance and relevance of further research into the course of

development of fatigue and potential interventions for fatigued individuals, notably in higher education.