The Fatigued Brain: Fatigue and Cognitive Functions in Young Adults

Plukaard, S.C.

2015

SUMMARY

Fatigue is an everyday experience that can become problematic when it persists over time. Medical students may be relatively vulnerable to such problems. Over the past years, a link between fatigue and cognitive declines has been established, but many questions as to underlying cognitive processes and neural mechanisms still remain. The studies presented in this thesis explored effects of fatigue on cognitive functions in medical students. To this end, behavioral, questionnaire and neuroimaging data were collected, and acute as well as chronic fatigue was evaluated.

Chapter 1 outlined the theoretical background on fatigue in relation to cognitive functions, and presented research questions that were addressed in the studies. The relevance of targeting university students was explained in the context of a wide range of cognitive challenges they experience during and after the transition from secondary to higher education. This chapter also elaborated on the concept of fatigue itself, its definition and its measurement, as well as on the potential of functional neuroimaging experiments in further understanding the relation between fatigue and cognition.

Chapter 2 described a behavioral experiment in which effects of fatigue on cognitive flexibility were examined in first year university students. Previous research suggested a link between fatigue and reduced cognitive flexibility, but the nature of this reduction remained unclear. The study in this chapter investigated switching between tasks of unequal difficulty. It also incorporated effects of a cognitive fatigue manipulation as well as individual differences in fatigue state at baseline. The results extend the current knowledge on the link between fatigue and task switching by showing that behavioral effects on task switching depend both on the operationalization of fatigue and on differences in task difficulty. In particular, we observed a positive relation between fatigue at baseline and the time it took to switch from one task to the other. Thus, irrespective of task rule, students who were more fatigued at baseline took longer to switch between tasks. Effects of fatigue induced by our cognitive fatigue induction

depended on task rule, as this manipulation resulted in slower switches from the difficult task rule to the easy task rule compared to the opposite direction.

Chapter 3 set out to evaluate the prevalence and associated factors of fatigue in medical bachelor students of the VU University Amsterdam, The Netherlands. This survey study focused on fatigue severity and duration, and on demographic, lifestyle and environmental correlates. In addition, the relative contribution of executive functions was examined. From this study we learned that nearly one third of all respondents were severely fatigued (defined in terms of general fatigue, concentration, motivation and physical activity), as indicated by levels of fatigue that were beyond a critical cutoff score. Also, longer duration of fatigue complaints was associated with higher levels of fatigue. Multiple regression analyses revealed that lifestyle factors contributed little to the level of fatigue reported by students. Results indicated that students who did not suffer from medical conditions, had fewer sleeping problems, engaged more in sports, were satisfied with their study habits, and who were living away from their parents reported lower levels of fatigue. On top of that, planning and self-monitoring appeared to significantly predict the level of fatigue, which confirmed the substantial role of executive functions in the experience of fatigue.

Chapters 4-7 were based on an extensive fMRI experiment in which 26 medical students with chronic fatigue were compared to 26 medical students without fatigue. In addition, cognitive fatigue was manipulated by subjecting both groups to a fatigue inducing session and a control session for 1.5 hours before they were scanned.

Chapter 4 investigated effects of fatigue on resting-state functional connectivity. We limited our examination to functionally relevant networks, i.e., anterior default-mode network, posterior default-mode network, right frontoparietal network, left frontoparietal network, executive control network, ventral stream network, dorsal attention network, and superior parietal network. Results indicated that chronically fatigued students were characterized by reduced functional connectivity in the anterior and posterior default mode network, ventral stream network and dorsal attention network. We interpreted this in terms of less robust intrinsic functional organization in chronically fatigued students. With respect to induced cognitive fatigue, we found increased functional connectivity in response to the fatigue manipulation within the anterior default mode network as well as the ventral stream network. We also found that this manipulation affected the groups differently on functional connectivity in the right frontoparietal network. That is, non-fatigued students increased functional connectivity whereas chronically fatigued students decreased functional connectivity within this network. This implied that chronically fatigued students employed this network less consistently during the fatigue manipulation, or that they made use of different strategies.

Chapter 5 examined effects of fatigue on neural activation when switching between tasks. The neuroimaging data showed that, compared to non-fatigued students, chronically fatigued students were characterized by greater anterior cingulate cortex activation. This was taken to indicate that chronically fatigued students recruited this area as additional brain resource to be able to successfully accomplish the task. A positive relation between activation of this area and the time it took to switch from one task to the other suggested that stronger recruitment of the anterior cingulate cortex coincides with performance declines. As to the fatigue manipulation, the left dorsolateral prefrontal cortex, left premotor cortex and precuneus were more engaged in non-fatigued students after the fatigue manipulation. In contrast, fatigued students engaged these areas more after the control session, but showed a substantial reduction in activation of these areas after the fatigue manipulation. Based on these findings, we suggested that chronically fatigued students exert more attentional effort at baseline, but they failed to do so with additional cognitive fatigue.

Chapter 6 focused on effects of fatigue on neural activation in the context of working memory capacity**.** The students performed a working memory task that consisted of a low, intermediate, and high load condition. Results showed that the pattern of loaddependent activation was different between students with and without chronic fatigue. At the highest load conditions, chronically fatigued students showed reduced neural activation compared to non-fatigued students in typical working memory areas, i.e., the dorsolateral prefrontal cortex, premotor cortex, anterior cingulate cortex and superior parietal cortex. This was accompanied by slower responses of the chronically fatigued students at intermediate and high load. Moreover, only the group of fatigued students showed a correlation between accuracy and activation of the prefrontal cortex and anterior insula/ frontal operculum. This implied that fatigued students could recruit this network as neural compensation. Based on the findings in this study, we suggested that fatigued students differed from their non-fatigued peers in working memory processing and capacity.

Chapter 7 addressed differences in emotion processing and emotion regulation in relation to fatigue. Even though fatigue has been associated with negative mood, increased irritability and reduced cognitive control, the interplay between fatigue and emotion processing has largely been unexplored. Again, differences between students with and without chronic fatigue as well as differences between a cognitive fatigue manipulation and a control manipulation were evaluated. All students performed an emotion regulation task that consisted of three conditions: attentively viewing neutral pictures, attentively viewing negative pictures and cognitive reappraisal of negative pictures. Group effects were limited to the condition in which the participants attentively viewed negative pictures, i.e., without the explicit instruction to reappraise, contrasted with viewing of neutral pictures. Chronically fatigued students showed stronger right amygdala activation, which indicated that chronically fatigued students were more reactive to negative emotional stimuli. Moreover, whereas non-fatigued students showed signs of spontaneous reappraisal in this condition, as indicated by a functional connection between left amygdala and the dorsolateral prefrontal cortex, this was not observed in chronically fatigued students. In the cognitive reappraisal condition, the fatigue manipulation resulted in enhanced activation of the middle frontal gyrus, suggesting an increase in prefrontal effort to exert cognitive control over emotion processes. Together, the results in this chapter suggested differences in the neural dynamics of emotion processing and emotion regulation in relation to fatigue.

Chapter 8 provided concluding remarks in which our findings were summarized and discussed in light of existing literature on fatigue and cognitive control. Functional neuroimaging proved to be an invaluable tool to explore effects of fatigue on cognitive processing. Whereas behavioral effects were relatively minimal and in some cases even absent, we observed robust changes in neural activation when comparing students with and without chronic fatigue as well as our fatigue manipulation and the control manipulation. Our findings contribute to our knowledge on the relation between fatigue and cognition by showing robust fatigue-related changes in neural activation during task switching, working memory performance and emotion regulation. In addition, differences in intrinsic brain activation showed reduced robustness of functional networks in chronic fatigue. A possible common mechanism of fatigue was considered, based on differences in neural effort and cognitive capacity. Higher fatigue was associated with higher neural effort, which was suggested to be based on limited cognitive reserve resources. Furthermore, this chapter also elaborated on practical implications and presented suggestions for future directions.