## Vulnerability of memory function and the hippocampus

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# SUMMARY

Memory is one of several cognitive functions needed to perform everyday tasks, and to successfully interact with and navigate the world. Memory also greatly shapes how we define ourselves and how we relate to the past, present, and future. Because of its significance, understanding why the human memory system is particularly vulnerable to damage and degeneration, is a key area of neuroscientific research. The aim of the present work was to study three distinct conditions that selectively affect memory function and the hippocampus. These conditions are cognitive aging, posttraumatic stress disorder (PTSD), and herpes simplex encephalitis (HSE).

Chapter 1 includes a general introduction to the background and aims of this dissertation. The human memory system and its neuroanatomical correlates are briefly described in order to provide a context for the research presented. Different types of memory function and systems, including short-term, long-term, and working memory, as well as explicit and implicit memory are defined. In addition, brain regions that are involved in memory processes such as encoding and retrieval are explained. This chapter subsequently introduces the vulnerability of memory function and the hippocampus. Within this context, a critical review of studies investigating this area of research is provided and specific goals of the present work are outlined.

Age-related cognitive decline is characterized by memory deficits; rate and degree of decline, however, highly vary between people. Chapter 2 focuses on the impact of everyday lifestyle factors (i.e., physical activity, alcohol consumption, smoking, sleep habits, and social engagement) on memory function in older adults. This research was based on the Longitudinal Aging Study Amsterdam (LASA), an ongoing, prospective, population based-study. A total of 1,966 men and women aged 65 and older provided information regarding their lifestyle habits and participated in neuropsychological assessments every three year over a period of 14 years. We found that physical activity, light to moderate alcohol consumption, and social engagement were associated with better memory function. Smoking tobacco and long sleep duration, on the other hand, were linked to worse memory function. The mechanism behind these findings is likely due to how physical activity, smoking, and alcohol affect cardiovascular health. Social engagement may serve as a type of "cognitive brain training" and indirectly motivate older adults to take care of their health, which in turn affects brain health.

In Chapter 3, we followed up on the LASA cohort by investigating how personality traits that are related to personal control beliefs and proneness to negative emotions, affect memory function in older adults. Analyses showed that higher levels of mastery and self-efficacy were linked to better memory function, while high neuroticism was associated with worse memory function. These findings may be explained by the effect that higher levels of mastery and self-efficacy have on the likelihood that older adults engage in socially and mentally stimulating activities. An independent and enriched lifestyle fosters increased cognitive activity in older adults, which may act as a protective mechanism against age-

related cognitive decline. High neuroticism is linked to chronic stress and anxiety, which can lead to impaired memory function as the hippocampus is highly susceptible to the effects of acute and chronic stress.

The aim of **Chapter 4** was to investigate to what degree PTSD and exposure to early life stressors is linked to shape abnormalities in the hippocampus and the amygdala, and to what degree it impairs memory function. A total of 70 combat veterans, with and without PTSD due to trauma exposure during their military deployment, participated in a Magnetic Resonance Imaging scan as well as memory assessments and clinical interviews. More severe PTSD symptoms were associated with expansion in hippocampal shape, and a higher number of early life stressors was associated with expansion in both hippocampal and amygdala shape. PTSD symptom severity was linked to deficits in memory encoding; however, these associations were not related to shape abnormalities. The involvement of the amygdala in processing emotions such as threat, stress, and fear, may explain shape expansion in this limbic region in individuals who experienced childhood adversity. Although speculative, shape expansion in the hippocampus may be due to a similar mechanism.

PTSD is highly co-morbid with alcohol use disorder. Hippocampal volume loss and memory deficits are linked to both disorders, raising the question whether a dual diagnosis leads to greater pathology in this brain region. **Chapter 5** presents a meta-analysis of voxel-based morphometry studies measuring gray matter volume loss in patients with PTSD and patients with alcohol use disorder, each compared to healthy control subjects. Examining spatial overlap showed volume loss bilaterally in the dorsal and rostral anterior cingulate cortex (ACC) but not in the hippocampus across both disorders. In PTSD, abnormalities in ACC function may lead to an inability to down-regulate emotional responses to trauma reminders or potential threats. In alcohol use disorder, impaired cognitive control may lead to continued drinking despite cessation efforts.

In **Chapter 6** of this dissertation, we present a unique case study of a young man with severe anterograde amnesia following extensive bilateral damage of the medial temporal lobe, including the hippocampus, following Herpes Simplex Encephalitis. This case presents the rare opportunity to study direct brain-behavior interactions. Results from detailed neuropsychological assessments and neuroimaging scans are presented in this chapter. Moreover, we illustrate how patient A.V., who is not able to form new declarative memories, utilizes smart technology to adapt to and compensate for his severe memory impairment. A. V. is likely able to learn how to use smart devices via intact procedural memory function and is able to navigate the technology via intact executive functions.

The final **Chapter 7** includes a summary of study findings as well as a discussion within the framework of current research, limitations, methodological considerations, and future directions.