Vulnerability of memory function and the hippocampus

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CHAPTER 1

GENERAL INTRODUCTION

Memory is a central cognitive function that is not only necessary for carrying out daily tasks, it is also critical for the ability to interact with the world in a meaningful way, including engaging in social interactions and maintaining relationships. Arguably, memory's most important role is to provide a person with the ability to form a sense of self-identity. The groundwork for our current understanding of the human memory system was laid by the famous patient H.M., who was left with severe amnesia following an experimental brain surgery that was performed in an attempt to treat his intractable epilepsy (Scoville & Milner, 1957). In 1962, Brenda Milner demonstrated that patient H.M. was able to learn a new motor skill despite having no conscious recollection of the actual practice sessions, providing evidence for the existence of two separate, independent memory systems (Milner, 1962). This understanding prompted decades of research with patient H.M. and an evolution of existing memory theories.

THE HUMAN MEMORY SYSTEM AND NEUROANATOMICAL CORRELATES

The memory system is divided into several subsystems, each carrying out distinct functions and relying on different brain regions. The next two paragraphs provide a simplified explanation of the different memory functions and their neuroanatomical correlates in order to provide a context for the work described in this dissertation. Memories that are stored and retrieved at a later time are called long-term memories. Memories that are held in working memory for very brief periods of time, on the other hand, are referred to as short-term memories (Baddeley, 2003). The process of forming memories is called encoding while the process of recalling memories is referred to as retrieval (Lezak, Howieson, Loring, & Fischer, 2004). Long-term memories consist of two distinct systems: explicit (or declarative) and implicit (or non-declarative) memory (Squire & Zola-Morgan, 1991). Explicit memory, which is further subdivided into semantic and episodic information, refers to the conscious recollection of facts and events, respectively (Squire & Zola-Morgan, 1991). Episodic memories are linked to time and place, and include autobiographical memories. Implicit memory refers to motor skills and behaviors that are formed unconsciously through conditioning, priming, or procedural learning (Squire & Zola-Morgan, 1991).

Both encoding and retrieval of explicit memories depend on the hippocampus and adjacent regions in the medial temporal lobe (MTL), while memories are stored throughout the cortex (Lezak et al., 2004). The hippocampus receives its main input from the entorhinal cortex, which in turn receives information (1) from the frontal, temporal, and parietal lobes through the perirhinal or parahippocampal cortices, or (2) directly from the superior temporal gyrus as well as the amygdala, orbital frontal, cingulate, and insular cortices (Phelps, 2004; Squire & Zola-Morgan, 1991). Emotional properties are attached to memories via the close neural connections between the hippocampus and the amygdala (Phelps, 2004). The prefrontal cortex is engaged during both encoding and retrieval of

information. Damage to the hippocampus and adjacent regions causes severe memory deficits, including anterograde amnesia (Scoville & Milner, 1957).

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VULNERABILITY OF THE MEMORY SYSTEM

The human memory system is vulnerable to damage and degeneration. Memory function is one of the first cognitive functions affected by the aging process; both normal aging and age-related neurodegenerative diseases like Alzheimer's disease are characterized by difficulties in learning and recalling information, in particular episodic memories (Lezak et al., 2004). While age-related decline of memory function is inevitable, there is a substantial difference in the rate of decline. This difference raises the question which factors influence how quickly or how slowly people experience memory problems with advancing age in the absence of dementia, and whether this process can be slowed down or accelerated by various factors including personality traits and lifestyle choices.

While research has shown an effect of certain lifestyle factors, including physical activity (Ku, Stevinson, & Chen, 2012), smoking tobacco (Anstey, von Sanden, Salim, & O'Kearney, 2007), sleep habits (Scullin & Bliwise, 2015), alcohol consumption (Ganguli, Vander Bilt, Saxton, Shen, & Dodge, 2005), and social engagement (James, Wilson, Barnes, & Bennett, 2011) on cognitive aging, there are only few longitudinal studies exploring these effects. In addition, existing research findings have been inconsistent and limited by methodological shortcomings, such as not controlling for co-morbidities or other confounding factors, subjective versus objective assessment tools, and the use of brief memory screenings as opposed to detailed neuropsychological testing. As a result, there is a need in the field for longitudinal studies that include large, well-characterized cohorts and that investigate the influence of lifestyle choices on memory decline over time.

Individual differences in dealing with stressful experiences, availability of coping skills when presented with challenges, as well as the presence and degree of negative thought patterns likely have an effect on brain health. Such attitudinal differences can be characterized by measurable personality constructs, which can provide important information regarding someone's proneness to experiencing stress as well as the likelihood to engage in activities that promote independency in older adults. There is a growing body of research showing that personality traits may affect the rate of cognitive decline (Curtis, Windsor, & Soubelet, 2015; Luchetti, Terracciano, Stephan, & Sutin, 2015). However, a direct link has not been adequately established (Jelicic et al., 2002; Wetherell, Reynolds, Gatz, & Pedersen, 2002).

Besides personality and lifestyle choices, environmental factors that are to some degree out of our control, can also affect our memory function. Chronic and acute stress can have harmful effects on the brain, in particular on the hippocampus (Kim & Diamond, 2002; Popoli, Yan, McEwen, & Sanacora, 2012). Individuals with Posttraumatic stress disorder (PTSD) experience chronic stress that is characterized by a number of symptoms affecting cognition, mood, and physical reactivity, including intrusive thoughts,

avoidance of reminders, negative beliefs and emotions, detachment, irritability, sleep disturbance, and hypervigilance, following exposure to an extremely stressful event that involved actual or threatened death, injury, or sexual violence (American Psychiatric Association, 2013). The role of memory in PTSD is multifold: (1) trauma-related memory symptoms such as flashbacks, avoidance of trauma reminders, intrusive memories, and difficulties remembering important aspects of the trauma as well as (2) deficits in learning and recalling emotionally neutral information accompanied by problems concentrating (American Psychiatric Association, 2013).

While both frontal and limbic regions, including the hippocampus, have been implicated in the neurobiology of PTSD (Logue et al., 2018; Nardo et al., 2013; O'Doherty et al., 2017; Zhang et al., 2011), which exact neural substrates underlie these symptoms is still unclear. This picture is further complicated by common co-morbidities or pre-disposing risk factors in individuals with PTSD. PTSD frequently co-occurs with alcohol use disorder; the presence of both disorders predicts more psychiatric problems (Driessen et al., 1998) and worse treatment outcomes (Najavits, Norman, Kivlahan, & Kosten, 2010) than either alone. In addition, research shows that individuals who develop PTSD following a traumatic event experienced during adulthood have often also experienced early life stress (ELS; Brewin, Andrews, & Valentine, 2000). It is unclear, however, how co-occurring psychiatric conditions or prior exposure to trauma affect the brain, and in particular the hippocampus, in individuals with PTSD.

While the hippocampus is extremely vulnerable to several distinct conditions, it also shows the potential for plasticity (Cotman, Berchtold, & Christie, 2007; Maguire et al., 2000; Schmidt-Hieber, Jonas, & Bischofberger, 2004). In addition, while stress can have direct negative effects on the hippocampus, there are also factors that have protective effects and that can promote cell growth. The aim of this dissertation is to understand this complex interplay between health conditions and both the hippocampus and memory function, as well as how to influence structural and functional changes in the hippocampus. Furthermore, we will investigate whether it is possible to compensate for severe memory loss and the implications of such interventions for memory disorders.

AIM AND OUTLINE OF THE THESIS

The present PhD research was conducted at the Vrije Universiteit Amsterdam Medical Center in collaboration with the Longitudinal Aging Study Amsterdam (LASA), the University of California, San Diego, as well as the Veterans Medical Center in San Diego, California. The aim of this research project was to investigate the vulnerability of the memory system from several different angles. In particular, I chose three distinct conditions (normal aging, PTSD, and herpes simplex encephalitis) that selectively target memory function and the hippocampus, and studied them from neuropsychological and neuroimaging perspectives. In addition, I investigated which factors may contribute to deteriorating memory function, and how to improve or compensate for impaired memory

function and amnesia. The main research question of this research project was: Which factors affect memory function and the hippocampus? This research question was broken down into sub-questions that are addressed in the different sections of this thesis.

I started this research project by assessing whether decline of memory function during the aging process is accelerated or slowed down by lifestyle factors or personality traits. Data to investigate these research questions was derived from LASA, an ongoing longitudinal research study that started in 1991. The aim of LASA is to collect information on cognitive, emotional, social, and physiological functioning in aging individuals (55 years and older) in the Netherlands.

The first research question was: To what degree do everyday life choices affect memory function? To investigate this question, we conducted neuropsychological analyses of the LASA cohort. Specifically, we studied the long-term impact of modifiable lifestyle factors (i.e., physical activity, alcohol consumption, smoking, sleeping problems, and social engagement) on memory function in men and women aged 65 years and older (N=1,966) over a period of 14 years (**Chapter 2**). We hypothesized that sleeping problems and smoking have harmful effects on memory function over time, and that physical and social activities, moderate alcohol consumption, as well as high sleep quality have long-term protective effects on memory function in older adults. Lifestyle was measured during clinical interviews and questionnaires. We included learning, recall, and retention measures as well as lifestyle factors in the analyses.

In order to further investigate which factors play a role in individual differences in age-related memory decline, the second research question was: To what degree do personality traits affect memory function? We were particularly interested in exploring to what degree the personality traits mastery, self-efficacy, and neuroticism account for differences in age-related memory decline in older men and women (N=1,966) over a 14-year period (**Chapter 3**). Personality was measured with self-rating questionnaires while episodic memory functioning was assessed with a list-learning task. We expected to find an association between slower memory decline and high levels of both mastery and self-efficacy as well as poorer memory function in those with personalities characterized by high neuroticism.

Besides lifestyle factors, personality traits, and lifestyle choices, we were interested in investigating the effects of trauma and chronic stress on the hippocampus and memory function. The third research question was therefore: What is the impact of posttraumatic stress and early life stress on hippocampal and amygdala shape and episodic memory function? In **Chapter 4**, we explore whether more severe PTSD symptoms and exposure to ELS are linked to structural changes in the hippocampus and the amygdala as well as memory impairments. The aim of the study was to complete a vertex-based shape analysis in addition to calculating overall volume of the hippocampus and the amygdala as there are only few studies using the former technique or both. Assessing shape allows the detection of both indentation and expansion of these subcortical brain structures. The study included male veterans (N=70), with an average age of 34 years, who were

exposed to a traumatic event during their deployment to a combat area. PTSD symptoms were assessed with both clinical interviews and questionnaires. Presence of ELS during childhood or adolescence included domestic violence as well as emotional, physical, and sexual abuse. Moreover, episodic memory function was assessed in this cohort.

A common co-morbidity of PTSD is alcohol use disorder (Norman, Haller, Hamblen, Southwick, & Pietrzak, 2018). Alcohol use disorder has been linked to volume loss in the hippocampus (Mechtcheriakov et al., 2007) as well as to deficits in memory function (Chanraud et al., 2009). The combined symptom load of both disorders poses a significant burden to the patient, yet neuroimaging research of structural changes in the brain that may be shared across both disorders is limited. The fifth research question was therefore: are co-morbid PTSD and alcohol use disorder associated with structural changes in the same brain regions? In **Chapter 5**, we present a dual meta-analysis of voxel-based morphometry (VBM) studies in order to assess the overlap in gray matter volume loss in PTSD and co-morbid alcohol use disorder. Meta-analyses were performed of eight studies exploring gray matter differences in patients with PTSD (N=165) vs healthy controls (N=173) as well as 13 studies comparing the brains of patients with alcohol use disorder (N=456) vs healthy controls (N=522). We subsequently explored the overlapping neural substrates of both disorders.

Patients with selective bilateral damage to the MTL offer the unique opportunity to investigate the direct relationship between the hippocampus and memory function, and to observe the functional outcomes of the damage in terms of everyday life. However, such cases are extremely rare and only occur in uncontrolled environments if the brain is infected with the herpes simplex virus. The herpes simplex virus shows a selective affinity for the medial temporal lobe (Damasio & Van Hoesen, 1985), leading to severe damage of the hippocampus and adjacent brain regions or to death if not immediately treated with antiviral medication (Sköldenberg et al., 1984). In the **Chapter 6** of this dissertation, we introduce a young man (A.V.) with profound anterograde amnesia following severe bilateral damage to the MTL, including the hippocampus, showing striking similarities to the neurological and cognitive profile of patient H.M. Patient A.V. participated in comprehensive neuropsychological assessments and neuroimaging scans over a period of 3 years. Results from these studies as well as implications for the understanding of the memory system are presented. In addition, this final chapter illustrates how patient A.V. uses smart technology to compensate for his memory impairment, suggesting that smart technology can take over the brain's declarative memory system. Implications of the use of these devises for the management of memory disorders and age-related memory decline are discussed.

A summary of all studies and a discussion of the findings are presented in **Chapter 7**. Implications for a better understanding and management of memory disorders are also discussed. Furthermore, limitations and shortcomings of the studies and recommendations for future research are provided.

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