Stress and memory in health and disease

Impact on Alzheimer's disease and memory mechanisms

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Preface

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In our modern society, individuals are regularly exposed to stress. Stress can involve challenging and threatening (physiological and psychological) experiences that ask for adaptive, often behavioural, responses, like the "flight, fright or fight" response. Homeostasis, the establishment of a dynamic internal equilibrium, plays a central role in one's adaptive responses upon stressful experiences[1–7]. Consequently, the physiological and behavioural responses experienced in response to stress are all intended to restore the changes in homeostasis evoked by stress. Such adaptive 'coping' with stress requires a rapid activation of numerous bodily systems in response to a stressor as well as an adequate termination when the stressor has seized.

Glucocorticoid hormones, which are released in elevanted levels from the adrenal glands in response to stressors, play a central role in such coping with stressful experiences. These hormones orchestrate the energy supply to challenged tissues and control the excitability of neuronal networks that underlie learning and memory processes. In particular, glucocorticoid hormones facilitate the acquisition and storage of new information, while promoting the extinction of less relevant information[8], thereby governing an adaptive and often protective response to stressors. Despite the undeniable relevance of stress for learning and memory and overall survival, exposure to stressful experiences and stress hormones have been related extensively to disruptive effects on homeostasis and to the risk for stress-related disorders such as depression, anxiety and posttraumatic stress disorder[9–13]. For example, it has been hypothesised that chronic stress increases the costs of reinstating homeostasis (allostatic load[2]), which increases the vulnerability for (mental) illnesses[14].

Although suffering from "stress" is considered a modern affliction (with the World Health Organisation proclaiming it to be the Health Epidemic of the 21st century), the awareness that exposure to stressors can have substantial consequences can be traced back to work done by ancient philosophers dating back as far as Aristotle and Hippocrates[15]. Over the centuries, various nonphysical phenomena have been proposed to either cause disease, or at least contribute to the development of psychological or biological disease[15]. The first "modern" definition of the term stress is considered to be posed by Hans Selye in the first half of the 20th century, after observing that chronic exposure to stressors, through overproduction of, at that time undefined, chemicals and hormones, resulted e.g. in ulcers and high blood pressure[6]. Although ulcers were later shown to be caused by bacteria rather than stress[16], his studies laid down the groundwork for a long line of research addressing the fundaments

between stress and disease.

Activation of the hypothalamic pituitary adrenal (HPA) axis, resulting in the synthesis and release of glucocorticoid hormones by the adrenal glands, plays an important role in adaptation to stress, a discovery for which Kendall, Hench, and Reichstein jointly received the Nobel Prize for Physiology and Medicine in 1950. The notion that glucocorticoids could affect higher brain regions was revealed by Bruce McEwen in 1968, when he showed that corticosterone was predominantly retained in hippocampal neurons[17], and by the discovery by Hans Reul and Ron de Kloet of the high-affinity mineralocorticoid receptor (MR) and the lower affinity glucocorticoid receptor (GR) in the brain[18]. We now know that the activation of MRs and GRs activates non-genomic and genomic pathways that are critical in the regulation of homeostasis, neuronal excitability and behavioural adaptation. Via activation of MRs and GRS, glucocorticoid hormones promote selective attention, memory retrieval, appraisal, and the expression of fear and emotion, as well as regulation executive function and memory storage[4].

Another conceptual advance in the history of early stress research came with the "Developmental Origins of Health and Disease" (DOHaD) hypothesis, which postulates that perinatal environmental factors play an important role in determining the risk to develop pathology later in life[19]. Initially, this theory centred around the effects of e.g. perinatal malnutrition on the development of later metabolic syndromes. However, also other adverse events early in life, such as experiencing emotional neglect, physical abuse or traumatic events have been associated with the risk for developing psychopathologies like anxiety disorders and depression[20–23], cognitive dysfunction in later life[24–26], accelerated aging[27] and an increased vulnerability to the development of age-related diseases such as Alzheimer's disease[28]. This suggests that programming of the brain and/or stress systems by events early in life can be a major determinant for the risk to develop later-life cognitive or emotional problems. Much effort is undertaken to identify the mediating mechanisms, and epigenetic modifications are believed to be an important mechanism by which early adversity can induce more or less persistent molecular (and behavioural) alterations[29], although additional mechanisms cannot be excluded.

With the development of the genomic toolbox that has become available over the past decades, the concept of genetic susceptibility to stress, or "gene x environment interactions", has attracted considerable research interest. For instance, polymorphisms of certain genes can render individuals more or less susceptible to stressful life events. Furthermore, the ability to model

the specific genetic components of e.g. Alzheimer disease by overexpressing different variants of single or combined genes, thereby modelling different aspects of the disease, have greatly accelerated research in this field. This allows for investigating the interaction between specific genetic factors and the individual's sensitivity to stress-related events. It should be mentioned though that the limitations of these models have by now also been appreciated, as many of the potential treatment targets arising from these genetic animal studies have subsequently failed in clinical trials, possibly due to a lack in construct validity of the models and/or timing of the interventions.

Finally, over the last decade, the advanced molecular techniques allowing for capturing and manipulating specific neurons have expanded exponentially. In particular, the discovery of opto- and chemogenetic tools to modify activity of specific neurons by the genetic or viral expression of artificial proteins (opsins or engineered receptors, respectively)[30,31], notably in predefined distinct neuronal populations, have advanced the field. Using e.g. light sources (for opsins) or exogenous compounds (for chemogenetic receptors), the activity of these neurons (and behaviour) can subsequently be manipulated. These techniques have enabled previously unimaginable levels of functional circuit mapping, and give rise to a plethora of unexplored research avenues in neuroscience.

Among these is the quest for "what is memory", and "how are these memory represented in the brain", including answers to questions as to where and how specific memories are stored, consolidated, and retrieved. This archaic question was first posed by Richard Semon in 1921 when he formulated the Engram Theory[32], which assumes that learning activates coordinated, and yet to be identified, "neuronal excitations" that he believed to be responsible for the formation of a memory. Building on his theory, neuroscientists now have the toolbox to recognise that learning activates a subpopulation of neurons responsible for a given memory trace, while reactivating these cells pharmacologically or by relevant cues results in the retrieval of the specific memory[33]. Using these novel techniques, researchers are now finally able to capture, manipulate or reactivate memory traces in live animals, which unveils an entire new level of understanding of how the brain functions, and also allows to study in a more direct and specific manner how stress hormones can modulate these functions and the circuits that encode them.

Outstanding questions addressed in this thesis

Standing on the imaginary shoulders of these, and many other giants, this

thesis aims to provide insight into some of the biological mechanisms underlying the effects of how environmental experiences and stress hormones influence learning and memory processes in health and disease.

The focus will be on how early life programming of the brain during a highly sensitive developmental time window can confer lasting effects on later brain plasticity and structure, and cognitive and emotional functioning. In these studies, I will focus on the effects of early life experiences on aging and age-related disease, with a specific focus on Alzheimer's disease. In addition, I studied the mechanisms of how stress hormones influence memory formation under healthy conditions. The following outstanding questions will be addressed:

I. Are experiences early in life critical for determining the later-life vulnerability to the development of Alzheimer's disease related symptomatology and pathology?

II. Which biological systems and processes underlie the early life stress-induced modulation of cognitive function and Alzheimer's disease related pathology?

III. How do stress hormones modify the properties of neurons that underlie learning and memory?

Why animal models?

Human literature has revealed various associations between early life experiences and later life cognitive and emotional functioning, underscoring the possible importance of the early postnatal period in shaping the brain. However, the long time lag between the early life environment and the onset of AD symptoms hampers a deeper understanding of the underlying causes and possible mechanisms. To address this, animal models allow for a more detailed investigation of this relationship that may help to identify the mechanisms by which environmental factors during the early life period can affect AD symptoms and pathology. The ability to e.g. model specific genetic (risk) factors for AD and the precise control over (timing of) life events makes such animal models highly suitable for investigating the pathological mechanisms underlying the interactions between genes, the (early) environment and AD. In addition, employing animal models enables the specific modulation of specific genes, employ viral vectors and/or other pharmacological compounds, that are required for an in-depth investigation into the abovementioned questions.

Outline of this thesis

The overarching goal of this thesis is to understand how stress, either chronically early in life or acutely after learning experiences, affects learning and memory processes in the adult and aging brain, and how such effects may arise. The first aim was to elucidate whether positive and/or negative early life experiences contribute to a different onset or exacerbation of cognitive decline in relation to Alzheimer's Disease (AD). To answer this question, I investigate the long-lasting consequences of early life experiences on synaptic plasticity, neuropathological parameters and on behaviour in wild type mice and in relevant transgenic mouse models for AD. I further studied whether early life adversity can be prevented by targeting the hypothalamus-pituitary-adrenal (HPA)-axis later in life. In the second part of this thesis, I focus on the role of the NMDA receptor as a mediator between early life stress, AD, and aging. In the final part of this thesis I study how glucocorticoid hormones, which are released in elevated levels upon activation of the HPA-axis, alter memory formation. I therefore study how these hormones regulate the number and properties of training-activated neurons ("memory engram cells") and whether these cells underlie the memory enhancing effects of glucocorticoid hormones.

Chapter 1 reviews literature on the effects of early life experiences on behaviour and functional plasticity of the brain, and how these effects are mediated. I discuss that early life experiences may long-lastingly alter HPA axis (re-)activity, thereby shaping behaviour and brain function during adult life and during aging, and address the hypothesis that early life experiences, either positive or negative, can alter the vulnerability for developing AD pathology.

Effects of early life experiences on AD development

In **Chapter 2,** I investigate the effects of positive and negative early life experiences, by manipulating the amount of maternal care that pups receive, on the lifespan of mice that express amyloid and tau AD neuropathology (biAT mice), and study whether these effects are associated with alterations in learning and memory, neuronal morphology, and in neuropathological hallmarks of AD in relevant brain regions for learning and memory.

Chapter 3 extends on these observations by investigating, in a different, well-characterised mouse model for amyloid-β-associated neuropathology (APPswe/PS1dE9 mice), whether enhanced levels of maternal care can prevent or delay the AD-induced changes in neuropathology and cognitive decline at different ages. I further investigate whether these alterations are paralleled

by alterations in HPA-axis reactivity and pathological markers in hippocampal subareas and the amygdala in adult animals.

To further investigate the role of the HPA axis in the effects of early life adversity on behavioural and pathological changes related to AD, I investigate in **Chapter 4** how early life stress affects Aβ-neuropathology in APPswe/PS1dE9 mice, another genetic mouse model for AD, and I study alterations in the amyloidogenic pathway that may underlie these early effects in 6 and 12 month old mice, i.e. before and after the onset of cognitive decline. In addition, I address whether glucocorticoid signalling is altered in these mice, and whether interventions targeting the glucocorticoid receptors at older age can reverse the early life stress-enhanced AD phenotype.

The role of the NMDA receptor in early life stress, aging and AD

In **Chapter 5** I test the hypothesis that the early life stress-induced cognitive deficits at 1 year of age are associated with alterations in synaptic plasticity. I investigate hippocampal synaptic plasticity in APPswe/PS1dE9 mice and wild type littermates, focusing specifically on the role of GluN2B containing NMDA receptors. I further evaluate how this affects emotional fear memory formation.

In addition, I explore the mechanisms underlying the alterations in synaptic plasticity and cognitive deficits in APPswe/PS1dE9 mice following early life stress in **Chapter 6**, by treating mice with the glutamate modulator riluzole. To further understand the relationship between early life stress, AD, and aging, I focus on the glutamatergic signalling pathway and the expression of the excitatory amino acid transporter 2.

In order to better understand how (early life) stress affects learning and memory processes in aging and an AD background, it is imperative to understand how these processes are regulated under non-pathological conditions. Therefore, in **Chapter 7** I investigate short-term and long-term synaptic plasticity in wild type mice, and I propose a central role for the NMDA receptor subunit 2B in mediating the effects of early life stress on emotional and/or hippocampus-dependent memory formation, glucocorticoid signalling and receptor expression.

The effects of acute glucocorticoid exposure on memory formation

In **Chapter 8**, I investigate whether brief administration of corticosterone after training enhances consolidation of fear memories. Using different auditory

fear conditioning paradigms, I evaluate how corticosterone influences the strength of the memory trace, and the ability to extinguish fear memory. I further test whether and how these effects are sex-dependent.

In **Chapter 9,** I describe the effects of acute glucocorticoid exposure on memory strength and specificity. I identifiy and characterise the neurons responsible that may be part of a so called "engram", and determine their electrophysiological and molecular properties. By capturing and manipulating these neurons I investigate whether these neurons are responsible for the effects of acute glucocorticoid exposure on memory formation.

Finally, in **Chapter 10,** I summarise the main outcomes of this thesis, and discuss them in a broader perspective. First, I discuss how early life experiences can program brain (or neuronal) architecture and function persistently, and how this may impact cognition and neuropathology in an AD background. I speculate that besides a direct modulation of AD neuropathology by the HPA axis, early life experiences may also shape the "brain reserve" or "cognitive reserve", thereby rendering an individual more resilient or vulnerable to AD-associated impairments. Secondly, I discuss how glucocorticoid hormones influence memory strength and memory specificity, and in particular the role of memory engram cells. Finally, I conclude with remaining outstanding questions that can be addressed in order to move the fields of how (early life) stress alters memory formation ahead.

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