Keep calm and age well:

Behavioural and electrophysiological investigations into the effects of cumulative stress exposure on ageing cognition

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Acknowledgements

At certain times in our lives we come across information that unifies many different phenomena we were wondering about under one explanation. Such moments are scarce and precious, they change our understanding of self and the world around us. They leave us staggered, amazed that we did not think of this explanation ourselves, and incredibly grateful that someone else has offered it. I had one of these moments during my second year of studying Psychology at graduate level when I was first taught that the brain is plastic; the structural connections between neurons develop, decay and are reformed as different pathways, depending on our experiences, our interactions with the world around us. The physiological process that translates into the person we are is malleable, nothing is set in stone!

Sitting in the dim lecture hall I thought back through the years remembering the time I first met my great uncle, my grandfather's identical twin. A six-year-old girl, I spent the week my great uncle and aunt stayed with us in a continual state of amazed puzzlement. My grandfather and great uncle were so alike: they spoke the same, they moved the same, they would chuckle at the same point in a story. But

what fascinated me even more than this uncanny similarity were the times at which, jarringly, they were different: my great uncle would all of a sudden make a comment my grandfather never would have made. Later in life, I would see them disagree, passionately arguing about a topic they both felt very differently about and my adolescent self would ponder the same question that had plagued the six-year-old girl: 'They look the same, so how can they be different?' became 'They have lived very different lives so it makes sense they are different people. But if their underlying physiological make-up is the same, where does the difference come from?' Here, so many years later I had the answer to this and to so many other questions I had gathered. I felt very fortunate that day and I was even more fortunate when the man who had given me this information later on accepted me as one of his PhD students to undertake my doctorate, exploring one of the ways in which experiences can shape the brain. I would therefore like to offer my heartfelt thanks to a number of people without whom this thesis would not be what it now is:

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"Danke – ich weiß.

Gern geschehen – glaube mir."

General abstract

The research presented in this thesis comprises a body of work dedicated to continuing and enriching past exploration into the impact cumulative life stress exerts on ageing cognition. In order to extend previous work into this topic, behavioural measures were paired with electroencephalographic recordings of the cortical oscillatory activity thought to underlie cognitive operations. In a theoretical sense, work presented in this thesis strengthens past investigations highlighting the adverse effects of life stress on elderly peoples' working memory abilities by replicating the effect under conditions of increased experimental rigour. It further provides evidence that the detrimental effects of cumulative stress extend to the domains of executive control and spatial memory. Electrophysiological findings obtained during task execution and at rest indicate pronounced changes in the oscillatory activity of aged high stress individuals' delta, theta, alpha and gamma bands and are thus the first to

demonstrate that cumulative stress affects the underlying neural processes related to successful task execution. As such, from a methodological standpoint, the current research strongly advocates the use of neuroscientific tools such as the electroencephalogram to gain an increased understanding of the mechanisms by which increased stress exposure evokes progressive cognitive decline in old age. Combined, the work presented in this thesis demonstrates the negative consequences of leading a highly stressful life for the integrity of multiple cognitive functions in old age and is the first to provide an indication of how cumulative stress affects both cortical and (indirectly) subcortical regions of the brain necessary for successful cognitive functioning.

Overview of chapters

This thesis is comprised of seven chapters which address the effects of cumulative life stress on ageing cognition by employing a wide-ranging repertoire of behavioural paradigms and neuroscientific tools. Chapter 1 introduces the main topics that concern this thesis: age-related changes to the brain and cognitive functioning as well as the effects of stress on the organism. Chapters 2 through 6 represent the empirical contributions of this work. As such, Chapter 2 explores differences of acute stress reactivity between elderly and young individuals, Chapter 3 investigates previously presented evidence on the way cumulative stress affects elderly participants' working memory performance and oscillatory activity, while Chapter 4 extends the findings of adverse effects of cumulative stress exposure on elderly peoples' behavioural and oscillatory performance into the realm of executive control. Chapter 5 investigates age- and stress-related performance decrements in a task and frequency band thought highly dependent on intact hippocampal performance, while Chapter 6 determines electrophysiological resting state power differences among both age and stress groups. Chapter 7 concludes with a general discussion about the

theoretical, methodological and practical implications of this work. A short summary of each chapter is provided below.

Chapter 1: An Introduction to Stress and the Ageing Brain

This chapter introduces the fundamental concepts and background relating to this thesis. As such, it provides an overview of the prominent age-related changes which take place in the brain on a morphological, chemical and electrophysiological level. It proceeds to document past research into cognitive performance decrements which are known to accompany old age, specifically in the domain of memory and executive inhibitory control, while taking into account certain health behaviours which have been implicated in either protecting or exacerbating ageing cognitive decline. Finally, it introduces the concept of stress and provides an overview of the different forms of stress and their known impact on the (human) organism.

Chapter 2: Acute Stress Reactivity

Building on past research indicating that elderly individuals may manifest an increased vulnerability to acute stress exposure as a result of decreased coping resources, the present chapter explores age differences in declarative memory performance (experiment 1) and electrophysiological processing patterns (experiment 2) over a series of two experiments while using galvanic skin recordings as a measure of stressor effectiveness. These experiments were undertaken in order to disassociate the possible impact of acute stress from long-term stress effects, addressed in later chapters of this thesis.

Chapter 3: Cumulative Stress and Ageing Working Memory

The research presented in this chapter was motivated by earlier reports about the adverse effects of cumulative life stress on elderly individuals' working memory capabilities. As such, we investigated stress-related age differences in the behavioural

and oscillatory domain on two working memory tasks, one of which required the co-ordination of multiple sub-processes relating to working memory (experiment 3), whereas the other differentiated between the different working memory stages (encoding, maintenance, retrieval) in serial fashion (experiment 4). By replicating this finding, we hoped to address a number of open questions such as controlling for the impact of certain behaviours known to have an effect on cognitive health and accounting for the perceived gravity of the stressful experience. Results of this chapter have recently been published in the journal 'Neurobiology of Aging'.

Chapter 4: Cumulative Stress and Ageing Executive Control

This chapter aimed to investigate whether the observed performance and oscillatory changes cumulative stress produced among elderly participants with regard to working memory extended into the related domain of executive inhibitory control while simultaneously addressing discrepancies within the literature relating to the inhibitory Flanker paradigm. This chapter therefore explores whether high levels of experienced stress produce behavioural shortcomings on a Flanker task as well as electrophysiological changes to the alpha bandwidth of the EEG (which is related to inhibitory processes). It also discusses the way in which results contribute to the on-going debate about the manifestation of age effects in the Flanker paradigm. The findings presented in this chapter have been submitted for publication.

Chapter 5: Cumulative Stress and Aged Spatial Performance

This chapter picks up on the large body of neuro-chemical investigations which highlight that hippocampal cells have a heightened vulnerability towards the adverse effects of stress. The present chapter therefore explores age- and stress-related performance differences on a spatial memory task thought sensitive to hippocampal impairments while simultaneously recording electrophysiological

activity in the theta frequency band which is proposed to indicate cortico-hippocampal interactions during the process of memory formation. Results of this chapter have recently been published in the journal 'Hippocampus'.

Chapter 6: Cumulative stress and resting state power changes

Research presented in this chapter aims to address whether the electrophysiological changes manifested by high stress elderly individuals during the completion of cognitive tasks were also apparent in the system at rest. The present chapter therefore compares stress- and age-group differences in resting state power across the delta, theta, alpha, beta and gamma frequency ranges by pooling the resting-state data collected from participants taking part in the above-mentioned studies.

Chapter 7: General discussion

The final chapter highlights the theoretical and methodological contributions of the presented work. Limitations, further research directions as well as practical implications highlighted by the current findings are discussed as well as concluding comments offered.

Author note

Each of the chapters 3 through 6 was written with the intention to be submitted for publication. As such, while a common theme connects them all, each can stand alone as an independent piece of research. As a consequence, certain methodological approaches and concepts are explained multiple times and this will necessarily cause some repetition throughout the text.

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Chapter 1: An Introduction to Stress and the Ageing Brain

The Ageing Brain and Ageing Cognition

General Morphological and Chemical Changes

The global share of older people (> 60 years) is steadily increasing at a rate of 2.5% per decade and as such, is expected to more than double from 841 million in 2013 to over 2 billion individuals by 2050 (UN, 2013). If this trend continues, elderly people are expected to exceed the number of children for the first time in 2047 (UN, 2013). This population ageing has major social and economic consequences which highlight our need to understand the mechanisms underlying age-related physiological and cognitive changes as well as devote resources towards researching ways in which health and independence can be preserved into high old age. The following chapter will summarise current knowledge about the way age impacts on the brain in a morphological, chemical and electrophysiological manner, as well as provide an overview of prevalent age-associated cognitive changes. To conclude, it will discuss prominent factors known to impact on the rate of age-related cognitive decline and introduce the concept of stress as one such factor.

Age-related changes in the brain have been well documented over past decades and have benefitted from technological advancements that enable a more detailed, in-depth picture of the way in which the brain changes with advancing age. Early autopsy studies of normally ageing individuals found age-related decreases in both brain volume and weight (Davis & Wright, 1977) and hypothesised that these might be the result of neuronal loss in areas such as the cerebral cortex, basal ganglia and brain stem (Bugiani et al., 1978; Morrison & Hof, 1997). The advent of magnetic resonance imaging (MRI) provided the opportunity to investigate changes in cortical and subcortical structures of living elderly individuals, and to date provides further evidence of volume loss in the form of increased compartments of cerebrospinal fluid

(CSF) and enlarged ventricular spaces in healthy elderly individuals (Resnick et al., 2000). Conducting an MRI investigation of age-related morphological changes in the brain among individuals aged 30 - 99 years, Jernigan and colleagues (2001) reported four noteworthy findings: 1) Age-occasioned loss of grey matter is significantly accelerated in the hippocampus relative to losses in other parts of the brain. 2) The frontal lobes are disproportionately affected by volume loss and white matter abnormality compared to other cerebral regions. 3) Loss of cerebral white matter occurs later but is ultimately greater than that of grey matter. 4) No noteworthy decline seems to take place in the thalamus or amygdala.

Early explanations for this age-related reduction in brain weight saw this phenomenon as the result of a progressive decline in cortical neuron density, which occurs from late childhood to old age (Coleman & Flood, 1987). However, these early reports of profound cell loss were confounded by various technical and methodological flaws (Burke & Barnes, 2006). The implementation of new stereological principles in the 1980s, allowing objective quantification of a number of objects in three dimensional space, were able to eliminate many of the confounding factors of earlier studies and indicate that in humans, non-human primates and rodents, significant cell death in areas of the hippocampus and neocortex is not characteristic of normal ageing (Pakkenberg & Gundersen, 1997; Keuker et al., 2003). Instead, atrophy of the ageing brain is due to more subtle changes such as shrinkage of cell bodies, regression of dendrites and dendritic spines or alterations in neurotransmitter receptors (Nakamura et al., 1985; Barnes, 1994; Rehman & Masson, 2001). For example, a study undertaken by de Brabander and colleagues (1998) explored basal dendritic branching patterns in the human

prefrontal cortex and reported a decrease of total dendritic length, number of dendrite segments and terminal length among elderly individuals which they were able to quantify as a total 9 - 11% decrease of length and a 50% decrease of spine density.

Morphological changes taking place within the human brain have wide-ranging effects, among which lie a change in the post-synaptic effects of neurotransmitters. In particular, the dendritic changes discovered in ageing cells are thought to affect the distribution of neurofilament proteins (Hof et al., 1990; Vickers et al., 1993) which in turn impact on the effective transmission of various core neurotransmitter arrangements such as the glutamatergic, cholingergic, serotonergic and dopaminergic systems (Dickstein et al., 2007). Past work investigating alterations of glutamatergic productivity in the ageing brain reports that changes occur primarily with regard to the density of N-methyl-D-aspartate (NMDA) receptors; one of three glutamate receptors found to be important for learning and memory functions within the hippocampus (Cotman & Lynch, 1989). Reviewing work into ageing changes of NMDA receptor density, Magnusson, Kresge and Supon (2006) discuss a number of studies reporting that among aged animals, NMDA receptor binding densities and associated memory functions progressively alter, reporting that long-term potentiation[1] is changed as a result of decreased receptor density either by increased decay of formed pathways or decreased firing amplitude among responsive cells (Barnes, 1979; Foster, 1999; Deupree et al., 1993). Similarly, a number of studies have linked behavioural changes among the elderly to alterations in GABAergic productivity (Rogers & Bloom, 1985; Caspary et al., 1995). As such, reductions of GABA associated enzyme glutamate decarboxylase have been

[1] Long-term potentiation refers to a cellular mechanism thought to underlie learning and memory which is partly initiated by NMDA receptors.

[2] The Binding Problem refers to the question of how the brain is able to form a unitary experience from sensory inputs originally processed in a modular way. On a second, higher

consistently described in both the ageing rodent and human inferior colliculus (Gutierrez et al., 1994; Raza, Arneric, Milbrandt & Caspary, 1994). However, a number of studies have found no GABA alterations within ageing individuals' central nervous systems (Wenk et al., 1991). For example, Caspary and colleagues (1999) investigated changes of GABA-A receptors in three subdivisions of the inferior colliculus in aged Fisher rats and found no changes in binding density. However, they discovered significant interactive changes between aged rodents' GABA-A receptors and picrotoxin binding sites which reflected increased sensitivity of receptors to GABAergic input. The authors interpreted their findings as a compensatory mechanism initiated to counteract age-occasioned presynaptic loss of inhibition and thus highlight the possibility that ageing changes of GABA expression may be more subtly expressed than originally assumed.

In terms of age-related changes among neuromodulators, the most prominent observations relate to acetylcholine. The cholinergic hypothesis tracing cognitive decline, and memory loss in particular, back to a deficiency of acetylcholine in the basal forebrain, originated in the 1970s based on the findings that age-related impairments could be reproduced in young individuals through treatment with anti-cholinergic agents (Drachman & Leavitt, 1974). The cholinergic hypothesis has since been supported by much subsequent evidence (Gallagher & Colombo, 1995) and to date research continues to link the presence and severity of cognitive decline to a disruption in the functioning of basal forebrain cholinergic neurons (Fischer, Nilsson & Björklund, 1991; Rapp & Amaral, 1992).

Further age-related changes have been reported for the serotonergic and dopaminergic systems. In their 1998 article, Meltzer and colleagues characterised the normal ageing process as accompanied by loss of serotonergic (5-HT) neurons and

neurotransmitters, arguing that the serotonergic system is involved in many regulatory functions which tend to alter with advancing age such as the regulation of mood, sleep and appetite. Similarly, disruptions to the serotonin system have been linked to increased vulnerability to contracting age-associated diseases such as diabetes or cardiovascular and Alzheimer's Disease (Fidalgo, Ivanov & Wood, 2012). With regard to age-related changes in dopamine distribution, most work has been undertaken investigating changes in the caudate nucleus and putamen, as both nuclei are located in the striatum, which receives large amounts of dopaminergic input. Evidence from investigations into pre- and post-synaptic dopamine markers in rodents (D_1 & D_2 receptor densities) provides a strong indication that ageing produces a decline in receptor density of the nigrostriatal dopamine system (Bäckmann et al., 2010). Similarly, autopsy studies report losses of D_1 and D_2 receptor density from early to late adulthood (Rinne et al., 1990; Severson et al., 1982) whose rate of decline has been quantified as just under 10% per decade and which is widely believed to form part of the normal ageing process (Bäckmann et al., 2010).

Changes in Electrophysiological Processing Activity

One of the prime neuroscientific tools that offers insight into the underlying changes age occasions with regard to cognitive processing activity is offered by the Electroencephalogram. Past work has heralded electroencephalography (EEG) as a promising means with which to characterise significant deviations between normal and pathological ageing and offer insights into the processes that occur in the normally ageing brain (Bonanni et al., 2015). Since its discovery by Hans Berger in the 1920s, the development of advanced analysis and display techniques for EEG sensory and cognitive evoked potentials has progressed substantially (Desmedt & Cheron, 1981). The EEG's advantage of offering high temporal resolution (Rossini,

Rossi, Babiloni & Polich, 2007) has enabled relatively precise means of localising neural sources and tracking their hierarchical connectivity in sustaining a given function. In their 2007 article, Rossini and colleagues classify the major role of neuroscience as identifying patterns of neural activity underlying cognitive functioning and defining how these change and are affected by maturation. They further characterise the electroencephalograph as a prominent tool with which to achieve this.

The overarching picture presented by the ageing EEG is one of oscillatory slowing, with heightened power in slow wave bands such as the theta (4 - 8Hz) and delta (0.1 - 4Hz) frequency, mirrored by reduced power and a slowing of individual peak frequency in higher wave bands such as the alpha (8 - 12Hz) frequency. Past theories have attributed this to a reduction of axon myelination which slows conductive speed between interactive neuronal assemblies (Peters, 2009; Penke et al., 2010) or a degradation of synaptic networks which results in an increased number of processing steps to complete a given task.

The delta frequency (0.1 – 4Hz).

Oscillatory activity in the slow wave delta frequency range can only be detected in the raw EEG trace during sleep or unconscious comatose states. In the waking EEG, high amplitude of slow wave delta activity is related to brain pathology, indicating the presence of dysfunctional brain tissue or an adverse change in brain metabolism and blood perfusion after trauma (Baayen et al., 2001; de Jongh et al., 2003; Niedermeyer & da Silva, 2005). A greater predominance of delta activity has also been found to occur in conjunction with psychiatric diseases such as depression, schizophrenia and posttraumatic stress disorder (Kolassa et al., 2007; Rockstroh et al., 2007; Fernandez et al., 2005). Ageing is known to produce changes in the delta

frequency band (Niedermeyer et al., 2005) which are found to be exacerbated among ageing individuals who suffer from age-related cognitive pathologies such as Alzheimer's Disease and Mild Cognitive Impairment (Vecchio et al., 2014). As such, a number of studies report increases of delta power among elderly relative to young individuals during periods of rest (Vecchio et al., 2014) and during task engagement (Dushanova & Christov, 2014). Exacerbated levels of delta activity among elderly individuals suffering from different types of dementia (Bian et al., 2014) has led to its occurrence being viewed as a marker for pathological cognitive ageing. Clinical studies have therefore utilised EEG delta measurements as a non-invasive means of determining the extent of cortical degeneration and have linked the amount of delta activity (usually observed in the raw trace with the naked eye) to reductions in both cognitive state (Fernandez et al., 2002) and cortical atrophy (Fernandez et al., 2015). However, among studies decomposing the raw EEG trace and investigating the power distribution specific to the different frequency bands, evidence exists suggesting that delta activity is not exclusively linked to pathology. For example, Meinzer and colleagues (2004) reported that elevated levels of delta activity can relate to favourable behavioural outcomes in patients undergoing speech and language therapy after experiencing a stroke. Furthermore, studies investigating increased delta activity among healthy ageing individuals report only marginal, non-significant changes (Leirer et al., 2011) which has opened up the question whether alterations in the delta frequency band can form a component of healthy ageing or whether they are exclusive to the development of age-related pathologies.

The theta frequency (4 – 8Hz).

The theta frequency band has been classified as the dominant (occipital) activation pattern found among young children (Alvarez, Valdez & Pascual, 1987).

With cortical and cognitive maturation, this is gradually replaced by alpha oscillations traditionally reported as dominant in the adult EEG (Klimesch, 1999). However, advancing age seems to produce a reversal towards increased prominence of the theta frequency with a corresponding decline in alpha power. As such, a number of studies report power increases in slow frequency ranges of 7Hz and below (van de Vijver, Cohen & Ridderinkhof, 2014; Obrist, 1954; Obrist et al., 1963). Furthermore, studies have established that increased theta power during rest and cognitive performance is even more pronounced in elderly individuals suffering from early stages of dementia and Mild Cognitive Impairment (MCI) (Coben, Danziger & Storandt, 1985; Grunwald et al., 2002). Coupled with longitudinal work reporting positive correlations between high levels of baseline theta power and cognitive deficits among normally ageing individuals, this seems to indicate that high levels of theta power are indicative of ageing cognitive decline and a heightened risk of developing age-related cognitive pathologies (Jelic et al., 2000; Prichep et al., 2006; Moretti et al., 2009). However, evidence implicating heightened theta power as a marker of increased cognitive decline is not as clear as the above work suggests. Conversely, a number of studies have consistently reported that among healthy ageing individuals, higher levels of theta power positively correlate with enhanced cognitive performance in tasks of verbal fluency, attention and executive functioning (Finnigan & Robertson, 2011). Similar findings report heightened levels of theta synchronisation among elderly participants during the successful completion of a variety of cognitive tasks (Mitchell, McNaughton, Flanagan & Kirk, 2008) and a reduction of theta power among low performing elderly individuals (Cummins & Finnigan, 2007; Cummins, Broughton & Finnigan, 2008). In an attempt to explain these contradictory findings, Finnigan and Robertson (2011) suggest the possibility of

two forms of theta oscillations, one of which may indicate healthy neurobiological functioning, whereas the other acts as an indicator of substantial and progressive cognitive decline. In Finnigan and Robertson's view, the latter form of oscillatory activity does not originate from electrical and chemical changes within neurons naturally producing theta oscillations but is the result of changes in the alpha frequency range which has been found to linearly slow with advancing age. As such, increased levels of theta power may signify intact cognitive functioning or compensatory mechanisms engaged in by elderly individuals, whereas the prominence of low frequency oscillations originally attributed to cognitive deficits reflected in the theta range may be due to the progressive slowing of the individual alpha peak frequency produced by age (see below for more on this phenomenon).

The alpha frequency (8 – 12Hz).

Alpha waves form the dominant oscillations in the adult waking EEG. As such, they were the first oscillations reported by Hans Berger in 1929. Originally found to predominate occipital cortical regions, more extensive research discovered a number of different alpha networks occurring over different areas of the cortex, such as the 'mu' rhythm over the sensorimotor area and the 'tau' rhythm expressed over the auditory cortex. Alpha waves are known to synchronise during periods of relaxation, especially if resting individuals are told to close their eyes. Eye opening or any form of cognitive engagement results in desynchronisation or suppression of the alpha rhythm, a phenomenon which led to the assumption that oscillations of alpha frequency were an indication of the brain in an unemployed and relaxed position, a state often referred to in the past as 'cortical idling' (Pfurtscheller, Stancak & Neuper, 1996). However, more recent opinion has moved away from this interpretation, as an increasing body of work indicates that alpha plays a role for a number of cognitive

processes (Klimesch, 1999). Furthermore, work conducted by Klimesch and colleagues (1999) indicates that broadband definitions of the alpha frequency may obscure some of its functional significance as the authors were able to link different sub-components to distinct cognitive processes. As such, Klimesch and colleagues (1997) have argued that activity in the lower alpha frequency (6 - 10Hz) occurring over widespread areas of the cortex may reflect attentional or inhibitory processes, whereas more local activity in the upper frequency range (10 - 12Hz) may be indicative of semantic memory processing. That age occasions changes in the alpha frequency has been well documented in the EEG literature. Alpha peak frequency has been found to increase from childhood to puberty at irregular intervals after which it has been found to linearly decrease with advancing age (Klimesch, 1999). This linear decrease was conceptualised by Kropruner and colleagues (1984) in the following formula: α peak frequency = 11.95 - (0.053*age). Applying this formula, a twenty-year old's alpha frequency is predicted to oscillate at approximately 10.89Hz, whereas an eighty-year old individual would experience a drop of 3.2Hz with peak frequency centring around 7.7Hz. Investigating age-related changes in alpha reactivity (the difference in alpha power between two baseline intervals or from a baseline to a test interval) and alpha event-related synchronisation (the difference in alpha activation relative to a resting baseline period) by reviewing a number of past studies, Klimesch (1999) reports a general reduction of alpha reactivity and oscillatory activity during task performance when comparing elderly to young counterparts.

However, despite numerous indications that alpha frequency slows with advancing age (see Klimesch 1999 for review), the general literature is yet to reach a consensus, as a few studies report only a marginal, non-significant drop in alpha

frequency between young and elderly (Duffy et al., 1984). Another line of thought disputes that age-related decreases of the alpha frequency peak are part of normal cognitive ageing, seeing it instead as the hallmark of early neurological disease (Hubbard et al., 1976; Torres et al., 1983).

The beta frequency (12 – 30Hz).

Similar to alpha activity, beta waves are often subdivided into lower (12 - 20Hz) and upper (20 - 30Hz) components. Studies investigating the functionality of beta oscillations report a number of contradictory findings and to date there is a controversy regarding their functional significance and whether synchronisation or suppression of beta oscillations constitutes active cognitive processing. A number of past studies have linked event-related desynchronisation (beta suppression) over central sensory motor areas in conjunction with mu suppression to motor actions, relating it to action planning and movement initiation (Leocani et al., 1997; Pfurtscheller et al., 2003), motor imagery (Alemanno et al., 2012) and action observation (Muthukumaraswamy & Singh, 2008). Proposals regarding the functional significance of beta oscillations expressed over non-motor areas also include cognitive aspects, linking increased oscillatory activity to attentional mechanisms (Heinrich et al., 2014) and the encoding of novel visual stimuli (Haenschel, Baldeweg, Croft, Whittington & Gruzelier, 2000; Kilavik, 2013). Further studies have also implicated beta with respect to working memory (WM) processes, however, findings deviate with regard to whether it is event-related synchronisation (Altamura et al., 2010) or desynchronisation (Pesonen et al., 2006; Tsoneva et al., 2011) that reflects active working memory processes. Age-related changes in beta frequency have been predominantly studied in conjunction with performance on WM tasks. Thus, Karrasch, Lain, Rapinoja & Krause (2004) report heightened and prolonged

beta desynchronisation among high functioning elderly individuals relative to young controls during the retrieval period of a WM task. Coupled with findings of reduced beta ERD among elderly participants suffering from Alzheimer's Disease and Mild Cognitive Impairment (Kurimoto et al., 2012), past work seems to indicate that heightened levels of beta ERD during WM task engagement may indicate a compensatory mechanism engaged in by healthy elderly individuals to maintain task performance.

The gamma frequency (30 – 80Hz).

Gamma activity generally refers to oscillations centring around 40Hz but can extend to encompass high frequency activity up to 80Hz and above. Interest in the gamma band surged throughout the 1990s due to propositions that high frequency gamma oscillations may constitute the mechanism by which the brain solves 'The Binding Problem'[2] (Basar-Eroglu et al., 1996; Engel & Singer, 2001). More recent thoughts have linked gamma to working memory, positing that the gamma period (oscillatory cycle from peak to troth) may frame the interval during which inputs can be received and integrated by cortical pyramidal neurons. This theory suggests that neural computations may be organised into periods defined by gamma oscillations. Building on this idea, Lisman and Idart (1995) proposed a theory by which to explain how multiple items could be held in the WM store at one time. Their hypothesis postulated that the number of gamma oscillations taking place within one theta cycle may correspond to the number of items maintained in the WM store which are held together by the temporal binding mechanism of the theta cycle.

[2] The Binding Problem refers to the question of how the brain is able to form a unitary experience from sensory inputs originally processed in a modular way. On a second, higher order level, it questions how a subjective, conscious experience is generated out of the combined sensory information available to the brain.

Investigations into age-related changes to the gamma frequency generally report a reduction of synchronous activity (Insel et al., 2012). For example, Gaetz, Roberts, Singh and Muthukumaraswamy (2011) investigated age-related changes of gamma band activity within area V1 of the visual cortex in response to visual stimuli. Paired with MRI recordings of grey and white matter density, the authors discovered a significant negative correlation between age and synchronous gamma activity, mirrored by a negative correlation between cortical thickness of the occipital lobe and age. Additionally, a number of studies report ageing reductions of gamma oscillatory activity coupled with reduced WM task performance among healthy elderly individuals (Missonnier et al., 2004) and elderly participants suffering from Mild Cognitive Impairment (Missonnier et al., 2011), thus indicating that ageing reductions of gamma synchronisation are accompanied by corresponding shortcomings in WM domains (Akimoto et al., 2014), whereas heightened levels of gamma activity among elderly relative to young has been linked to an upkeep of task performance (Barr et al., 2014).

Changes in Cognitive Functioning

The general lay consensus sees advancing age as accompanied by a progressive loss of cognitive functioning. In many cognitive domains, this view has been corroborated by scientific study. However, the study of ageing individuals has also highlighted that certain cognitive abilities remain unaffected by normal ageing. Based on this, the ageing literature distinguishes between unaffected and compromised cognitive domains which, despite the controversy surrounding both terms, are commonly classed into fluid (found to decline with age) and crystallised abilities which remain unchanged until high stages of old age (Anstey & Low, 2004). Crystallised domains include acquired abilities such as general knowledge and

learned expertise and are related to measures such as verbal fluency, performance on which has been reported as unvarying with advancing age by multiple investigations (Zamarian et al., 2015; Anstey & Low, 2004). Fluid abilities are thought to encompass processing speed and the ability to problem solve by forming associations and deductions from pre-existing patterns. The general nature of fluid abilities means that decrements to these extend to many further cognitive abilities such as for example memory performance. As such, a dominant proposition in the late 1990s advocated that ageing did not selectively affect certain cognitive domains but resulted in impaired processing speed which formed the global factor underlying multiple cognitive domains and thereby produced the wide-ranging behavioural shortcomings observed among the elderly (Salthouse, 1996).

Long-term declarative memory.

Investigations into age-related memory decrements have highlighted that decline takes place in memory domains which are largely dependent on intact frontal/temporal lobe functioning as well as hippocampal integrity (Woodruff-Pak, 1997) and rely heavily on 'fluid' cognitive abilities such as processing speed. As such, ageing predominantly produces decline in long-term declarative memory and short-term working memory, both of which rely on medial-temporal lobe/hippocampal circuitry (Golomb et al., 1993) as well as interconnections between the frontal lobes and hippocampus. Declarative memory refers to a set of memories relating to oneself (episodic, autobiographical memory) and general factual information (semantic memory) that can be consciously recalled and recounted.

In a paper discussing the occurrence of age-related differences in episodic memory, Holland and Rabbitt (1990) highlight that the recall of

autobiographical memory progresses in multiple stages. According to the authors, successful episodic memory recall begins with retrieving the general context of the situation and then proceeds to differentiate this from similar situations and semantic knowledge of what would be appropriate to occur in this context. Therefore, episodic recall can be viewed as a progressive isolation of the sought after memory trace. Prominent findings during this reconstructive process indicate that general, higher order aspects tend to be recalled accurately, whereas lower order details are more likely to be forgotten and replaced by semantic knowledge or expectations of what should have happened (Kintsch & vanDijk, 1978; Rabinowitz, Ackerman, Craik & Hinchley, 1982). In their 1990 paper, Holland and Rabbitt highlight that impairments to working memory capacity as well as compromised attentional resources known to accompany advancing age may impair the encoding of details, forcing elderly individuals to rely on general encoding of events, an impairment which not only leads to less detail being recalled but which simultaneously makes the memory harder to access as it is less easy to differentiate from other contexts. Corroborating this idea, Zelinsky, Light and Gilewski (1984) found that elderly participants recalled as many general points of a given story as young individuals but showed poorer recall of details, findings which have been reported by a number of episodic memory studies (Meyer & Rice, 1981; Byrd, 1985; Spilich, 1983). Similarly, reduced recall of fine detail has been found to make elderly individuals more likely to confabulate when recalling prose passages. Elderly participants are thought to make up for loss of detail by inserting information they know to be true of the world to enrich the memory trace (Spilich, 1983).

A number of studies have likewise reported that advanced age coincides with decreased performance on semantic memory tasks (Kausler 1991; Salthouse 1991; Nyberg et al., 1996). Additionally, a number of neuropsychological studies, pairing behavioural tasks with EEG measures of underlying processing activity, highlight that elderly individuals tend to display over-recruitment of the same brain regions used by young participants during successful semantic memory performance (Chiang et al., 2014), especially in ambiguous situations where a more effortful memory search is required (Galdo-Alvarez et al., 2009). As a possible result of increased effort being needed to retrieve semantic knowledge, elderly individuals have been found to place less reliance on contextual semantic cues aiding comprehension. For example, Wlotko and Federmeier (2012) observed that elderly participants showed increased contextual restraint in a sentence comprehension task guided by contextual cues, manifesting a reduced and delayed N400 component compared to young individuals who freely made use of contextual guidance. Similarly, elderly participants were found to exhibit a greatly diminished N400 in weak contextual cue situations, indicating decreased sensitivity to contextual semantic information. However, a number of investigations into ageing semantic memory have also reported no performance differences among elderly and young participants (Walsh & Baldwin, 1977), especially after accounting for demographical factors (Nyberg et al., 1996). Addressing this discrepancy, Grieder and colleagues (2012) hypothesised that automated forms of semantic memory processing may be left intact by advancing age, whereas performance reductions in

controlled semantic memory processing domains may be significantly affected by advancing age.

Short-term working memory.

Short-term working memory (WM) refers to the temporary use and storage of knowledge which is necessary to guide behaviour, plan ahead and form a continuous narrative of thought (Milner & Petrides, 1984). In the past, the definition of short-term memory referred to a static repository of recent memories to be transferred to the long-term store (Shiffrin & Atkinson, 1969), whereas working memory emphasised an active engagement with the memory trace (Baddeley & Hitch, 1974). As such, past research has referred to working memory as 'the mind's blackboard' which illustrates its function as a malleable temporary storage device in which recollections can be freely manipulated to facilitate behaviour (Goldman-Rakic, 1995). Nowadays, both terms are often used interchangeably, however, in previous theories memories were only thought accessible once retrieved from the short-term repository and entered into the working memory store (Shiffrin & Atkinson, 1969). Among ageing humans, WM impairments are predominantly viewed as the result of decreased storage capacity with advancing age (Salthouse et al., 1989). This theory is based on the common finding that performance decrements among the elderly become apparent as task complexity increases (Wiegersma & Meertse, 1990), whereas no age differences exist in tasks that place low demands on storage capacity (Woodruff-Pak, 1997). The electrophysiological literature has placed a large focus on age-related changes to WM performance and as such, a number of EEG studies have focused on oscillatory processes occurring while participants are engaged in solving

perceptual working memory tasks (Karrasch et al., 2004; van de Vijver et al., 2014; Manard et al., 2014). As such, as well as pronounced behavioural performance deficits (Salthouse & Babcock, 1991), a number of EEG studies have demonstrated that advanced age coincides with reduced theta and alpha event-related synchronisation (Missonnier et al., 2011; Deiber et al., 2009; Karrasch et al., 2004), whereas heightened gamma event-related synchronisation among elderly relative to young participants has been found to coincide with an upkeep of task performance (Barr et al., 2014). A striking finding regarding the oscillatory patterns produced by WM performance among the elderly is a resemblance to those of children engaged in WM task performance. This similarity has led to the assumption that late-developing brain regions necessary for successful memory performance may also be the first to be affected by ageing decline (Krause et al., 2001).

Executive control processes.

Executive control processes refer to cognitive functions dealing with the selection, scheduling and co-ordination of processes that govern perception, memory and action execution. Within the ageing literature, the way in which age affects executive processes and how their impairment may extend into other cognitive domains, has received large amounts of interest which is reflected in a substantial number of studies comparing the executive performances of elderly and young (Kramer, Hahn & Gopher, 1999; Cepeda et al., 2001; Vasquez, Binns & Anderson, 2014). Among researchers investigating age-related executive changes, the Frontal Lobe Hypothesis of Cognitive Ageing (Dempster, 1992) has gained wide-reaching support. The theory posits that age-related decrements are particularly prominent in tasks

that rely heavily on processes executed by frontal brain regions. In accordance with this idea, PET and more recent MRI imaging studies have indicated that age-related morphological changes do not take place uniformly across the brain but seem to progress faster and more substantially in higher order associative areas compared to purely sensory domains (Pfefferbaum et al., 1992; Behrman-Lay et al., 2014). In conjunction, large behavioural shortcomings among elderly individuals have been reported consistently for tasks thought reliant on intact frontal lobe functioning, whereas tasks independent of frontal lobe integrity indicate small behavioural change with advancing age (Ardila & Rosselli, 1989; Daigneault, Braun & Whitaker, 1992; Shimamura & Jurica, 1994). Since its proposal in 1992, the Frontal Lobe Hypothesis of Cognitive Ageing has received support from a large amount of behavioural and neuroimaging work and is thus still considered a valid theory for explaining a certain amount of behavioural change with advancing age.

The general consensus within the ageing literature is that advanced age coincides with a reduction of executive capabilities (Gazzaley & D'Esposito, 2007). However, the literature investigating age-related executive performance in relation to the different executive paradigms presents varied findings. Paradigms developed to assess executive capabilities can be classed into tasks measuring distractor (Stroop Task, Simon/Task Switching Paradigm, Flanker Task) or response inhibition (Go/No-Go Task). With regard to distractor inhibition, certain paradigms (such as the Simon or the Stroop Task) present a homogenous picture with numerous studies reporting that ageing negatively impacts on executive task performance (Bialystock et

al., 2004; Maylor, Birak & Schlaghecken, 2011; Zurron et al., 2014; Van der Elst et al., 2006; Peña-Casanova et al., 2009). Conversely, studies employing other distractor inhibition tasks present conflicting findings. As such, research into executive age-differences using the Flanker as well as the Task Switching paradigm present dichotomous findings of age-related executive decline (Verhaeghen & Basak, 2005; Zhu et al., 2014; Zeef et al., 1996; McDowd & Craik, 1988) or of intact executive control performance (Botwinick, Brinley & Robin, 1958; Kopp et al., 2014; Nieuwenhuis et al., 2002). This discrepancy has given rise to the hypothesis that executive control may be comprised of numerous different sub-components (West, 1996; Shallice, 1994; Rogers & Monsell, 1995) which are differentially affected by advancing age and captured to different extents by different versions of inhibitory tasks. In line with this idea, work by Rogers and Monsell (1995) has highlighted that the above paradigms may capture two distinct executive control processes, one of which is internally driven (endogenous), whereas the other is externally triggered (exogenous). The endogenous executive component is thought to involve processes such as goal shifting and rule de-/activation which can be performed in anticipation of the stimulus (Rubinstein et al., 2001), whereas the exogenous process can only be accomplished once the stimulus is encountered. Work investigating age-related impairments to executive functioning in light of these sub-processes has indeed highlighted that ageing seems to have a pronounced negative impact on anticipatory endogenous processes (Bugg, 2014; Kopp et al., 2014) which coincides with increased reliance on intact exogenous components (Tam et al., 2014; Hasher & Zacks, 1988). Given these findings, research has argued that elderly participants may

resort to more cautious strategies during executive task execution. These are though to confer differing levels of advantage depending on the versions of the distractor inhibition tasks to be performed and may therefore give rise to the discrepant findings within the literature (Hasher & Zacks, 1988; Joyce et al., 2014).

With regard to response inhibition, the ageing literature portrays a clear speed/accuracy trade-off, highlighting that elderly individuals seem to favour more cautious response strategies, valuing a correct over a speedy response and, as a result, show significantly increased latencies compared to young participants (Lucci et al., 2013). An interesting finding which is in line with this strategy, reports that elderly individuals tend to perform with higher accuracy on prolonged Go/No-Go tasks. For example, Staub and colleagues (2014) observed older adults were able to maintain prolonged attentional performance, whereas young individuals displayed vigilance shortcomings after a certain time had elapsed.

Impact Factors on Cognitive Decline

The emergence of cognitive and bodily decline with progressing years is an unavoidable occurrence for all higher order biological organisms. However, it is well established, both in lay terms and within scientific circles, that not all people age the same way. An edifying example of this is provided by the work of Harrison, Weintraub, Mesulam and Rogalski (2012) who followed-up anecdotal reports of individuals reaching a high age without experiencing age-related memory impairment. In order to test whether unimpaired memory performance was reflected in reduced cortical atrophy among these ‘Super Agers’, Harrison and colleagues selected 12 individuals

based on their age (≥ 80 years) and superior performance (equivalent to that of individuals 20 - 30 years younger) on the Rey Auditory Verbal Learning Memory Test (RAVLT). These Super Agers were compared to 10 age-matched controls and 14 middle-aged controls (50 – 65 years) displaying age-appropriate performance on the memory task. Analysis of the structural MRI scan obtained from individuals revealed that the cerebral cortex of Super Agers was significantly thicker than that of healthy age matched controls and showed no atrophy compared to 50 - 65 year olds. Additionally, a region of the left anterior cingulate cortex was found to be significantly thicker among Super Agers compared to both elderly and middle-aged controls.

Harrison and colleagues' study provides an extreme but nevertheless valid example of individual differences when it comes to ageing and demonstrates that age-related decline and loss of cognitive function can in certain individuals be resisted into high old age. Studies to this effect highlight the importance of understanding which aspects contribute to successful ageing. Factors affecting a person's life and ultimately the way in which he or she ages are manifold. Consequently, a large body of research is engaged in determining impact factors thought to range from genetic/molecular make-up (Stessman et al., 2005) over lifestyle choices (Emery et al., 1995) to psychological factors such as social support and a sense of belonging. Research into this, in terms of the most prominent factors within the current ageing literature, is summarised below.

Genetic factors.

A genome-wide association study undertaken by Bis and colleagues in 2012, which drew data from 9232 dementia-free individuals, reported that

genes related to apoptosis[3] (HRK), oxidative stress[4] (MSR3B), ubiquitination[5] (FBXW8) and neural migration (ASTN2) may be implicated in age-related hippocampal volume reductions and act as a possible risk factor for developing cognitive decline and dementia. A further prominent gene that has been specified as a risk factor for age-related morbidities is Apolipoprotein E, a gene responsible for transporting cholesterol to neurons within the central nervous system. Apolipoprotein E4 has been linked to acquiring diseases such as Alzheimer's Disease (Saunders et al., 1996) and frontotemporal lobar degeneration (FTLD) (Rubino et al., 2013) in old age. However, the literature concerning Apolipoprotein E's role in developing age-related morbidities is not consistent to this effect. A systematic meta-review of all case studies detailing an association between APOE and FTLD up to December 2011 conducted by Rubino and colleagues (2013) confirmed the previously reported link between APOE and the development of FTLD. However, a study conducted by Pendleton and colleagues in 2002 to investigate whether Apolipoprotein E4 polimorphisms may also extend to producing a decline in intelligence among normally ageing elderly individuals found no association. Finally, results published by Lopez and colleagues (2012) tested six genes thought to be related to increased longevity among 1000 participants of the Lothian Birth Cohort study[6]. Genes were genotyped and tested for

[3] **Apoptosis**: programmed cell death, a highly controlled process necessary for synthesis of new cells and the organism's progression through the lifecycle.
[4] **oxidative stress:** imbalance between the presence of chemically reactive molecules within a cell and the cell's ability to detoxify the reactive elements and repair damage resulting from their conversion.
[5] **ubiquitination**: highly specific degradation of specific proteins within a cell which is achieved via the addition of ubiquitin molecules to the targeted protein.
[6] The Lothian Birth Cohort comprises 70,805 individuals who undertook a mental ability test at age 11 as a requirement for attending Scottish schools in 1963, thus

associations with cognition and cognitive ageing. After both study and meta-analytic replication, the authors were able to report the SYNJ2 gene, involved in the vesicle un-coating of neurons, as a factor whose variation is potentially associated with protective effects against cognitive decline among ageing individuals.

Physical exercise.

Within the ageing literature, moderate amounts of physical exercise have been found to exert a beneficial influence on bodily health among elderly individuals and have also been implicated in stalling age-related cognitive decline. Evidence for the protective effect of exercise comes from cross-sectional survey data (Emery et al., 1995), randomised controlled trials (Chang & Etnier, 2009) and prospective studies (Williams & Lord, 1997). Despite some studies failing to obtain a significant effect of exercise on cognitive ageing (Pierce et al., 1993), most studies offer support for the role of physical exercise in healthy ageing. Exercise has been hypothesised to prolong intact levels of cognitive performance by promoting well maintained cerebral perfusion and general levels of cerebrovascular health (Rogers et al., 1990). Despite large amounts of evidence in favour of the protective effects of physical exercise, it must be noted that many of these studies rely on self-reports about the amount of physical activity engaged in. However, a number of studies addressed this shortcoming by employing electronic measures of performed exercise (Kimura et al., 2012) or enrolling participants in exercise programs to be completed over several months (Williams & Lord, 1997).

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offering the almost unique opportunity of providing a baseline starting point from which to study the impact of ageing factors on lifetime cognitive change. To this effect, individuals completed an extensive battery of cognitive tests on measures of logical reasoning, memory, information processing speed and executive functioning.

These studies similarly report on the beneficial effects of moderate physical exercise on ageing cognition and well-being. A further affirmation for the protective effect of exercise comes from the Lothian Birth Cohort study (Deary et al., 2007). Evaluating the effect of proposed impact factors with respect to cognitive performance at age 11 as a baseline called into question a number of factors which had established themselves as influencing the rate of cognitive decline. However, the relationship between exercise and successful cognitive ageing remained reliably significant when matching participants exhibiting the same performance levels at age 11.

Cigarette and alcohol intake.

The impact of both cigarette and alcohol intake on cognitive performance has remained controversial within the ageing literature. As such, some evidence points to their short-term protective functions when consumed in moderate amounts, while other studies have implicated them as risk factors furthering the rate of cognitive decline and increasing the risk of contracting age-associated diseases. Early studies into the effects of smoking reported that nicotine had the ability to improve short-term cognitive functioning (Elrod, Bucafusco & Jackson, 1988). However, research has also linked cigarette consumption to an increased risk of acquiring diseases such as vascular dementia (Brayne, 2000). A meta-analysis of case studies investigating the association between smoking and Alzheimer's Disease further reported mixed results, finding support for the protective effect of nicotine when analysing individual case studies but finding the opposite effect when pooling the data (Almeida et al., 2002). In order to address this uncertainty, Anstey and colleagues (2007) conducted a meta-analysis of 19 prospective studies

including a minimum of 12 months follow-up. Drawing data from 43,397 participants, the authors reported that current smokers suffered from increased risks of contracting Alzheimer's Disease and vascular dementia and further exhibited enhanced rates of annual decline in Mini-Mental state scores compared to never-smokers. The authors therefore concluded that smoking forms a risk factor for contracting dementias and for increased rates of cognitive decline.

Despite the established damaging effect of excessive alcohol consumption on memory, a number of studies report findings suggesting that moderate amounts of alcohol intake may have a beneficial impact on the rate of cognitive ageing. The hypothesis that certain forms of alcohol can protect against the effects and risk factors of ageing originates from reports that elderly individuals reporting moderate levels of alcohol consumption, especially red wine, throughout most of their lives show reduced levels of cognitive decline compared to age-matched counterparts with less or less frequent rates of alcohol consumption. The causality of this longitudinal relationship is hard to establish, however, studies have proposed a number of mechanisms by which alcohol may stall cognitive decline and reduce the risk of dementia. To this effect, studies have suggested that antioxidant properties of flavenoids in wine could prevent the oxidative damage implicated as one of the causes of dementia (Tedesco et al., 2000). However, a primary concern of correlational studies investigating the long-term relationship between cognitive performance and the amount of alcohol intake is the inability to account and correct for prior cognitive abilities. This potential confound was addressed by the Lothian Birth Cohort 1936 Ageing Study whose measures of

alcohol consumption were obtained via self-report questionnaires. The study's results indicated positive relationships between moderate to substantial drinkers (> 2 units/day) and cognitive ability. However, after adjusting for childhood IQ levels and adult social status, most of these relationships were either eliminated or substantially reduced. After full adjustment, a small positive association remained between alcohol consumption and semantic memory for both genders and alcohol consumption and verbal ability for females. The Lothian Birth Cohort Study therefore illustrates that the beneficial effect of alcohol intake on cognitive performance may be mediated to some extent by baseline cognitive performance levels and may not be as strong or robust as previously supposed.

Social support.

A number of studies investigating the impact of social resources on longevity and cognitive ageing report that a sense of social belonging seems to promote healthy ageing and reduce morbidity rates. Blazer (1982) reported that the frequency of social interactions, the perceived social support and the availability of close relationships negatively predicted mortality rates followed-up over 30 months among 331 community dwelling elderly participants (aged > 65), even when controlling for physical health, age, race, gender, economic status and self-care capacity. However, a number of studies have also reported no association between the amount of social support and rates of cognitive decline and morbidity. Seeking to investigate whether social contacts and perceived social integration delays mortality, Olsen and colleagues (1991) instructed trained nurses to interview 1,752 individuals aged between 70 - 100 years to obtain measures of current health and

estimates of the amount and quality of social networks. Participants were followed-up for the subsequent 13 years during which 1,501 participants died. When correlating mortality rates with the amount of social relationships, the authors found no association between both measures. Illustrating a possible cause for these discrepant findings, a study conducted by Penninx and colleagues (1997) indicates that the type of social support received may be crucial to the effect it exerts over longevity and cognitive functioning among elderly individuals. The authors reported findings from 2,829 non-institutionalised participants aged 55 - 85 years who took part in the Longitudinal Aging Study Amsterdam. Distinguishing their study from those mentioned above, Penninx and colleagues classified social support into structural, functional and perceived aspects. While controlling for age, gender, the presence/absence of chronic disease and self-reported health, regression analysis revealed that elderly individuals receiving moderate to high levels of emotional support showed reduced levels of mortality risk. However, higher levels of instrumental support were found to relate to increased levels of mortality risk, possibly by impacting on the individual's sense of self-sufficiency and independence.

Stress, Cognition and the Ageing Brain

A definition of stress.

The concept of stress has been known for centuries but only the past few decades have seen it systematically conceptualised and defined as a topic of research. Widely seen as the founder of stress research, Hans Selye was one of the first to strive for a unifying conceptualisation of stress, thus laying the groundwork for scientific inquiry into the effects and consequences of stress

exposure. To achieve this, Selye sought to combine previously unspecific stress observations into fixed concepts held together by specific definitions of space (three bodily symptoms observed to coincide with stress exposure: adrenal cortex hypertrophy; atrophy of thymus, lymph nodes and spleen; gastrointestinal ulcers) and time (alarm, resistance and exhaustion stage). Early definitions classified stress either in terms of the stimulus (focusing on events such as natural disasters) or noxious conditions and diseases (which disrupted the body's natural homeostatic equilibrium). Along these lines Selye's biological definition (1936) classified stress as an orchestrated set of bodily defences (encompassing both chemical and changes in the somatic nervous system) set to combat any form of harmful stimuli, a reaction he termed the "General Adaptation Syndrome". Further pioneering work undertaken in the field of stress research was performed by Mason (1971) and McEwen (1998), who in addition to Selye's work on concrete physiological stressors, extended stress inducing stimuli to include psychological and experiential factors such as fear, anxiety, novelty or the anticipation of punishment (Mason, 1975). Mason did not believe in the presence of a general, non-specific stress response, advocating that individual factors such as coping strategies constantly shaped the body's endocrine response to stressors. Pursuing this line of thought, Mason went on to coin the phrase 'psycho-endocrinology' highlighting that personal mental processes may occasion certain amounts of variance in the body's stress response. In line with this, more recent definitions emphasise the relationship between person and environment, taking into account the characteristics of the individual and

the nature of the encountered event. Thus, Lazarus and Folkman (1984, pg. 19) define psychological stress as:

"*A relationship between person and environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being."*

The work into stress research undertaken by McEwen (1998, 2000) and Sterling and Eyer (1988) formed the basis of allostatic load theories by proposing an adaptive process of bodily responses initiated to combat the stressor. The state of the organism engaged in regulating the body's point of equilibrium outside of the normal homeostatic state they termed allostasis. McEwen and colleagues proposed that this allostatic state was achieved by regulating the parameters of various physiological systems to accommodate the changed demands produced by the stressor. They advocated that the allostatic process could have harmful consequences for the organism if prolonged or called on too frequently, a scenario they referred to as allostatic load. Allostatic load can be measured as chemical imbalances in the autonomic nervous system, the central nervous system as well as in changes to the neuroendocrine and immune system. Allostatic load models have found great acclaim within the scientific community and are frequently used to conceptualise stress response and outcome in current investigations (Shannon, King & Kennedy, 2007; Weiss et al., 2007; Juster, McEwen & Lupien, 2010).

Acute, chronic and cumulative stress.

In lay terms, the word stress is often used as a distinct reference when it is in fact a broad umbrella term and as such encompasses different forms of stress. In the

scientific domain, these need to be distinguished as they are known to affect the human organism in different ways. The three most prominent forms which will be discussed in the following section, are acute, chronic and cumulative stress. Within the stress literature, each form has been predominantly studied in relation to a certain concept; therefore, the overview of each will necessarily include an introduction of the domain in which it has been extensively studied.

Acute stress and performance.

A large body of work is to be found regarding the effects of acute stress on the human organism. One of the most well known publications in this domain is the inverted U-curve hypothesis (Yerkes and Dodson, 1908; Broadhurst, 1959) which details the quadratic relationship between arousal and cognitive/physical performance. According to the model, arousal in low or high concentrations will result in lower performance levels, whereas moderate amounts are thought to act as a stimulator without overtaxing the system, thereby leading to optimal performance. In addition to its impact on physical performance, a number of studies in the acute stress literature highlight that acute stress is able to affect both working and declarative memory. In this regard, a number of studies have reported that acute stress can both impair and, in certain situations, enhance memory encoding and subsequent recall (Buchanan & Lovallo, 2001). The literature explains this enhancing effect by advocating that acute stress may occasion a change of strategy, diverting cognitive resources to more salient items. In keeping with this idea, acute stress has been found to enhance recall of emotional material with a corresponding detriment to neutral stimuli (Jelici et al., 2004). In the past, large numbers of studies investigating acute stress relied on administering substances that either mirrored or induced the effects of steroid hormones. However, due to rising concerns about ecological validity, studies

moved on to investigate the effects of acute stress as produced by constructed tasks or situations (such as the Trier Social Stress Test developed by Kirschbaum & colleagues, 1993) exacting high psycho-social demands. Research has since shown that individuals subjected to these contrived stressful situations demonstrate reduced memory performance as well as significantly increased cortisol levels (Domes et al., 2004; Kirschbaum et al., 1996; Jelici et al., 2004).

In terms of age differences in dealing with acute stress exposure, elderly individuals are found to be less adaptive to novel and changing situations. Furthermore, due to a natural decline in cognitive functions, they are hypothesised to have less resources to control the increased demands generated by the stressful situation. As such, studies indicate that elderly suffer more from the negative effects of acute stress, showing decreased memory performance after exposure (Lupien et al., 1994; Kukolja et al., 2008).

Chronic stress and health.

Despite awareness that stress in measured amounts can be beneficial, much of the literature classifies stress, especially in its chronic form, as a disruptive factor impinging on the organism's homeostatic equilibrium (McEwen & Stellar, 1993; McEwen & Wingfield, 2003). In their "reactive scope model" constituting a refinement of the allostatic concept, Romero and colleagues (2009) state that individuals of each species live within a certain range of environmental conditions in which resources permit regulatory processes to operate without requiring adaptive changes. If, however, the situation exceeds this range or the individual's resources have been depleted and are no longer adequate to cover the situation, the stimulus will be perceived as a stressor and produce a stress response. Chronic stress has been largely viewed as a factor depleting the organism's coping abilities, thereby

producing long-term disruption of the body's natural homeostatic state. As mentioned above, the long-term damaging effects produced by (chronic) stress are referred to as allostatic load. The amount of allostatic load which builds up in an individual is thought to hinge on multiple aspects, including the efficiency of the stress response, how many stressful experiences are encountered in a certain time frame, genetic make-up, early development and learned behaviours such as diet, exercise, smoking and drinking alcohol. In their paper discussing the protective and damaging effects of stress mediators, McEwen and Seeman (1999) emphasise that allostatic load, although most commonly the result of chronic stress, can also occur through an inability to habituate to a stressful event (Kirschbaum et al., 1995) or shut-off the hormonal stress response once it has occurred, thus being more widespread than originally assumed. A prominent example of the negative consequences produced by prolonged allostatic load is the occurrence of type 2 diabetes, resulting from increased levels of catecholamines necessary for adjusting heart rate and blood pressure. Further incidents include abdominal obesity, atherosclerosis and hypertension resulting from insulin resistance due to overactivity of the HPA system (Brindley & Rolland, 1989). Stress has also been known to negatively impact on the immune system where adrenal steroids promote movement of the immune cells to areas where they are needed to fight infection. However, chronic secretion of these can lead to immunosuppressive effects (Dhabhar & McEwen, 1997). Optimal levels of these mediators are required to maintain the balance between competing factors within the immune system, and the absence of sufficient levels of glucocorticoids and catecholamines can allow other immune mediators to overreact, thereby increasing the risk of autoimmune and inflammatory disorders (Sternberg, 1997). Chronic stress has also been strongly linked to the development of depression (Willner, 1997; Zhang

et al., 2015; McEwen, 2004) which it is thought to induce by encouraging the production of cytokines (small proteins implicated in cell signalling which are thought to cause depression via their link to the body's immune system). The connection between chronic stress and depression is further highlighted by the comorbidity between depression and Post Traumatic Stress Disorder (Campbell, Renshaw & Righter, 2015).

Cumulative life stress and cognitive ageing.

A more recent idea forming within the stress literature is the theory that the impact of stress may extend to the realm of ageing, possibly impacting on the cognitive capabilities or the rate of cognitive decline experienced by elderly individuals. Based on the assumption that incidents of prominent but not necessarily major or traumatic stressful experiences may sum over the lifespan to act as one of the factors producing different rates of cognitive decline among the general population, past studies investigating this hypothesis have relied on experienced stressful events as an indicator of stress. At this point, it is important to note the distinction between chronic and cumulative stress. Whereas chronic stress refers to the prolonged exposure to high levels of stress, cumulative stress encompasses the experience of multiple stressful experiences. These can encompass both minor and more prominent stressors which in turn can last for short or longer time periods. The idea that cumulative stress may contribute to age-related cognitive decline corresponds to the known structural damage that stress can produce in certain brain regions imperative for successful cognitive operations which will be discussed in the following section.

To date, a relatively small number of studies have explored the suspected impact of cumulative stress on cognitive ageing. For example, Pesonen and colleagues published the results of a longitudinal study in 2013 which focused on stressful experiences encountered in early childhood. Comparing the cognitive performances of elderly individuals (aged 70) who had been separated from their parents during World War II to age matched controls, the authors reported that elderly individuals who had suffered parental separation performed worse on a number of tasks assessing memory function, verbal fluency and executive functioning. Crucially, the authors had recourse to data gathered from a cognitive test battery performed by the same individuals at age 20, in which no cognitive differences between both groups were apparent. Findings to this effect highlight the damaging long-term effects of stressful experiences. Research investigating the impact of stressful encounters in early life highlight that they may cause changes to the body's natural homeostatic state and produce an over-reaction of bodily stress response systems when encountering further stressors, thus producing highly anxious individuals who are more at risk from stressful occurrences. To this effect, Alastalo and colleagues (2013) reported that individuals suffering an early life stressful event had significantly higher levels of systolic and diastolic blood pressure compared to individuals who spent a largely stress free childhood. A further longitudinal study conducted by Peavy and colleagues (2009) investigated the cumulative effect of stressors encountered by elderly individuals in the course of three years. The authors reported that among elderly individuals suffering from Mild Cognitive Impairment, higher incidents of stressful experiences correlated with reduced cognitive

performance. Observations similar to the above have likewise been reported in cross-sectional studies (Grimby & Berg, 1995; Persson & Skoog, 1996; Tschanz et al., 2013). An example to this effect was provided by Dickinson and colleagues (2011) who found that the total number of stressors experienced over the lifespan positively correlated with a decline in working memory performance among elderly participants when holding age and level of education constant. As cross-sectional evidence corresponds to longitudinal work, it complements the picture indicating that long-term cumulative stress may adversely impact on cognitive functioning. However, within the cross-sectional literature the picture is not quite as clear. Certain findings suggest that it is not the experienced event causing damage but rather the subjective experience of its gravity which may vary from individual to individual (Sands, 1981). In keeping with this idea, some studies report no impact on cognitive ageing from the aggregate scores of stressful experiences, but a significant decline when considering certain events such as major monetary problems (Rosnick et al., 2007). For example, Comijs and colleagues (2011) examined the isolated impact of stressful life experiences on ageing cognitive decline to report a differential effect of stressful life experiences in which certain mild to moderate stressful events elevated cognitive performance, while highly stressful, chronic events impaired cognitive functioning in later life. The authors concluded that prolonged stressful-experiences seem associated with accelerated ageing cognitive decline, whereas mild stressors may have an arousing effect which leads to elevated cognitive performance among elderly individuals.

The impact of chronic and cumulative stress on the (ageing) brain.

Research investigating the changes stressful experiences cause in the brain have highlighted both the frontal cortex and hippocampus as regions particularly vulnerable to the adverse effects of stress. Damage to the neocortex, most particularly the frontal cortex is thought to be sustained through an increased number of micro lesions produced by higher, stress-induced levels of hypertonic blood flow (Rabbitt, 2005). In turn, the hippocampus is seen as particularly susceptible to glucocorticoids which are produced predominantly by the hippothalamic pituitary adrenal (HPA) axis. Short-term elevation of this particular steroid hormone facilitates the formation of strong, emotional memories (McGaugh, 2004). Long-term exposure, however, is associated with impairments to cognitive functioning and damage to hippocampal brain structures (Lupien & McEwen, 1997; McEwen & Sapolsky, 1995). Hippocampal neurons posses two receptors responding to and circulating adrenal steroids (McEwen, Weiss & Schwartz, 1968): Type1(mineralocorticoid) and type2 (glucocorticoid). These receptors mediate a variety of effects on neuronal excitability, neurochemistry and structural plasticity (DeKloet et al., 1998). The hippocampus also displays sensitivity to gonadal hormones thought to participate in functional and structural changes in adult life as well as translating the influences of early stressful life experiences (McEwen, 2001). In his 2001 paper discussing the neurobiology of stress, McEwen focuses on two types of structural change stressful experiences induce in the hippocampus: remodelling dendrites of hippocampal pyramidal neurons and inhibition of granule cell neurogenesis in the dentate gyrus.

That remodelling of dendrites can be the result of experiencing stress has been demonstrated by a number of studies to date. A study conducted by McKittrick and colleagues (2000) demonstrated that chronic restraint stress experienced by rats over

21 days resulted in atypical, atrophied dendrites of CA3 pyramidal neurons. Furthermore, a recent study using a stress paradigm sustained over four weeks (Sousa et al., 2000) found remodelling of dendrites was not confined to the CA3 area but occurred in the dentate gyrus and the area of CA1. The authors concluded that this widespread change might provide an indication that remodelling of dendrites could be a factor in the shrinkage of the hippocampus reported in ageing coupled with mild cognitive impairment (McEwen, 1999; Sapolsky, 1999). These dendritic changes have been mainly ascribed to the acting influence of glucocorticoids which have been thought to affect dendritic expression in several ways: 1) adrenal steroids have been found to modulate expression of NMDA receptors in the hippocampus (Bartanusz et al., 1995) with chronic exposure to glucocorticoids leading to increased expression of NMDA receptor bindings (Weiland, 1997); 2) glucocorticoids have also been shown to affect the expression of mRNA levels of specific subunits of GABAa receptors in the CA3 area and dentate gyrus, suggesting they may alter the excitability of hippocampal neurons through the regulation of GABAa receptor expression; 3) studies have evidenced that adrenal steroids regulate the release of glutamate (Lowy, Gault & Yamamoto, 1993).

That neurogenesis declines as part of the ageing process has been reported by a number of animal studies, demonstrating age-associated decline in the dentate gyrus of rodents (Kempermann et al., 1997) and rhesus monkeys (Amrein et al., 2011). Moreover, Lupien and colleagues (2002) demonstrated that performing an adrenalectomy was able to reverse this decline, suggesting that the occurrence can be traced back to age-related increases in hippothalamic pituitary adrenal axis activity and glucocorticoid levels (Landfield, 1987). Adrenal steroid suppression of neurogenesis is thought to occur by means of an NMDA-receptor mechanism

(McEwen & Magarinos, 2001). Studies to this effect have been able to demonstrate that granule neuron birth is accelerated by blocking NMDA receptors or lesioning the excitatory perforant pathways deriving input from the entorhinal cortex. Impairments to neurogenesis have been linked to cognitive functioning, as decreased volume of the dentate gyrus in chronically stressed tree shrews was found to be coupled with impaired spatial learning and memory (Ohl & Fuchs, 1999).

A further mechanism by which stress may impact on the hippocampus was recently introduced by Sidrauski and colleagues (2013) and Sekine and colleagues (2015). Both research teams discovered that a certain molecule, integrated stress response inhibitor (ISRIB), is able to enhance rodent memory by impacting on the brain's cellular response to stress. The authors were able to demonstrate that ISRIB increases activity of the gene eIF2B. This gene forms an essential factor for protein synthesis and additionally has the propensity to bind tightly to eIF2(αP). Phosphorisation of the α-sub-unit of this latter gene takes place in response to stress hormones and occasions both the suppression of bulk protein synthesis and conversely the presence of certain transcription factors to synthesise particular proteins needed to mount an adaptive response. This mechanism has been implicated as an important regulator of hippocampal synaptic plasticity as it has the ability to induce both long-term depression of hippocampal cells as well as inhibit long-term potentiation. However, mutations to gene structure which occur when eIF2B binds to eIF2(αP) make the latter less susceptible to stress response α phosphorisation. Thus, by promoting the expression of eIF2B, ISRIB has been found to dampen long-term depression (Di Prisco et al., 2014) and enhance rodent memory dependent on long-term potentiation of hippocampal neurons (Costa-Mattioli et al., 2007) by reducing the integrated stress response mechanism.

That stress impacts negatively on the ageing process and development of associated neurodegenerative disorders is suspected but has as yet not been subjected to in-depth research. This is partially due to the complex relationship observed between stress and ageing. In her 2007 review, Pardon classifies this relationship into three aspects: 1) quality of ageing and life expectancy are genetically determined by the same genes also responsible for stress tolerance; 2) this stress resistance is further modulated by the amount of stressful experiences encountered in old age; 3) stress and ageing can interact in multiple ways with stress being able to either exacerbate or relieve the process of ageing, while similarly ageing can modulate the impact of stress on the organism. In addition to Pardon's second point, it should be noted that a number of studies also highly emphasise the impact of early stressful life events on this relationship, highlighting that high amounts of early life stress may produce increased reactivity among bodily stress response systems which in turn exacerbates stressful experiences throughout the lifespan (Liu, 1997; McEwen, 1998). While the HPA axis remains the main stress response system and glucocorticoids, in humans specifically cortisol, the main stress hormone, studies investigating age-related changes within these domains report that glucocorticoid receptors decline with age, resulting in impaired regulation of the HPA axis and altered stress responses (Lupien et al., 2005; Bao et al., 2008). These changes have been associated with an impaired ability to terminate the stress response, resulting in an increased vulnerability to the adverse effects of stress (Meaney et al., 1995). This in turn has lead to the suggestion that hippocampal neuronal loss, impaired plasticity and associated cognitive decline is the combined result of elevated glucocorticoid levels and stress (Pedersen et al., 2001). Studies confirming this supposed association have focused on the effect of early stressful life experiences. Thus, neonatal handling of new-born rats has been

found to produce animals with lower HPA activity and resulting lower rates of brain ageing measured in terms of reduced loss of cognitive functioning, whereas pre- and postnatal stress has been suspected of causing increased HPA activity over the lifespan leading to increased rates of brain ageing due to elevated cortisol levels (Liu, 1997). Many of these studies were inspired by the "glucocorticoid cascade hypothesis of ageing" (Sapolsky et al., 1986) which posits that age-related increase of glucocorticoid production, hippocampal neuronal death and resulting cognitive impairments form an ongoing downward spiral with each event causing and/or exacerbating the next. However, later studies were unable to replicate the damaging effects of glucocorticoid overexposure (Leverenz et al., 1999), and a more recent pharmacological study conducted by Fenoglio and colleagues (2005) showed that glucocorticoid influence may be more indirectly mediated via CRH, a hormone produced in the hypothalamus and responsible for controlling the release of glucocorticoids.

Chapter Summary

The first half of the above chapter details the effects of age on the brain and cognitive performance. The work reviewed in this chapter demonstrates that ageing causes considerable change to the human brain which is apparent on a structural (volume reductions resulting from loss of dendritic arbours and spines, shrinkage of cell bodies and disruption of myelin sheaths), chemical (reduction of NMDA receptors, increased sensitivity of GABA-A receptors, as well as deficiencies in cholinergic, serotonergic and dopaminergic systems) and electrophysiological functional level (increased power in slow wave bands (delta/theta) with corresponding power decreases in higher frequencies (alpha/gamma)). These age-related changes to human brain make-up coincide with pronounced alterations in

certain cognitive domains, particularly those dependent on frontal-hippocampal circuitry which is known to significantly alter with advancing age. As such, elderly individuals display significant impairments in long-term declarative and short-term working memory domains, as well as reduced performance in tasks measuring executive inhibitory control. However, with regard to the latter, the picture presented in the literature remains unclear. To date, findings highlight the possibility that executive control is a multifaceted concept, containing at least two sub-components, one of which (endogenous) is adversely affected by advancing age whereas the other (exogenous) process is left intact. Research further points out that the necessitated over-reliance on stimulus-bound exogenous inhibitory processes (as a result of impairments to the preparatory endogenous process) may lead elderly individuals to adopt more cautious response strategies which lead to differing performance levels on executive control tasks.

The second half of the chapter reviews the effects of stress on the human organism, discussing its damaging effects on health, well-being and cognition. In these domains, research has consistently demonstrated that in moderate to large or prolonged amounts, acute as well as chronic stress can impinge on successful cognitive performance and promote the development of certain forms of disease and illness. A more recent line of research has investigated the impact of cumulative life stress on ageing cognition. Promising findings from longitudinal as well as cross-sectional investigations highlight that the amount of stress experienced by individuals throughout their lifespan may constitute one of the factors producing individual differences in the rate of cognitive decline in the general population. These findings are supported by the way stress is known to affect certain brain regions. Animal as well as neuroimaging work indicates that stress causes damage to both the frontal

cortex and hippocampus – the same brain regions which are selectively vulnerable to age-related decline and are integral to successful cognitive performance.

The aim of this thesis is to further investigate the way in which cumulative life stress impacts on the rate of cognitive decline and the associated electrophysiological changes experienced by ageing individuals, thus enabling insight into the way in which cumulative stress affects underlying brain mechanisms linked to successful cognitive performance. To achieve this, it will begin by exploring the effects of acute stress on ageing performance and on the electrophysiological frequency bands of interest (Chapter 2) in order to reliably disassociate these from the effects of long-term cumulative stress. It will then proceed to investigate the cumulative stress effects on age in the cognitive domains of working memory (Chapter 3), executive inhibitory control (Chapter 4) as well as spatial memory (Chapter 5), each of which are thought to rely on brain regions selectively vulnerable to the adverse effects of both ageing and stress. In order to further understanding of the interactive way in which stress and age may affect cognitive execution, all behavioural measures will be paired with electroencephalographic recordings to provide insight into the underlying electrophysiological processing patterns employed during task execution. To conclude our investigations, Chapter 6 will investigate whether changes to electrophysiological processing patterns are likewise modulated by stress when the system is at rest and whether this is differentially expressed in elderly and young individuals.

Chapter 2: Acute Stress Reactivity

Abstract

Acute stress enhances or impairs memory, depending on stimulus material or the time point of stress encounter. This effect has been suggested to differ between age groups. Moreover, neuropsychological studies have indicated that acute stress exposure causes alterations in brain activity related to cognitive performance. Experiment 1 investigated declarative memory performance of 20 elderly and 20 young participants, half of which were asked to complete the Trier Social Stress Test, while the other half were allocated to a non-stressful control condition. Galvanic skin responses (GSR) as well as self-reported anxiety measures confirmed the effectiveness of the stressor, however, no performance differences were observed between stress groups. Experiment 2 explored the changes acute stress has been found to occasion in electrophysiological processing activity. To this effect, event-related theta frequency (ERS) as well as the amplitudes of N1 and P3 event-related components were recorded from 30 elderly and 30 young participants completing the mental arithmetic condition of the Trier Stress Test, while GSR were recorded to ascertain the impact of the stressor. Elderly participants displayed larger theta ERS and larger N1 and P3a amplitudes when compared to young participants. However, only N1 amplitude correlated with increased GSR, thus suggesting that heightened activity in the theta range as well as increased P3a amplitude were related to task demands rather than acute stress. Combined, findings suggest that the impact of acute stress on cognitive performance and the electrophysiological processing patterns associated with it is negligible and does not differ between age groups.

Introduction

A large body of work details the effects of acute stress exposure on performance. Acute stress has been discovered as either enhancing or debilitating to both physical and cognitive achievement, depending on the amount, form and situation in which it is encountered (Yerkes & Dodson, 1908, Broadhurst, 1959). In terms of the affected cognitive domain, altered performance is most commonly observed in declarative and working memory which rely strongly on areas of the brain identified as vulnerable to the influence of stress, such as the hippocampus and neocortex (Zeithamova et al., 2012). For example, on a declarative word learning task, Buchanan and Lovallo (2001) reported better recall of emotive material among acutely stressed participants, whereas Jelici and colleagues (2004) found exposure to an acute stressor resulted in impaired recollection of neutral words. Research into the effects of acute stress exposure also indicates age-related differences, highlighting that elderly individuals may be more prone to adverse effects of acute stress due to decreased coping and adaptational resources (Lupien et al., 2009). As such, studies have reported that relative to young people, elderly participants exhibit steeper performance decreases on declarative memory tasks after exposure to an acutely stressful situation (Kukolja et al., 2008).

In conclusion of a review into the effects of acute stress on underlying brain mechanisms, Arnstein and Goldman-Racik (1985) stated that acutely stressful situations make the brain switch from a thoughtful, reflective mode towards a faster, more reflexive form of processing. Awareness of acute stress' impact on underlying cognitive processes has led research to address these changes in the domains of both event-related potentials (ERPs) and

event-related oscillations. For example, Banis and Lorist (2012) found acute noise stress reduced the amplitude of the P3 component during a gambling feedback task. The P3 is thought to reflect higher order cognitive processes, such as template matching and updating of the working memory store. The authors surmised that expression of this component reflected mental processes of behavioural adaptation to received feedback which, in keeping with the electrophysiological data, participants in the acute noise stress condition were less able to accomplish. The magnitude of P3 amplitude has been observed to differ among elderly and young individuals. For example, Vesco, Bone, Ryan and Polich (1993) investigated age differences in P3, N1 and P2 amplitudes in response to different auditory stimuli of different intensities. The authors discovered young individuals manifested significantly larger P3 amplitudes compared to elderly participants. Similarly, Knott and colleagues (2003) reported steeper P3 amplitude gradients among young relative to elderly participants in a cognitive discrimination task.

A further component of interest to the current investigation is the N1 complex. The N1 is related to early forms of perceptual processing and has been implicated in auditory stimulus perception (Tremblay et al., 2001). Similar to the P3, the expression of N1 amplitude has been found to differ between old and young age groups. As such, Ford and colleagues (1995) reported that compared to the elderly, young individuals demonstrated N1 amplitudes three times as large in response to a startling tone. This finding led the authors to conclude that decreased N1 amplitude may reflect decreased early perceptual awareness among elderly individuals. In terms of oscillatory activity, studies have reported an increase of fronto-temporal theta event-

related synchronisation (ERS) in response to stress inducing negative feedback (Cohen, Elger & Ranganath, 2007; van de Vijver et al., 2011) whose expression has likewise been liked to cognitive processes necessary for behavioural adaptation towards a more favourable outcome (Gärtner, Grimm & Bajbouj, 2015).

Acute stress has been reliably evoked using the Trier Social Stress Test (Kirschbaum et al., 1993). As briefly discussed in Chapter 1, the TSST has been widely used to induce psychosocial stress (Domes et al., 2004; Kirschbaum et al., 1996) and is often paired with measures of Galvanic Skin Response (GSR) to assess its impact and effectiveness (Romero-Martinez et al., 2013). Studies pairing both report a reliable increase in GSR after completion of the Trier Social Stress Test (Jezova et al., 2004). Regarding performance indicators, the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1941) is an established measure of declarative memory which is primarily affected by acute stress exposure. As a result, the RAVLT has been used by a number of studies investigating the impact of stressors on memory performance. For example, Hidalgo, Almela, Villada and Salvador (2014) compared the RAVLT performance of 67 elderly and 67 young participants after exposure to the Trier Social Stress Test. Completing the Trier Stress Test produced an increase of cortisol secretion in both young and elderly but only elderly participants showed related performance impairments in immediate word recall, whereas young participants' behavioural performance remained unaffected by acute stress exposure.

In the current chapter, we examined acute stress instead of the lifetime cumulative impact of stress on cognitive ageing. Acute stress has been found

to produce changes in cognitive performance and have a greater impact on elderly compared to young individuals in this regard (Hidalgo et al., 2014). Furthermore, acute stress has been found to modulate or produce electrophysiological processing patterns (van de Vijver et al., 2011; Gärtner et al., 2014). Based on this, it is important to assess the impact of acute stress on both behaviour and electrophysiological occurrences, to reliably disassociate the impact of acute stress (which may be produced by assessment in novel laboratory surroundings) from the long-term effects of experienced stress assessed in later experiments. Two experiments were conducted to investigate the effects of acute stress among elderly and young participants. Experiment 1 aimed to investigate the behavioural impact of acute stress and therefore assessed declarative memory performance on the RAVLT task among both elderly and young participants after completing the Trier Stress Test. The second experiment aimed to assess whether acute stress exposure produced different electrophysiological processing patterns between elderly and young individuals. To this effect, it compared the amplitudes of ERPs N1 and P3 as well as the amount of theta ERS between elderly and young while these performed the mental arithmetic condition of the Trier Stress Test. In order to assess the effectiveness of the stressor, galvanic skin recordings were obtained in both experiments. Additionally, experiment 1 obtained measures of state anxiety both before and after completion of the Trier Stress Test, thus providing a subjective measure of stressor effectiveness. With regard to experiment 1, the hypotheses were as follows: Should acute stress have a significant impact on performance and have a stronger impact on elderly individuals, findings in line with Hidalgo and colleagues (2014) are expected.

As such, as well as a main effect of stress, results will indicate that elderly participants who completed the Trier Stress Test will display significantly larger memory decrements than both elderly participants who completed the control condition and young participants who undertook the Stress Test. Should the impact of acute stress be negligible, no performance differences among stress groups are expected to occur.

GSR recordings as well as state anxiety scores are hypothesised to be higher in the resting period after completion of the Trier Stress Test compared to a baseline rest recording obtained before completion of the test. No such differences are expected for the control condition.

With regard to experiment 2, elderly participants were hypothesised to display a larger amount of fronto-temporal theta event-related synchronisation which was hypothesised to positively correlate with galvanic skin responses based on past work, demonstrating that heightened amounts of acute stress produce an increase of theta ERS (Cohen et al., 2007; van de Vijver et al., 2011). Further age-related changes were expected to occur in N1 and P3a/b components whose expression is related to the nature of the task (completing the mental arithmetic). Based on past work investigating age-differences in N1 and P3 amplitudes in perceptual and cognitive tasks (Ford et al., 1995; Knott et al., 2003), elderly individuals were hypothesised to display reduced N1 and P3 amplitudes when compared to young participants.

The amplitudes of both N1 and P3 components were hypothesised to negatively correlate with increased galvanic skin responses in elderly but not young participants. This was hypothesised to indicate age-related performance difficulties as a result of elderly participants' increased vulnerability to the

stressful component of the task. Should the effects of acute stress be negligible, no significant correlations were expected for either young or elderly individuals. Due to no previous work finding stress related differences in ERP latencies these were disregarded in the current analysis.

Experiment 1

Materials and Method

Participant selection.

Young participants consisted of twenty University of Essex students who participated in the study in response to e-mail advertising (Mean age = 22.8 (2.75); Range = 20 - 30; 9 males). Elderly participants consisted of twenty individuals recruited via an advertisement placed in the local branch of the U3A newsletter (Mean age = 69.6 (7.27); Range = 62 - 87; 10 males). Demographics of both age groups can be viewed in Table 2.1. below. Exclusion criteria included major medical conditions (i.e. diabetes, heart disease), major neurological damage (i.e. stroke) and a current diagnosis of a mental or psychiatric disorder (dementia, depression or anxiety disorder) as well as the use of psychoactive medication and a history of substance abuse. In order to ensure against undiagnosed cognitive pathologies, all elderly participants completed the Mini Mental State Examination (Folstein, Folstein & McHugh, 1975) in which all scored full marks. All participants provided written informed consent. The study was approved by the University of Essex Ethics Committee.

Table 2.1. Demographics and performance means for elderly and young participants in the control and acute stress conditions.

	Elderly		Young	
	Control	Stress	Control	Stress
Group Size	10	10	10	10
Age	69.2 (7.4)	70 (7.5)	23.8 (3.4)	21.8 (1.5)
Gender	5 ♂	5 ♂	4 ♂	5 ♂
Native Speakers	10	10	5	4
Mini Mental Score	30	30	\	\
Trait Anxiety Score	2.1 (0.4)	1.7 (0.4)	2.0 (0.3)	2.1 (0.5)
Total Immediate	11.6 (4.1)	11.7 (2.6)	13.1 (2.3)	13.2 (2.5)
Total Confabulations	0.3 (0.4)	0.3 (0.3)	0.3 (0.3)	0.2 (0.2)
Delayed Recall	1.0 (1.0)	1.6 (2.5)	1.7 (1.7)	0.8 (1.8)
Recognition	18.67 (1.9)	19.1 (0.9)	19.5 (0.5)	19.8 (0.4)
Recognition False Positives	1.0 (1.0)	1.6 (2.5)	1.7 (1.7)	0.8 (1.8)

Note: Within each age group, demographical differences between control and stress groups were assessed with t-/chi-square tests. All results were non-significant (lowest p-value: 0.14 for Trait Anxiety Scores among elderly control and stress participant groups, all other p-values > .23).

Materials.

The State Trait Anxiety Inventory (STAI) developed by Spielberger (1968) comprises two 20-item questionnaires designed to assess respondents' general levels of trait anxiety and momentary levels of current anxiety. Items for the general trait assessment include statements such as 'I feel pleasant' or 'I feel inadequate' to which participants are asked to respond according to their general feelings about the statements.

Assessment of momentary anxiety levels includes items such as 'I feel calm' and 'I feel upset' which respondents are told to answer in accordance with how they feel at the present moment. Positively worded items are reverse scored for both questionnaires so that higher scores on either scale correspond to heightened levels of state and trait anxiety.

Participants were further required to complete a demographics assessment asking after their age, gender, educational level (below High School - PhD) and whether English was their first language or not (only individuals who rated themselves as proficient in English were invited to complete the study).

Declarative memory performance was assessed using a modified version of the Rey Auditory Verbal Learning Test (Rey, 1941) with 20 instead of the standard 15 words. The original 15 words were taken from Learning List A, the supplemented 5 words were taken from the AB 52-word recognition list which was also used for the recognition trial.

Psychophysiological recordings.

Galvanic skin responses were collected at a rate of 32 samples per second using a NeXus 10 recording kit and BioTrace+ software (Mind Media B.V., Netherlands, 2004 - 2010). Recordings were obtained from two electrodes attached to middle and index fingers of the non-dominant hand.

Procedure.

Participants began the experimental session by providing demographical information and completing both versions of the STAI questionnaire, followed by a two-minute recording of their resting state GSR response. After this, they completed either the Trier Social Stress Test (TSST)

or a control condition based on their allocation to the acute stress or control group. Participants were counter-balanced across both sessions based on gender and time of testing (9am or 11am). For the TSST, participants were asked to spend five minutes preparing a job interview speech which they were then required to present in the subsequent five minutes. In accordance with the protocol commonly observed for the test, participants received these instructions from two investigators who then left the room for the five-minute preparation phase and re-entered for the presentation of the speech. The final five minutes consisted of completing a challenging mental arithmetic task with negative feedback. For this, participants were asked to subtract the number thirteen from the starting number of 1053 in serial fashion. Each time a subtraction was miscalculated, participants were instructed to start from the beginning again. All three conditions were performed in front of two investigators.

The control condition consisted of a five minute reading task, followed by a 'leisurely chat' between investigators and participant. In the final session of the control condition, participants were asked to fill the time by counting out loud. After completion of either condition, participants were once more asked to complete the STAI state anxiety questionnaire, and post stressor GSR recordings were once again obtained during a two-minute resting session.

The TSST or control condition was followed by the RAVLT which consisted of 5 immediate recall trials. For these, 20 words were read out loud to participants after which they were instructed to orally reproduce as many of the words as they could still remember, regardless of their order. This procedure was carried out five times for each of the immediate recall trials.

Participants proceeded to watch a 30-minute video after which they were again asked to reproduce as many of the 20 words as they could still remember. The task concluded with a recognition condition in which 52 words (containing the 20 targets and 32 lures) were read out to participants. Participants were asked to indicate for each word whether it had been part of the original recall lists or not.

Results

Preliminary analysis revealed no significant differences between stress and control groups in levels of trait anxiety ($t_{38} = .77$, $p = .448$) or education ($t_{38} = 1.03$, $p = .236$) prior to the Stressor task. Furthermore, the amount of non-native English speakers was relatively equal among stress (6 individuals) and control groups (5 individuals).

Stressor effectiveness.

The galvanic skin recordings were analysed by means of a 2 (Time: pre vs. post task) x 2 (Age: old vs. young) x 2 (Condition: stressor vs. control) mixed measures ANOVA in which time acted as the within-subjects factor. Results revealed a main effect of time ($F_{1, 36} = 79.67$, $p < .001$), indicating that galvanic skin responses were significantly higher in the post-task resting condition compared to the pre-task baseline. A further main effect emerged for age ($F_{1, 36} = 7.73$, $p = .009$), indicating higher GSR measurements among young compared to elderly individuals. The main effect of time was qualified by a significant time x condition interaction ($F_{1, 36} = 5.99$, $p = .019$). This interaction was decomposed by simple effects contrasts which revealed a significant difference between pre and post GSR responses in the stressor condition ($F_{1, 36} = 3.23$, $p = .041$). This demonstrated that post GSR scores in

the stressor condition were significantly higher compared to pre stressor GSR recordings (see Figure 2.1.). No other comparisons reached significance (p_s > .05).

The same analysis was repeated with pre and post stressor scores on the STAI state anxiety questionnaire as the within subjects factor. This revealed a main effect for time ($F_{1, 37}$ = 11.94, p = .001) which indicated higher post than pre task anxiety scores. A further main effect emerged for condition ($F_{1, 37}$ = 9.3, p = .004), highlighting higher anxiety scores in the stressor relative to the control condition. Both main effects were qualified by a significant time x condition interaction ($F_{1, 37}$ = 16.84, p < .001). Follow-up analysis of this revealed a significant difference between pre-task and post-task state anxiety scores for the stressor condition ($F_{1, 37}$ = 19.5, p < .001), highlighting that relative to pre-task scores, post-task anxiety levels were significantly higher in the stressor condition. No other comparisons reached significance (p_s > .05).

Declarative memory performance.

Based on previous work investigating acute stress related performance differences between elderly and young participants on the RAVLT task (Hidalgo et al., 2014), the five performance variables displayed in Table 2.2. were chosen for analyses.

Performance differences were subsequently analysed using a 2 (Condition: stressor vs. control) by 2 (Age: old vs. young) between-subjects ANOVA for each of the specified variables.

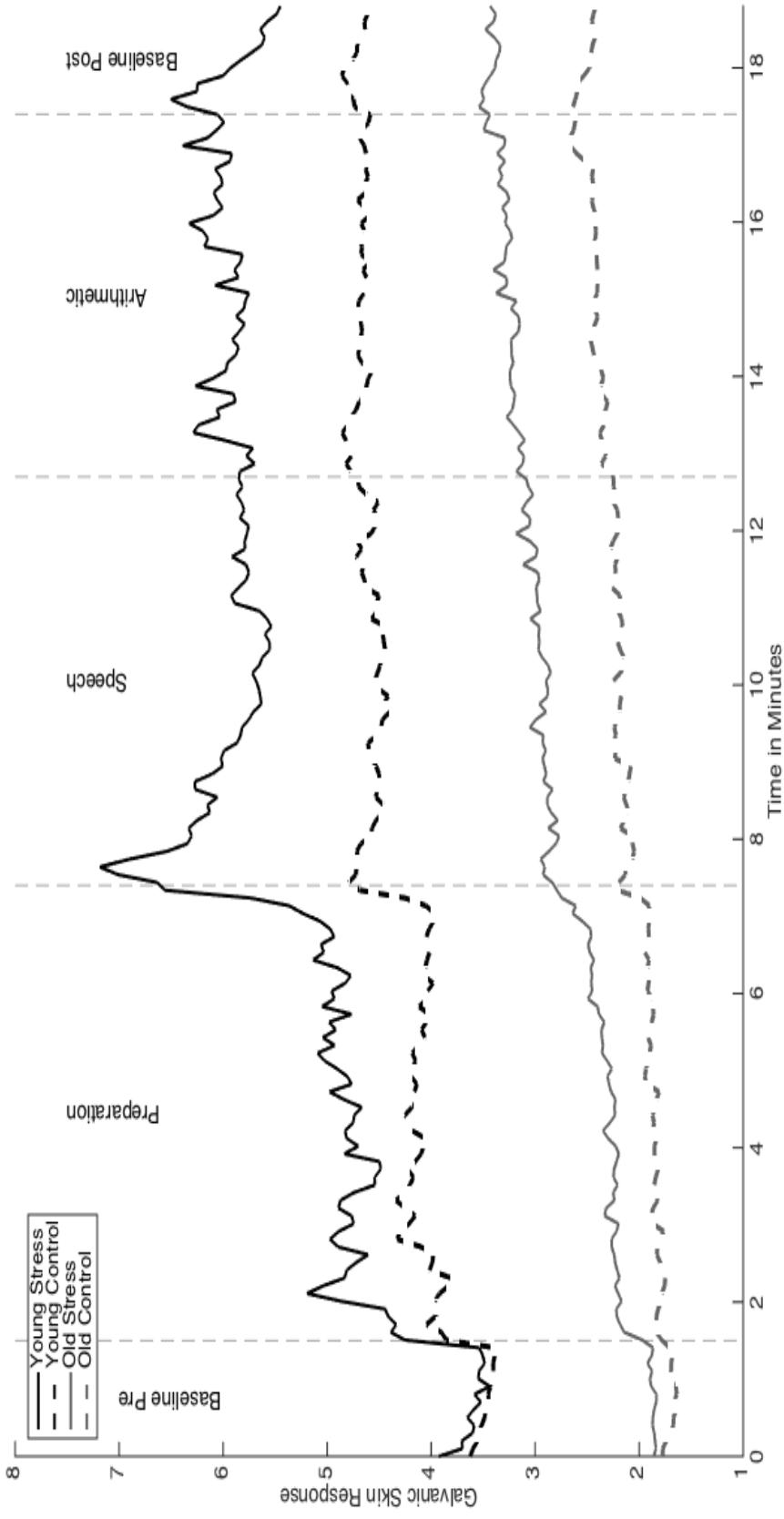


Figure 2.1. Galvanic skin response curves of elderly and young participants in the three different phases of the Trier Stress and Control condition.

Note. Results indicated significantly elevated galvanic skin recordings between the pre and post GSR baseline recordings for both age groups in the experimental group, thus highlighting the effectiveness of the stressor.

A significant main effect emerged for the total number of immediate recall variables ($F_{1, 36} = 5.52$, $p = .024$), indicating higher scores for young compared to elderly individuals. However, no significant main effects or interactions were found for any of the other performance parameters ($p_s > .05$).

Table 2.2. RAVLT performance measures chosen for analysis.

RAVLT variables	Description
Immediate Recall Total 1-5	Sum of correctly recalled words averaged over 5 immediate recall trials
Immediate Recall Confabulations 1-5	Sum of confabulations averaged over 5 immediate recall trials
Delayed Recall	Number of words correctly recalled after 30 minute delay
Recognition	Number of words correctly identified after 30 minute delay on recognition trial
Recognition False positive error	Number of words incorrectly identified on the recognition trial

Interim Discussion

This study's aim was to investigate whether the effects of acute stress exposure on declarative memory performance varied between elderly and young individuals. Analysing the effectiveness of the Trier Stress Test to evoke acute stress found that undertaking the task produced significantly higher galvanic skin responses and anxiety ratings compared to a pre test baseline. As no such differences emerged for the control condition, this indicates that the test acted as an effective tool for evoking acute stress among participants of the current study. In terms of galvanic skin responses, elderly participants were found to have overall lower responses compared to young

individuals. This finding is commonly observed in studies comparing skin conductance between old and young age groups and has been attributed to the reduced perspiratory rate commonly found among older individuals (Kenney & Munce, 2003). However, as no simple main effect emerged for the condition x age interaction, acute stress was not found to affect elderly participants more or less strongly than young counterparts. This finding was mirrored in the anxiety scores which likewise did not differ between elderly and young individuals in the stressor condition.

Analysis of the behavioural results found a main effect of age for the total number of immediately recalled words pooled over all five trials, indicating that young participants correctly recalled more items than elderly individuals. However, no further main effects of age emerged. This demonstrates that elderly and young participants did equally well in both the recognition and delayed free recall conditions. Furthermore, no main effect of stressor was observed, highlighting that overall completing the Trier Stress Test did not disrupt memory performance. Most importantly, no significant age x condition interaction emerged. Therefore, elderly participants' performance did not selectively suffer under the adverse influence of acute stress exposure. The current experiment hereby demonstrates that elderly participants' memory performance does not suffer under the influence of acute stress and is not more vulnerable to the presumed disruptive influence of acute stress when compared to young individuals. Similarly, galvanic skin responses and anxiety ratings likewise indicate that elderly participants' acute stress reactivity does not diverge from that of young counterparts.

Experiment 2

Materials and Method

Participant selection.

A sample of 30 elderly (Mean age = 66.7 (5.9); Range = 60 - 82; 16 males) and 30 young (Mean age = 23.3 (3.8); Range = 19 - 30; 15 males) right-handed volunteers participated in the study. Whereas young participants were recruited by email through the University of Essex participant pool, elderly participants were recruited by a number of presentations delivered to local clubs and societies (University of the 3rd Age; choirs and fitness/sports clubs). Demographical information about the participant sample can be viewed in Table 2.3. below. Exclusion criteria for participants included a history of brain damage, depression, anxiety disorders, substance abuse and the use of psychoactive medication. These exclusion criteria were mentioned during recruitment, and checked for in an interview immediately prior to testing. All elderly participants were further required to complete the Mini Mental State Examination (Folstein, Folstein & McHugh, 1975) to screen for age-related cognitive pathologies on which all participants scored full marks. All participants provided written informed consent. The study was approved by the University of Essex Ethics Committee whose ethical requirements are in accordance with the APA guidelines for ethical research conduct.

Materials.

The stimulus for the stressor task consisted of a 500Hz tone presented at 60dBs via the internal speakers of a Dell OptiPlex 755 computer.

Table 2.3. Demographics for both age groups undertaking the mental arithmetic stressor task.

	Elderly	Young
Group Size	30	30
Age	66.7 (5.9)	23.3 (3.8)
Gender	16 ♂	15 ♂
Mini Mental Score	30	\
Education	3.3	4.1

Note: Education ranging from 1 (lower than High School) – 6 (University PhD degree)

Procedure.

The protocol began with an eye calibration session (Croft & Barry, 1998), followed by a two-minute recording of participants' galvanic skin response at rest. To this effect, participants were instructed to move as little as possible and relax while concentrating on their own regular breathing. After completion, participants were given the starting number of 1053 and instructed to serially subtract the number thirteen each time they heard a short tone. The tone was presented with a variable inter-stimulus-interval ranging from 500 - 3000ms to avoid anticipatory effects in the EEG trace. Participants were told to perform the mental calculations silently in their head but nevertheless aim for the best possible result as good performance depended on the success of the experiment. They were also informed that they would be asked for their final calculation as a performance indicator. Should they lose the sequence at any point in the experiment, participants were told to roughly estimate the point at which they had been and continue the subtraction. The experimental session ended with a further two-minute GSR resting recording.

Psychophysiological recordings and data preparation.

EEG was recorded from 64 electrodes placed within a soft-cap according to the 10 - 20 method of electrode positioning. Recording was referenced to a point midway between Cz and CPz. Impedances were lowered to below 10kΩ in all electrodes before acquisition. The EEG signals were recorded and subsequently analysed using a Neuroscan Synamps2 system coupled with SCAN 4.5 software (Compumedics, Melbourne, Australia). Data were collected at a sampling rate of 1000Hz with a band-pass of 0.05 - 200Hz.

Acquired data was visually inspected and noisy data blocks, general artefacts and bad electrodes subsequently rejected. Ocular artefact rejection was carried out by performing principal component analysis on the acquired eye movement data to obtain the components reflecting saccades and blinks (Vigario et al., 2000). These were subsequently subtracted from the task data traces. All data was re-referenced to a common average reference. Data segments were subsequently cut into epochs ranging from 1000ms before stimulus onset to 1000ms after presentation of the tone. The first and last 500ms were later discarded to control for filter warm-up artefacts, leaving a 1000ms period (baseline and experimental epoch) for later analysis. Using the event-related band power transformation (SCAN 4.5 editing software), data underwent complex demodulation and filtering (zero phase-shift, 24dB roll-off, envelope computed) into the theta (4 - 6Hz) bandwidth. Event-related activity was calculated as a percentage change between the active and reference period based on the formula: [((reference – test)/reference)x100], developed by Pfurtscheller and Lopez da Silva (1999). According to this method, positive values represent desynchronisation of the theta frequency

band and synchronous activity is indicated by negative values. ERP data were baseline corrected using the 500ms pre stimulus interval, low-pass filtered (30Hz) and then averaged. Consequently, baseline-to-peak amplitude was computed for each participant. The electrode site with maximum baseline-to-peak amplitude was assessed from grand average ERPs collapsed across age groups which resulted in the same electrode being measured for all participants. As such, FC2 was selected for investigation of the N1 and P3a component, whereas electrode POz was selected for the P3b component.

Results

Event-related band power.

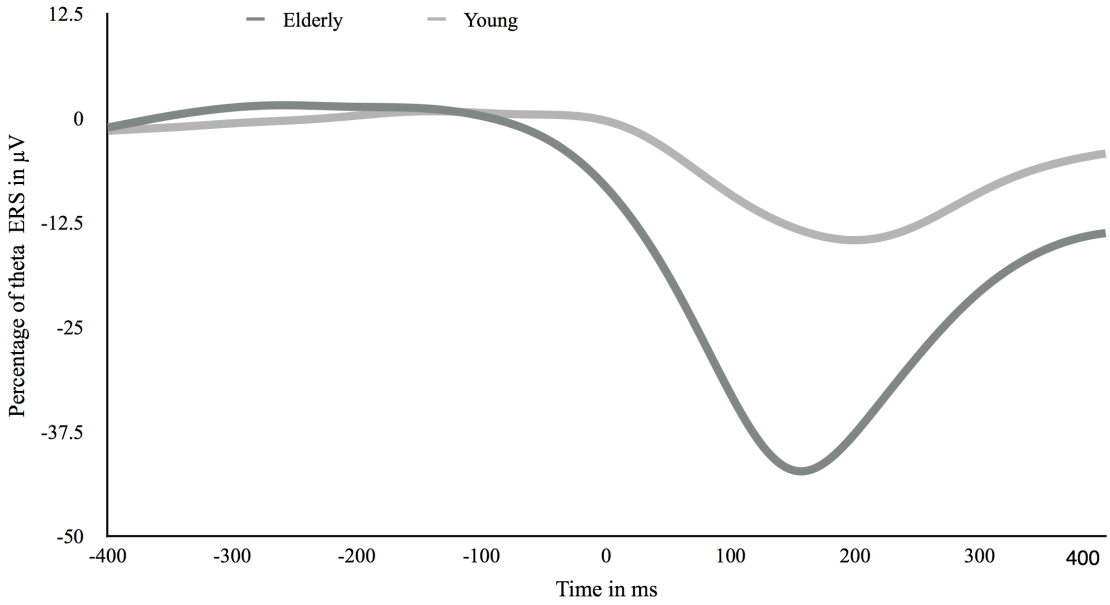
Event-related band power changes in the theta frequency range during completion of the stressor task were investigated by means of a 2 (Age: old vs. young) x 3 (Sagitality: frontal vs. central vs. posterior) x 3 (Laterality: left vs. mid vs. right) mixed measures ANOVA with repeated measures on the two latter factors. Results revealed a main effect for age ($F_{1,58} = 8.2$, $p = .006$), indicating that elderly participants showed higher levels of theta synchronisation over the entire scalp area relative to young participants (see Figure 2.2.). No further main effects or interactions reached significance ($p_s > .05$).

Event-related potentials.

Age differences among ERP components N1 and P3a/b during completion of the stressor task were investigated by means of a 3 (ERP: N1 vs. P3a vs. P3b) x 2 (Age: old vs. young) mixed measures ANOVA in which ERP acted as the within-subjects factor. Results indicated a significant ERP x age group interaction ($F_{2,49} = 28.23$, $p < .001$). Bonferroni corrected follow-up comparisons (corrected p-value .008) found a significant age difference for the N1 ($F_{1,51} = 19.35$, $p < .001$) and the

P3a component ($F_{1,51}$ = 10.42, p = .002) for both of which elderly participants exhibited larger amplitudes relative to young counterparts (see Figure 2.3.).

Figure 2.2. Grand average waveforms computed over the entire cortex for the theta frequency range.

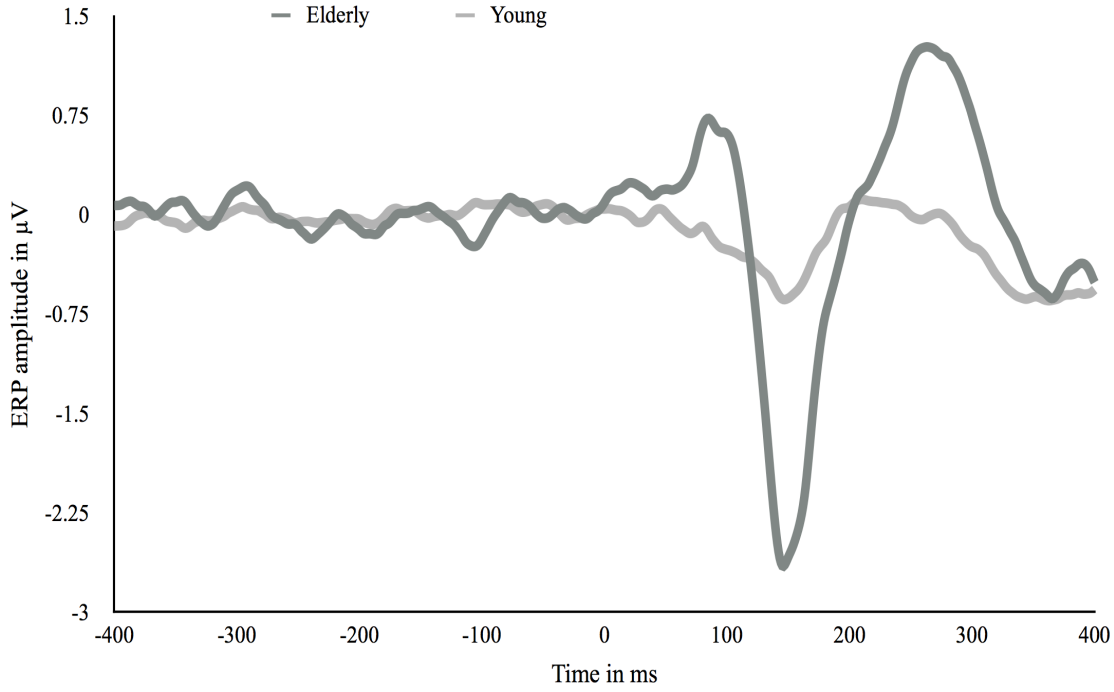


Note. Waveforms indicate the significant increase of theta ERS displayed by elderly individuals during completion of the mental arithmetic task (negative values represent ERS).

Galvanic skin responses.

Potential age differences in galvanic skin recordings were investigated by means of a 2 (Time: pre vs. post stressor) x 2 (Age: old vs. young) mixed measures ANOVA in which time acted as the within-subjects factor. Results indicated a main effect of time ($F_{1,50}$ = 25.5, p < .001) which demonstrated that galvanic skin responses significantly rose in the post relative to the pre stressor baseline recording condition.

Figure 2.3. Amplitude expression of the N1 and P3a components of both elderly and young participants during completion of the mental arithmetic task.

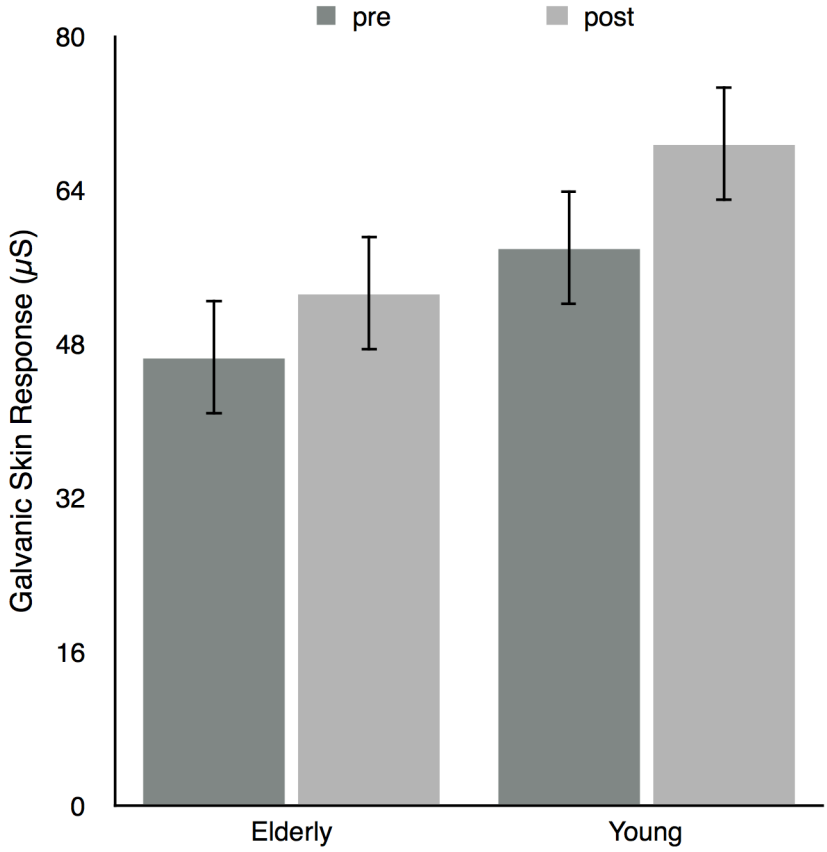


Note. Results demonstrate markedly higher N1 and P3a amplitudes among elderly compared to young participants.

A further main effect was found for age ($F_{1,50} = 4.23$, $p = .045$) which indicated that elderly participants displayed an overall reduced level of GSR when compared to young participants (see Figure 2.4.). The interaction term, however, remained non-significant, indicating that responses to the stressful condition did not differ between elderly and young individuals ($p > .26$).

Correlating both theta synchronisation and N1, P3a magnitudes with galvanic skin response during completion of the mental arithmetic found a significant correlation for the N1 component ($r_{58} = 0.38$, $p = .007$), indicating that as galvanic skin responses increased, N1 amplitude decreased. Decomposing the correlation by age found that this relationship was stronger for the elderly participant sample ($r_{28} = 0.41$, $p = .043$) ($p > .05$ for young participants).

Figure 2.4. Means of GSR responses for both elderly and young participants in the pre and post stressor recording sessions.



Note. Analysis revealed a main effect for both condition and age, indicating that skin conductance was markedly higher in the stressor compared to the control condition and among young relative to elderly participants (error bars represent SEM).

Summary Discussion

The present chapter set out to determine whether elderly and young participants showed different behavioural and psychophysiological responses as a result of acute stress exposure. To this effect, experiment 1 investigated whether acute stress exposure (in the form of completing the Trier Stress Test) differentially affected elderly and young participants' performance on a declarative memory task. Behavioural findings indicated that neither elderly nor young individuals suffered memory impairments as a result of acute stress exposure. Experiment 2 explored

whether completing the mental arithmetic condition of the Trier Stress Test produced differing ERP and oscillatory patterns among elderly and young participants. Results found that compared to young participants, elderly individuals displayed a global increase of theta event-related synchronisation as well as greater amplitudes of N1 and P3a components during completion of the mental calculation task.

Experiment 1: acute stress and performance.

As touched on in the interim discussion, analysis of galvanic skin responses and anxiety ratings produced a significant interaction between time and condition, indicating increased levels of skin conductance and higher anxiety levels in the post stressor baseline compared to the pre-stressor recording. This indicates the Trier Social Stress Test acted as an effective tool to evoke acute stress in the current experiment.

However, contrary to reports in the literature suggesting that acute stress strongly impacts on declarative memory performance (Wolf, 2008), current results did not produce a significant main effect of condition but indicated that performance in the stressor condition was similar to that of participants in the control condition. Some past studies have reported no effects of acute stress on declarative memory. For example, Lupien, Gillin and Hauger (1999) investigated the effects of administering the stress hormone hydrocortisone on working and declarative memory. Whereas the authors found a significant acute effect for the highest dose of hydrocortisone on working memory, declarative memory performance remained unaffected. The authors therefore concluded that declarative memory may be less sensitive to the effects of acute stress than working memory. However, such findings remain in the minority as most studies report either a general decline in declarative memory performance (McEwen & Sapolsky, 1995) or enhanced recall of salient material such as emotive

words (Buchanan & Lovallo, 2001) with a corresponding impairment of more neutral stimulus material (Jelici et al., 2004).

Similarly, findings did not show a significant performance difference between elderly and young participants in the stressor condition. This differs from reports that elderly individuals are more prone to the adverse effects of acute stress encounter (Kukolja et al., 2008). For example, using the same task design as the present study, Hidalgo and colleagues (2014) found RAVLT performance selectively declined among elderly individuals completing the Trier Social Stress Test, while young participants in the stressor condition remained unaffected. Similarly, Lupien and colleagues (1997) reported decreased declarative memory performance among elderly individuals placed in a stress inducing public speaking condition, while young participants' performance did not suffer from the same treatment.

In keeping with the behavioural findings, analysis of galvanic skin response recordings between age groups did not find any significant differences between elderly and young individuals in the control or the stressor condition. This indicates that elderly did not manifest a stronger physiological stress response compared to young participants. However, contrary to behavioural results, a number of studies report similar findings when comparing physiological age differences in response to acute stress (Ohashi et al., 1986). As such, Kudielka and colleagues (2004) pooled data from five independent studies to investigate gender and age differences of Hypothalamic-Pituitary-Adrenal axis responses to undertaking the Trier Stress Test. Investigating the cortisol responses of 102 participants (30 elderly, 41 young, 31 children), the authors found a significant gender difference but no age differences in cortisol response. Therefore, while our behavioural results are discrepant with regard to age differences in the acute stress literature, our GSR findings (similarly reporting

no age differences) are more in keeping with reports concerning the physiological stress responses manifested by elderly and young.

Experiment 2: acute stress and electrophysiological activity.

Physiological results obtained while both elderly and young participants performed the mental arithmetic condition of the Trier Social Stress Test produced a main effect of time in the galvanic skin response data, indicating increased anxiety in the post stressor relative to the pre-stressor baseline. This indicates that the mental arithmetic condition acted as an effective means by which to evoke acute stress.

Electroencephalographic recordings indicated that, compared to young, elderly participants demonstrated an increase in global theta synchronisation as well as larger amplitudes of the N1 and P3a components while performing the demanding mental calculations. The heightened theta ERS observed among elderly relative to young participants during completion of the stressor task corresponds to the work of Cohen and colleagues (2007) who observed increased theta synchronisation over fronto-temporal scalp sites in response to negative feedback. However, contrary to reports that acute stress selectively affects frontal scalp areas, results indicated a general increase of theta ERS over the entire cortex. Increased theta synchronisation in response to acute stress has been linked to cognitive control processes designed to evaluate and, if necessary, amend a stressful situation. However, in this capacity increased theta ERS has been predominantly observed over frontal scalp areas (Gärtner et al., 2014). In an influential paper, Vogel, Broverman and Klaiber (1968) hypothesised that increases of theta ERS may reflect widespread inhibition or a change of strategy towards more reflexive, automatic functioning. This hypothesis would correspond to the view of Arnsten and Goldman-Racik (1985) that acute stress exposure occasions the brain to switch from reflective to automised functioning.

However, no correlation was established between increased theta synchronisation and increased stress reactivity in form of higher galvanic skin recordings during the experimental time period. This suggests that, rather than experiencing acute stress, increases in theta ERS among elderly participants reflects the increased task demands the cognitive nature of the task placed on elderly participants relative to young. Higher levels of theta ERS may therefore reflect increased resource allocation to deal with task demands or a change of strategy in keeping with the suggestion of Vogel and colleagues (1968).

The increased amplitudes of the N1 and P3a components in elderly individuals with respect to young participants differ from age differences commonly reported in the literature (Vesco et al., 1993; Ford et al., 1995). However, findings to this effect may likewise indicate a heightened electrophysiological response as a result of heightened task demands among elderly participants. The N1 component has been implicated in early stimulus processing and discrimination (Vogel & Luck, 2000), whereas the P3a component has been linked to higher order cognitive processes such as template matching in conjunction with updating of the working memory store (Polich, 2003). Amplitudes of the later occurring P3b component have been observed to decrease with increased memory demands, either as a result of decreased resources (McEvoy, 1998) or because of overlap with negative slow-wave components related to complex stimulus processing (Meckliner, Kramer & Strayer, 1992). Conversely, amplitude increases in the earlier P3a component have been linked to greater allocation of attentional resources in keeping with its proposed role of template matching (Polich, 2007). Similarly, the N1 component's amplitude has been reported to increase with heightened allocation of attentional resources (Vogel & Luck, 2000). Similar to observations with regard to theta ERS, no correlation between higher GSR

recordings and P3a amplitude was discovered which again highlights that differences between elderly and young participants occurred due to the cognitive nature of the task rather than as a result of an age specific acute stress difference. For example, elderly individuals may perceive the cognitive demands inherent in the mental arithmetic as more demanding and therefore exhibit an increased stimulus monitoring response in order to deal with task demands.

However, a significant negative relationship was discovered between N1 amplitude and galvanic skin response which was most strongly expressed among elderly participants. Galvanic skin results demonstrating that N1 amplitude declines as a function of increased anxiety among elderly participants indicates that acute stress may impact on elderly participants' early stimulus monitoring. In their 2010 article, investigating the effects of acute stress on working memory performance, Weerda and colleagues hypothesise that acute stress may make a task more difficult by increasing the overall performance load. The increased demands of acute stress may therefore cause a reduction of the N1 amplitude due to task demands exceeding elderly participants' allocation of reduced resources.

Similar to findings in experiment 1, analysis of the galvanic skin response data indicated a main effect of age, highlighting that elderly participants manifested a significantly reduced galvanic skin response in the resting as well as the stressor condition when compared to young counterparts. This finding is common in the literature and is thought to be a result of reduced perspiratory levels with advancing age (Kenney & Munce, 2003). More importantly, results found no significant age difference in participants' stress reactivity, thereby once again highlighting that compared to young, elderly participants did not show higher levels of anxiety during acute stress encounter.

Further directions and conclusion.

Combined, findings from experiments 1 and 2 indicate no pronounced age differences in dealing with acute stress. Contrary to findings in the literature, suggesting that elderly individuals suffer from increased vulnerability towards the influence of acute stress (Lupien et al., 1994), behavioural as well as physiological results in the form of galvanic skin recordings suggest no age differences in the way acute stress is experienced and acts on performance. With regard to experiment 1, behavioural findings were contrary to results reported in the literature, suggesting that, compared to young, elderly individuals' performance suffers more from the adverse effects of acute stress. In light of this, it is necessary to point out that, as only one main effect of age for one of the five performance variables and no main effect of condition emerged, the possibility remains that the RAVLT task was not of sufficient difficulty to produce an effect of acute stress exposure among high performing elderly participants. However, the RAVLT has proven to be a reliable measure in producing age differences as a result of acute stress exposure by a number of studies employing the same task design as experiment 1 (Hidalgo et al., 2014; Almela et al., 2011). Moreover, to address the high performance displayed by the elderly participant sample, the task difficulty was increased (20 instead of the standard 15 items). Despite studies indicating that acute stress selectively affects the performance of elderly individuals, this area of research still remains under-researched (Hidalgo et al., 2014). Paired with reports that cortisol responses as a result of acute stress exposure do not differ between elderly and young people, this suggests that findings, indicating that acute stress exposure selectively impairs elderly participants' performance, should be interpreted with caution. To this effect, results of the current study indicate that on a moderately taxing declarative memory task, elderly

participants' performance does not differ from that of young individuals after acute stress exposure. Results of experiment 2 did produce an age difference linked to acute stress exposure, demonstrating that among elderly individuals higher anxiety levels correlated with a reduction of N1 ERP amplitude. As N1 amplitude was generally higher among elderly compared to young participants, this suggests that acute stress may adversely affect the compensatory mechanisms engaged in by elderly individuals when confronted with strenuous task demands. However, this effect seems bound to early perceptual processes of stimulus monitoring as it was not found for the later P3a component or the theta synchronisation manifested during completion of the mental arithmetic task.

A final point to note regarding the galvanic skin recordings is that the reduced conductance response consistently manifested by elderly individuals makes a direct comparison between elderly and young individuals non-informative. Therefore, all comparisons made between elderly and young participants in this chapter were of an interactive nature, taking into account age-related differences with regard to a pre- and post-stressor baseline recording.

To conclude, the current chapter's findings indicate that the immediate impact of acute stress on performance and electrophysiological occurrences is negligible and does not markedly differ between elderly and young individuals. The moderate amounts of acute stress experienced by performing cognitive tasks in a laboratory setting are therefore unlikely to significantly moderate or distort any possible impact of lifetime cumulative stress exposure on cognitive ageing which is the main focus of this thesis and will be addressed in the following chapters.

Chapter 3: Cumulative Stress and Aged Working Memory

The Effects of Long-term Stress Exposure on Ageing Cognition: A Behavioural and EEG Investigation

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Abstract

A large field of research seeks to explore and understand the factors that may cause different rates of age-related cognitive decline within the general population. However, the impact of experienced stress on the human ageing process has remained an under-researched possibility. This study explored the association between cumulative stressful experiences and cognitive ageing, addressing whether higher levels of experienced stress correlate with impaired performance on two working memory tasks. Behavioural performance was paired with electroencephalographic recordings to enable insight into the underlying neural processes impacted on by cumulative stress. Thus, the Electroencephalogram (EEG) was recorded while both young and elderly performed two different working memory tasks (a Sternberg and N-back paradigm) and cortical oscillatory activity in the theta, alpha and gamma bandwidths was measured. Behavioural data indicated that a higher stress score among elderly participants related to impaired performance on both tasks. Electrophysiological findings revealed a reduction in alpha and gamma event-related synchronisation among high stress group elderly participants, indicating that higher levels of experienced stress may impact on their ability to actively maintain a stimulus in working memory and inhibit extraneous information from interfering with successful maintenance. Findings provide evidence that cumulative experienced stress adversely affects cognitive ageing.

Introduction

An ageing population places increasing demands on healthcare and welfare systems. A growing body of research is devoted to pinpointing factors that might moderate different rates of cognitive decline experienced by these individuals. One such factor, chronic or cumulative stress, is capable of causing structural damage to areas of the hippocampus and neocortex which may result in a detriment to cognitive functioning. Specifically, increased levels of glucocorticoid stress hormones may produce dendritic atrophy and inhibit neurogenesis in areas of the hippocampus (Sapolsky & Meaney, 1986; Miller & O'Callaghan, 2003), and heightened levels of hypertonic blood flow have been shown to produce an increased number of micro lesions in the neocortex (Rabbitt, 2005). Unsurprisingly then, chronic stress has been identified as a risk factor for developing pathological forms of cognitive impairment in old age such as Alzheimer's Disease and dementia (Daulatzai, 2014).

In a rare longitudinal study, Peavy and colleagues (2009) reported that higher incidences of cumulative stressful experiences over the course of three years resulted in decreased memory performance among elderly participants suffering from Mild Cognitive Impairment. Additionally, cross sectional studies have established a link between heightened exposure to cumulative life stress and reduced memory performance in old age, regardless of age or level of education (Dickinson et al., 2011; Tschanz et al., 2013). While presenting robust behavioural findings, the above cross sectional studies fail to control for health behaviours which have been found to affect cognitive ageing such as the amount of cigarette and alcohol consumption (Kalminjn et al., 2002), the amount of physical exercise (Kimura et al., 2013) or the presence of a physical disability. More importantly, these studies do not recognise the importance of the subjective appraisal of the stress experience (Sands, 1981;

Aggarwal et al., 2014). A further factor to highlight at this point is that certain studies have argued against employing the aggregate score of stressful events, noting that certain stressful experiences can have a detrimental effect on memory performance, whereas others can have an opposite, enhancing effect. Thus, for example Rosnick and colleagues (2007) advocate the use of a single item approach, as in their experience, the opposing effects of stressful experiences negate each other when combined.

The present study aimed to explore the relationship between cumulative life stress and cognitive ageing while accounting for a range of mediating factors (see Table 3.1.), including a measure of stress tolerance to address previous shortcomings highlighted by Sands (1981). In addition to this, it aimed to further investigate whether the aggregate stress score employed by past studies proves an accurate predictor of elderlies' stress related memory shortcomings. A further objective of this study was to investigate the way in which cumulative stress affects maturation of the human brain. A good method to achieve this is the study of oscillatory dynamics (in the form of rhythmic fluctuation in the electrical activity across the cortex). These are increasingly seen as reflecting the brain's storage and manipulation of information necessary for successful behavioural performance (Buzsaki & Draghun, 2004; Engels, Fries & Singer, 2001; Varela et al., 2001). Oscillatory dynamics can be split into a number of different bands which oscillate at different frequencies ranging from 0.5Hz to > 60Hz. Specifically, increased synchronous activity in the theta (4 - 6Hz), alpha (8 - 12Hz) and gamma (30 - 60Hz) bands has been observed to predict cognitive performance (Burgess & Gruzelier, 2000; Burgess & Ali, 2002). For instance, synchronous activity in the alpha band has been linked to the efficient suppression of task-irrelevant information during memory maintenance periods

(Klimesch et al., 2007; Sauseng et al., 2009), whereas theta and gamma activity have been linked to the successful maintenance and recognition of a retained memory set (Perez et al., 2013; Roux & Uhlhaas, 2014; Burgess & Gruzelier, 1997).

The predominant form of studying oscillatory dynamics is by means of the Electroencephalogram (EEG) whose high temporal resolution enables the study of oscillatory processes unfolding on a millisecond-by-millisecond basis. EEG recordings are predominantly used to record cortical oscillatory activity, however, recent studies have indicated that they may also provide insight into subcortical cognitive processes. To this effect, both theta and gamma frequencies have been hypothesised to reflect a dynamic interaction between the hippocampus and neocortex during periods of memory maintenance (Bastiaansen & Hagoort, 2003). Moreover, Babiloni and colleagues (2009) found a significant correlation between hippocampal volume and cortical alpha power over parietal, occipital and temporal regions.

One of the cognitive domains most commonly studied in conjunction with EEG recordings is working memory (Berger et al., 2014; Enriquez-Geppert et al., 2014). Working memory (WM) is thought of as the brain's capacity to store and manipulate information necessary for successful performance in a given situation (Baddeley & Hitch, 1974) and has received large amounts of interest in the general ageing and EEG literature. As such, a number of studies have demonstrated that the amount of items held in WM declines with advancing age (Salthouse & Babcock, 1991), while numerous EEG studies have reported age-related reductions of theta, alpha and gamma activity during WM task engagement (Karrasch et al., 2004; van de Vijver et al., 2014; Manard et al., 2014).

Two protocols prominently used in the EEG literature to assess WM are the N-

back (Kirchner, 1958) and Sternberg (Sternberg, 1966) tasks. One of the merits of using a combination of both to assess WM lies in the different demands inherent to both tasks. The Sternberg task measures the different stages of WM in serial fashion. This allows a clear distinction between encoding, maintenance and retrieval processes (Jensen et al., 2002). Conversely, the N-back task measures the co-ordination of multiple processes relating to WM (simultaneous maintenance and updating of the WM store in conjunction with retrieval and interim stimulus inhibition). Both tasks have been used extensively to study age-related behavioural changes in conjunction with EEG (Deiber et al., 2009; Barr et al., 2014; Karrasch et al., 2004) and have proven reliable measures of age-related impairments to both WM performance and the associated oscillatory processes. Although age-related performance differences have been uniformly observed for the Sternberg task, mixed findings have been reported for the different conditions of the N-back task. Specifically, oscillatory age-differences reliably manifest for the 2-back condition (Verhaeghen & Basak, 2005), especially during early time windows of stimulus processing (Krause et al., 2000), whereas mixed observations have been reported for the 3-back condition (Mattay et al., 2006). This study therefore employed a 2-back condition to assess oscillatory and performance differences between elderly and young individuals.

In general, modulation of cortical oscillations during performance of both tasks has been reported to take place in the alpha, theta and gamma bands. Prominent findings report an increase in alpha event-related synchronisation (ERS) during mid to late maintenance periods of the Sternberg task (Jensen, Gelfand, Konunios & Lisman, 2002). Similarly, both alpha and theta ERS have been reported to increase with N-back task demands (Brouwer et al., 2012), whereas excessive gamma ERS has been linked to reduced N-back task performance, particularly among patients

suffering from schizophrenia (Díez et al., 2014). Pronounced age differences have been reported in both the alpha and theta frequency range for the Sternberg paradigm (Karrasch, Laine, Rapinoja & Krause, 2004; Karrasch et al., 2006) and in the theta, alpha and gamma frequency ranges for the N-back task (Barr et al., 2014; Missonnier et al., 2011).

At the time of writing, investigations into the way cumulative experienced stress may affect cognitive ageing have been undertaken on a behavioural level. A useful addition to the literature would therefore lie in pairing behavioural measures with an insight into the way stress affects the neural mechanisms underlying task performance. Accordingly, the present research aims to employ EEG to examine whether the impact of stressful life experiences on cognitive performance is accompanied by corresponding changes in brain activation.

Based on the hypothesis that long-term stress exposure may adversely affect brain structures necessary for cognitive functioning, highly stressed elderly participants were predicted to display reduced levels of behavioural performance, coupled with oscillatory changes, compared to young and low stress group elderly participants. Reduced event-related synchronisation among elderly high stress group participants was predicted to occur in the theta, alpha and gamma frequency bands for the N-back and (based on the pronounced age differences discovered in these frequency bands when using this paradigm) in the theta and alpha bands for the Sternberg task.

Experiment 3

Materials and Method

Participant selection.

A sample of 30 elderly (Mean age = 66.7 (5.9); Range = 60 - 82; 16 males) and 30 young (Mean age = 23.3 (3.8); Range = 19 - 30; 15 males) (see Table 3.1.) right-handed volunteers participated in the study. Whereas young participants were recruited by email through the University of Essex participant pool, elderly participants were recruited by a number of presentations delivered to local clubs and societies (University of the 3rd Age; choirs and fitness/sports clubs). Exclusion criteria for participants included a history of brain damage, depression, anxiety disorders, substance abuse and the use of psychoactive medication. These exclusion criteria were mentioned during recruitment and checked for in an interview immediately prior to testing. All elderly participants were further required to complete the Mini Mental State Examination (Folstein, Folstein & McHugh, 1975) to screen for age-related cognitive pathologies in which all participants scored full marks. All participants provided written informed consent. The study was approved by the University of Essex Ethics Committee whose requirements accord with the APA guidelines for ethical research conduct.

Stress and demographical measures.

The present study focussed on the detrimental effect of experienced stress, accumulated over the course of a lifetime, on cognitive performance. However, given that our elderly participants have on average three times the age of the younger participants, they are likely to have experienced more stressful events. In addition, the types of stressful events are likely to be different for both our populations. Thus, in order to assess prolonged stress exposure appropriate to each age group and make the

argument that the long-term effects of cumulative stress exposure are responsible for behavioural shortcomings and not purely high amounts of immediate stress, different instruments had to be used for elderly and young participants.

Table 3.1. Demographical variables of the participant sample split by age and experienced stress group.

	Elderly		Young	
	Low Stress	High Stress	Low Stress	High Stress
Group size	14	16	15	15
Age	66.8 (5.3)	67.2 (6.4)	23.1 (3.5)	23.5 (4.3)
Gender	8 ♂	8 ♂	8 ♂	7 ♂
Education	3.0 (0.8)	3.77 (1.2)	3.85 (0.6)	3.0 (1.1)
Cigarette Consumption	0.15 (0.6)	0	0	0
Alcohol Consumption	3.2 (2.4)	3.5 (2.7)	4.5 (3.5)	3.7 (3.1)
Presence of Physical Disability	2	4	0	0
Exercise	2.3 (0.8)	2.4 (1.0)	2.3 (0.1)	2.3 (0.8)
Mini Mental State Score	30	30	n.a	n.a
Experienced Stress Score	455.4* (122.1)	841.9* (149.9)	443.5* (132.3)	792.2* (126.8)

Note. Education ranging from 1 (lower than High School) – 6 (University PhD degree); Cigarette Consumption: cigarettes per day; Alcohol Consumption: units per week; Exercise: hours per week; *$p<.05$ represents significant stress group differences within age groups

Both the Social Readjustment Rating Scale (Holmes & Rahe, 1967; for elderly participants) and the Student Life Events Scale (Clements & Turpin 1996; for young participants) have a similar format, consisting of a brief, self-report scale (43 and 36

items respectively) containing incidents ranging from extremely stressful (i.e. 'Death of Spouse/Parent') to mildly stressful (i.e. 'Finding a part-time job'). Participants' scores range from 0 - 1466 for the Social Readjustment Rating Scale and 0 - 1849 for the Student Life Events Scale with higher scores reflecting high amounts of experienced stress. To ensure values measured from different scales contributed equally to the analysis, the scores for each participant were standardised within age groups.

Stress tolerance was assessed via the Perceived Stress Scale (Cohen, 1983), a 10-item self-report scale assessing how unpredictable and stressful respondents have experienced their lives over the past month. Items include questions such as ('In the last month, how often have you felt nervous and stressed?'). Further background demographics included participants' age, gender, level of education, cigarette and alcohol intake, amount of physical exercise and whether respondents suffered from a disability which might compromise performance on the tasks. Units and time frames of demographics assessment can be viewed in Table 3.1..

Procedure.

Each session began by completing an eye-movement calibration session (Croft & Barry, 1998), followed by a two-minute eyes closed/resting EEG session. Participants then moved on to complete the experimental task.

For the N-back task, participants viewed white numbers 1 to 4 (Helvetica) embedded within a 50% random noise grey patch with an additional blank 50% noise square for the control task. For the 2-back task, participants were asked to memorise the last two presented numbers and respond each time the number matched the one seen two positions previously. The control task consisted of responding each time a blank square appeared within the sequence. Participants responded to targets by

pressing a response pad button with their right index finger. Each condition began with a blank screen presented for 200ms, after which the numbers were presented for 500ms with an inter-trial interval of 2500ms. Each condition of the N-back protocol comprised 120 trials. In the 2-back condition, 39 numbers acted as targets and 81 numbers as non-targets. In the zero-back condition, 39 blank grey squares acted as targets and 81 numbers as non-targets. No response was required for non-targets. Each condition was split into three blocks of 40 trials by two breaks lasting for 10 seconds in the control and 40 seconds in the experimental condition. Control and 2-back conditions were presented to participants in counter-balanced order. Consequently, half the participants completed the control trials first, then moved on to the 2-back condition. The other half of participants experienced the reverse order.

Psychophysiological recording and analysis.

EEG was recorded from 64 electrodes placed within a soft-cap according to the 10 - 10 method of electrode positioning. Recording was referenced to a point midway between Cz and CPz. Impedances were lowered to below 10kΩ in all electrodes before acquisition and rechecked between tasks. The EEG signals were recorded and subsequently analysed using a Neuroscan Synamps2 system coupled with SCAN 4.5 software (Compumedics, Melbourne, Australia). Data was collected at a sampling rate of 1000Hz with a band-pass of 0.05 - 200Hz.

Acquired data was visually inspected and noisy data blocks, general artefacts and bad electrodes subsequently rejected. Ocular artefact rejection was carried out by performing principal component analysis on the acquired eye-movement data to obtain the components reflecting saccades and blinks (Vigario et al., 2000). These were subsequently subtracted from the task data traces. All data was re-referenced to a common average reference. In order to investigate age and stress related group

differences in response to completing both tasks, the 64 electrodes were averaged into nine brain regions: left (FP1, AF3, F7, F5, F3, F1, FT7, FC5, FC3, FC1), mid (FPz, Fz, FCz) and right (FP2, AF4, F8, F6, F4, F2, FT8, FC6, FC4, FC2) frontal; left (T7, C5, C3, C1, TP7, CP5, CP3, CP1), mid (Cz, CPz) and right (T8, C6, C4, C2, TP8, CP6, CP4, CP2) central; left (P7, P5, P3, P1, PO7, PO5, PO3, CB1, O1), mid (Pz, POz, Oz) and right (P8, P6, P4, P2, PO8, PO6, PO4, CB2, O2) posterior.

Based on Krause and colleagues' (2000) reports of oscillatory differences manifesting 100 - 500ms after stimulus onset in a 2-back task, data segments for calculation of event-related synchronisation and desynchronisation (ERD/S) for control and 2-back conditions of the N-back task were cut into a 500ms (after stimulus onset) test interval used for subsequent analysis. In order to avoid movement related artefacts, only epochs for correct non-target trials, in which no response was made, were included for analysis. The reference period for the N-back task lasted for 500ms and ranged from -500 to 0ms.

Using the Event-related-band-power transformation (SCAN 4.5 editing software), data underwent complex demodulation and filtering (zero phase-shift, 24dB roll-off, envelope computed) into the theta (4 - 6Hz), lower (8 - 9), upper alpha (10 - 12), lower (30 - 42) and upper gamma (43 - 80Hz) bandwidth. Past exploration of the alpha and gamma frequency bands highlights the importance of splitting both into upper and lower frequency components as they may reflect different attentional states and have been found to selectively respond to differing task demands (Hanslmayr et al., 2011; Trimper et al., 2014). Event-related activity was calculated as a percentage change between the active and reference period according to the following formula: [((reference – test)/reference)x100]. According to this method adapted from Pfurtscheller and Lopez da Silva (1999), positive values indicate

desynchronisation of the frequency bands under investigation, while negative values indicate synchronisation.

Data preparation.

For the behavioural analysis of the N-back task, numbers for all predictors were standardised. The formula (Zscored Hits – Zscored False Positives) was used to compute d' – a value representing the relative proportion of correct responses minus the false alarms given by participants. This was subsequently used as the Dependent Variable for the behavioural analysis. In order to assess reaction times, all correct response trials were averaged.

To investigate the impact of experienced stress on cortical oscillations, experienced stress scores of young and elderly participants were grouped into high and low stress groups employing the median split of scores from the Social Readjustment Rating Scale for elderly (Median Split value 671) and the Student Life Events Scale for young participants (Median Split value 568). No significant group differences in Mini Mental State performance, age, gender, level of education, cigarette and alcohol consumption or amounts of exercise were observed between stress groups.

Results

Behavioural analysis.

Participants' cognitive performance on the N-back task was analysed by means of hierarchical linear regressions. In separate regressions, performance (accuracy or rt's) was regressed on participants' experienced stress score and age group (coded -1 for young and 1 for elderly participants). In the second step, the interaction of experienced stress by age was added. In the final model, we controlled for participants' gender, physical disability, alcohol intake, level of exercise and

perceived stress score.

Looking at the N-back accuracy data, the first model accounted for a significant 17% of the variance ($F_{2,57} = 5.90$, $p = .005$). In terms of individual predictors, only participants' age was positively associated with decreased performance. The inclusion of the age by experienced stress interaction accounted for an additional 15% of variance ($\Delta F_{1,56} = 12.23$, $p = .001$). Simple slopes analysis (see Figure 3.1.) found a significant age difference when experienced stress was high ($t_{59} = 6.74$, $p < .001$). No other comparisons reached significance. Importantly, the interaction remained significant after control variables were included (step 3).

In terms of investigating the relationship between age, experienced stress and reaction times, the model proved significant in the first step ($F_{2,57} = 4.2$, $p = .043$). Age as the only independent predictor accounted for 9% of the variance in reaction times. Adding the interaction term and demographical factors in the following stages produced non-significant models ($p > .05$) in which only age acted as a significant predictor of reaction times.

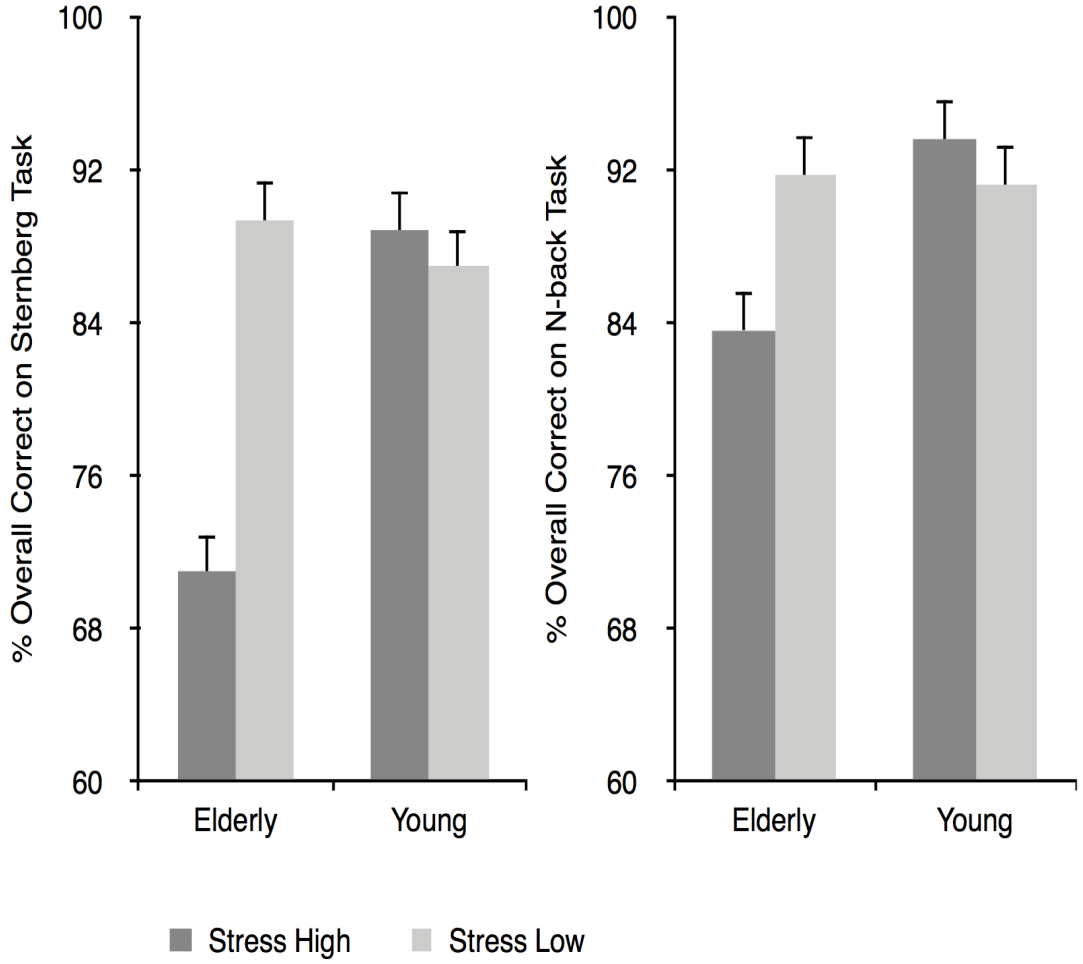
Electrophysiological analysis.

Based on previous findings in the theta, alpha and gamma frequencies, upper/lower alpha, upper/lower gamma and theta frequencies were analysed to investigate the underlying oscillatory markers of N-back task performance.

This was done using a 3 (Laterality: left vs. mid vs. right cortical regions) x 3 (Sagitality: frontal vs. central vs. posterior cortical regions) x 2 (Condition: control vs. 2-back) x 2 (Age: old vs. young) x 2 (Experienced Stress: high vs. low) mixed measures ANOVA. The former three factors comprise within-subjects variables. A main effect of age was found for the upper gamma frequency band in which young participants showed more synchronisation compared to elderly counterparts ($F_{1,44} =$

7.5, p = .009).

Figure 3.1. Performance scores of young and elderly participants split into high and low experienced stress groups.



Note. For both the Sternberg and N-back task, the difference between high and low stress group elderly participants reached significance. Error bars represent SEM.

Results further revealed a significant condition x age x experienced stress interaction ($F_{1,44} = 5.56$, p = .023). To decompose this, the analysis was run with two separate ANOVAs for both stress groups. For the low experienced stress group, the condition x age interaction was not significant (p > .05). The model for the high experienced stress group showed a significant condition x age interaction ($F_{1, 20} = 5.2$, p = .034). Follow-up comparisons indicated a significant age difference for the 2-back condition ($F_{1, 20} = 6.4$, p = .02) in which elderly participants showed lower levels

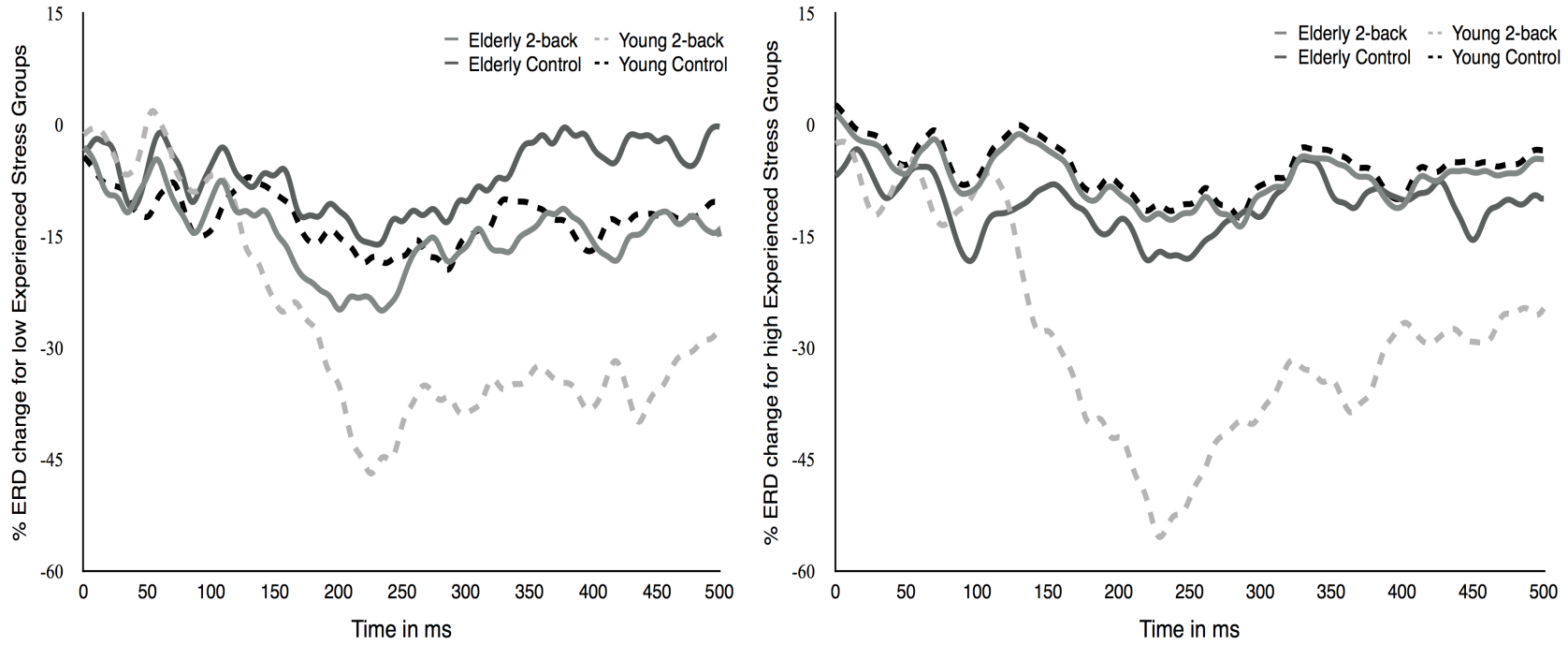
of upper gamma synchronisation compared to young (see Figure 3.2.).

Furthermore, a significant difference was observed between the control and 2-back condition for high stress group elderly ($F_{1, 20} = 5.4$, $p = .031$) in which higher levels of upper gamma synchronisation were shown in the control detection condition compared to the 2-back condition (see Figure 3.2.). Both differences were observed over the entire cortex. No significant main effect or interactions were discovered for the theta or upper/lower alpha frequency range ($p_s > .05$).

Electrophysiological and behavioural correlations.

To determine the functional significance of upper gamma activity, correlational analyses were conducted over the entire cortical region with overall correct performance on the task (d'). Results revealed a negative correlation for the entire participant sample ($r = -.30$, $p = .039$) in the high gamma frequency range, indicating that increased high gamma ERS coincided with increased performance on the N-back task.

Figure 3.2. Grand average waveforms for the high gamma range computed over the entire cortex during N-back sequence monitoring for both the 2-back and the non-memory control task



Note. Among the high experienced stress groups, the difference between elderly and young participants reached significance, as well as the difference between the control and the 2-back task for elderly participants. Low experienced stress group averages show the increase in high gamma ERS among elderly individuals when moving from the control to the 2-back task which is reversed for high stress group elderly participants.

Interim Discussion

The aim of the above experiment was to further investigate the adverse impact cumulative experienced stress is known to exert on elderly individuals' working memory performance. In addition, we aimed to extend these findings by pairing behavioural indicators with EEG measures of underlying oscillatory dynamics, thus providing insight into which cognitive processes are affected by increased lifetime stress exposure. Analysing the overall accuracy (d') of elderly and young participants on the N-back task found that higher levels of cumulative life stress coincided with reduced performance among elderly but not young individuals. This corresponds to earlier behavioural work in the domain of WM (Dickinson et al., 2011; Peavy et al., 2009) and demonstrates that the adverse effects of stress exposure on ageing cognition remain stable even after controlling for prominent health behaviours which may have confounded earlier findings. In addition, our electrophysiological results extend these behavioural findings by highlighting that the behavioural shortcomings manifested by elderly high stress individuals correspond to a decrease of upper gamma event-related synchronisation during monitoring of the N-back stimulus sequence. As noted in the introduction, the nature of the N-back task requires the simultaneous co-ordination of multiple aspects and stages of WM. Specifically, participants are required to continuously update their WM store with encountered items, maintain the item for two stimulus iterations while retrieving and matching the retained item to the stimulus they are currently presented with.

In addition, the successful matching process requires the inhibition of the intervening stimulus item. As such, the N-back task places very high cognitive demands on the system. Increased amplitude in the gamma frequency range has traditionally been interpreted as indexing the active maintenance and rehearsal of

stimulus material (Sauseng et al., 2009; Roux & Uhlhaas, 2014) and has been shown to increase in response to conscious recollection of stimulus material (Burgess & Ali, 2002). Therefore, our electrophysiological findings with regard to the N-back task seem to indicate that in a memory task that requires the co-ordination of numerous sub-processes and places high demands on individuals' cognitive systems, high levels of cumulative life stress impact on elderlies' ability to actively maintain to-be-remembered stimulus material.

Experiment 4

Materials and Method

The data presented in experiments 3 and 4 was obtained from a single testing session in which participants completed both the N-back and the Sternberg WM tasks in counter-balanced order. As such, the participants who took part in experiment 4 were the same as presented above for experiment 3. In addition, the measures used to obtain demographical and experienced stress variables were the same, as was the psychophysiological recording process and the data preparation.

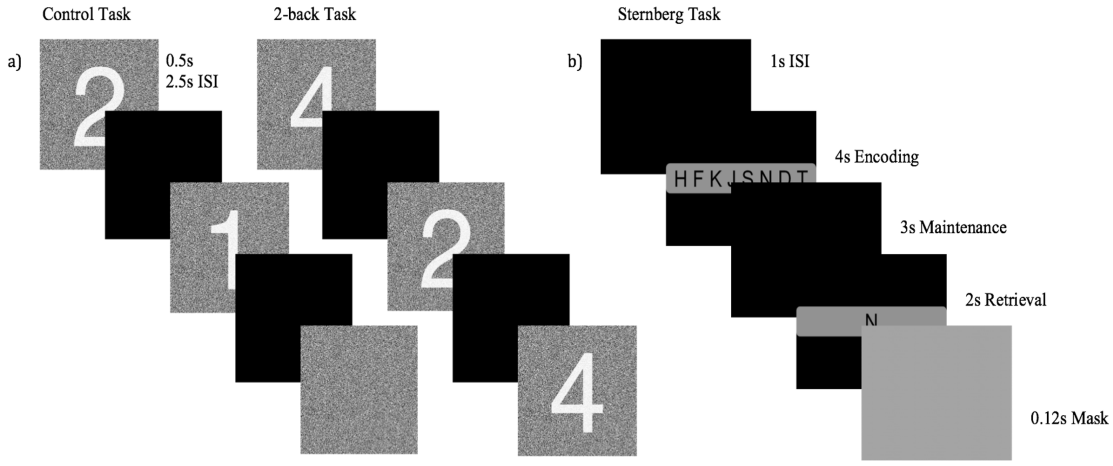
Procedure.

Each session began by completing an eye-movement calibration session (Croft & Barry, 1998), followed by a two-minute eyes closed/resting EEG session.

For the Sternberg protocol (see Figure 3.3.), participants viewed a sequence consisting of a blank screen presented for 1000ms, followed by a letter-set displayed for 4000ms. Letter-sets and single probe letters consisted of 15 pseudo-randomly combined consonants (Helvetica) enclosed within a 5% noise grey patch. After a further blank screen presented for 3000ms, a single probe letter appeared for 2000ms during which participants were asked to indicate whether the letter had been part of

the original letter-set or not. Participants responded by pressing a button on the response pad with their right index finger each time they believed the probe had been part of the original letter-set. The sequence ended with a brief 115ms masking stimulus. The Sternberg task was comprised of 100 trials of which 60 included a target probe letter and 40 a non-target probe. No response was required for non-targets. Participants were given the opportunity to take a break after 50 trials.

Figure 3.3. Schematic representation of the N-back and Sternberg paradigms.



Note. a) Control and 2-back versions of the N-back task. The correct response would be to the third stimulus for both: respond to an empty square for the control task, or to a number repeated over two stimulus iterations for the 2-back task b) Schematic representation of the Sternberg task, indicating the duration each image was presented. Participants were asked to memorise the 8-letter sequence and respond each time the single probe letter was included in the foregone array.

Psychophysiological recording and analyses.

Electrophysiological recording and data preparation involved the same steps as referenced in the above section concerning the N-back task. To investigate ERD/S activity during the maintenance period of the Sternberg task, data segments were cut into a 3000ms retention test period used for subsequent analysis. This was based on findings by Jensen and colleagues (2002) who reported oscillatory differences, as a function of memory load, manifested in the last 2 seconds of the retention interval.

The reference period consisted of 1000ms at the beginning of each sequence during which participants viewed a blank screen. Calculation of the ERD/S activity for the Sternberg maintenance period included epochs from correct (target and non-target) trials, as no motor response was required during this period.

Data preparation.

Akin to data preparation for the N-back task, d' (Zscored Hits – Zscored False Positives) was computed as an overall reflection of individuals' performance accuracy on the Sternberg task and used as the Dependent Variable for the subsequent behavioural analysis. For reaction times, all response times for correct trials were averaged. Additionally, young and elderly participants were split into high and low experienced stress groups based on their Median Split values from appropriate scales as reported above (Median Split value 671 for elderly; 568 for young participants).

Results

Behavioural analysis.

For the Sternberg accuracy data (see Table 3.2.), the first model was significant, accounting for 18% of the variance in performance ($F_{2, 57} = 6.31$, $p = .003$). Both age and experienced stress scores were independently associated with a decrease in accuracy. The inclusion of the interaction of age x experienced stress accounted for an additional 11% of the variance ($\Delta F_{1, 56} = 8.72$, $p = .003$).
Simple slopes analysis was conducted. An age-group difference emerged when experienced stress was high ($t_{59} = 9.12$, $p < .001$). No other comparison was significant.

Table 3.2. Linear regression models of demographics and experienced stress by age interactions predicting scores on the behavioural paradigms.

	Sternberg			N-back		
Independent Variable	Step 1	Step 2	Step 3	Step 1	Step 2	Step 3
Experienced stress score	-.312*	-.281*	-.289*	-.234	-.199	-.251
Age	-.290*	-.290*	-.404**	-.343**	-.343**	-.231
Experienced stress by age		-.334**	-.282*		-.387**	-.464**
Gender			.024			.035
Education			-.098			.032
Physical disability			.167			-.076
Alcohol intake			-.055			.197
Exercise			.192			.114
Perceived stress score			.153			.210
F	6.31**	7.69**	2.93**	5.91**	8.81**	3.71**
df	2/57	3/56	9/50	2/57	3/56	9/50
R^2	.18	.29	.37	.17	.32	.43
ΔF		8.72**	0.93		12.24**	1.36
Δdf		1/56	6/50		1/56	6/50
ΔR^2		.11	.08		.15	.11

This suggests that being a member of the older age group coupled with high experienced stress scores was associated with decreased cognitive performance on the Sternberg task. Crucially, the nature of this interaction was identical when controlling for other variables in step 3.

For the rt data, the association between age, experienced stress and reaction times produced an overall significant model ($F_{2, 57} = 4.17$, $p = .036$) which accounted

for 11% of variance in reaction times. Age was the sole predictor showing that elderly participants were generally slower. Neither the addition of the interaction (step 2), nor the addition of the control variables improved the model ($p_s > .05$).

Electrophysiological analysis.

After inspecting the averages for both age groups, the 3s retention period of the Sternberg task was split into 1s early, mid and late epochs. Based on previously discussed findings, reporting predominant age differences in alpha and theta frequency bands, especially in mid to late periods of the Sternberg maintenance period (Jensen et al., 2002), upper/lower alpha and theta frequencies during the mid and late epochs were analysed. This was done with two 3 (Laterality: left vs. mid vs. right cortical regions) x 3 (Sagitality: frontal vs. central vs. posterior cortical regions) x 2 (Age: old vs. young) x 2 (Experienced Stress: high vs. low) mixed measures ANOVAs.

Sternberg mid (1000 to 2000ms) maintenance period.

Analysis of the mid period indicated a significant Laterality x Sagitality x Age x Experienced Stress interaction for the upper alpha frequency range ($F_{4, 224} = 2.69$, $p = .032$). To further decompose this interaction, a Laterality x Sagitality x Age ANOVA was conducted separately for both stress groups. The three-way interaction for the low stress group was not significant ($p > .20$). The three-way interaction for the high stress group approached near significance ($F_{4, 112} = 2.84$, $p = .058$). Due to the exploratory nature of the present study and given that hypotheses related to simple main effects, follow-up comparisons were conducted for this interaction. These revealed that among individuals with high experienced stress scores, young participants, compared to elderly counterparts, showed substantially increased upper alpha synchronisation over left central ($F_{1, 56} = 4.28$, $p = .043$) and right posterior ($F_{1,}$

$_{56}$ = 5.63, p = .021) regions (see Figure 3.4.). No significant main effect or interactions were discovered in the lower alpha or theta frequency range (p_s > .05).

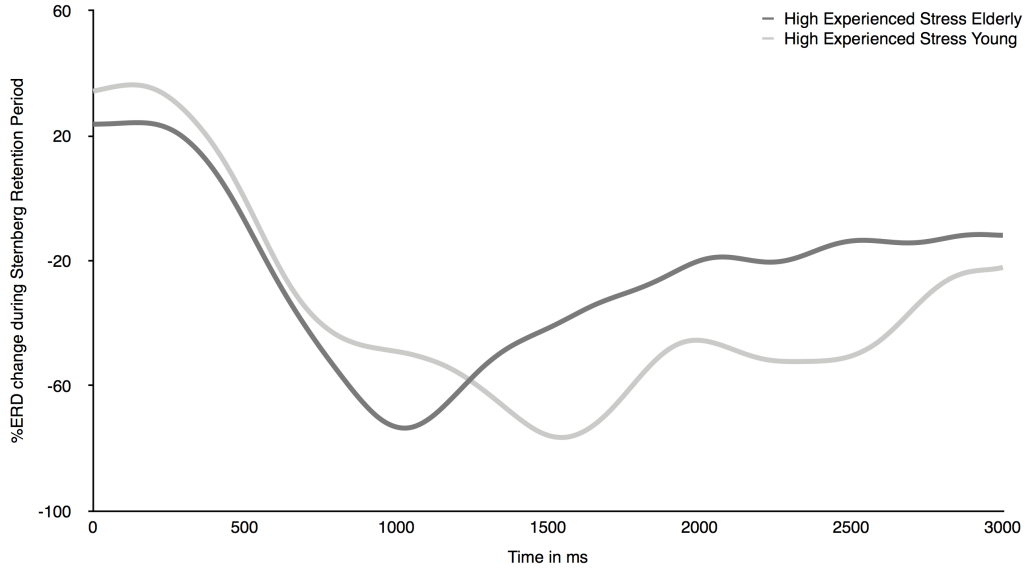
Sternberg late (2000 to 3000ms) maintenance period.

Results revealed a significant main effect of age for the upper alpha ($F_{1, 56}$ = 5.80, p = .019) and theta frequency band ($F_{1, 56}$ = 11.04, p = .002). Both main effects indicated that elderly participants displayed reduced levels of ERS compared to young counterparts. No interactions or main effects were discovered for the lower alpha frequency range (p >.05).

Electrophysiological and behavioural correlations.

In order to classify the functional significance of upper alpha activity during the middle interval of the maintenance period (during which the interaction between age and stress was found) for overall task performance, correlational analyses were conducted over left central and right posterior regions and behavioural scores on the task (d'). Results showed a significant negative correlation over the left central cortex for the entire participant sample (r = -.43, p = .001). These correlations indicate that lower levels of synchronisation in the left central area of the cortex coincided with decreased overall performance on the task.

Figure 3.4 High alpha grand average waveforms computed over the right posterior cortex for both high stress age groups.



Note. Figure indicates reduced high alpha synchronisation of high stress elderly participants during the Sternberg maintenance period when compared to high stress group young counterparts.

Summary Discussion

The present study explored the possible impact of cumulative experienced stress on cognitive ageing in the domain of working memory. To this effect, experiment 3 investigated the adverse effects of cumulative lifetime stress on WM performance in a task that required the continuous co-ordination of multiple WM aspects, whereas experiment 2 explored the same effect in a paradigm which clearly distinguished between different working memory stages. The aim of work presented in this chapter was to extend previous findings on the way cumulative stress affects elderly individuals' WM performance by providing an electrophysiological indication of the underlying cognitive processes which are impacted on by heightened lifetime stress exposure. Results indicated that experienced stress negatively affected elderly participants' performance, as elderly participants with high levels of cumulative experienced stress displayed lower overall performance scores (d') on both N-back

and Sternberg tasks. Furthermore, reduced behavioural performance among the elderly participant sample was found to coincide with differences in oscillatory dynamics linked to successful cognitive task execution.

Experiment 3: cumulative stress and N-back performance.

Performance scores on the N-back task found a significant age difference between young and elderly participants which only occurred among individuals with high cumulative experienced stress scores. Behavioural results therefore indicate that experienced stress has selectively compromised elderly participants' ability to perform successfully on a cognitive WM paradigm that requires the on-going co-ordination of various WM aspects and stages. Behavioural results remain stable after controlling for a number of mediating factors, including perceived stress. This supports both previous longitudinal and cross-sectional work (Pesonen et al., 2013; Dickinson et al., 2011) reporting that larger amounts of cumulative experienced stress coincide with decreased WM performance among elderly individuals and strengthens their findings by ruling out the confounding impact of factors which feature prominently in the cognitive ageing literature. In addition, our findings speak to past reports indicating that the aggregate score of stressful experiences, regardless of their subjective appraisal, acts as a reliable predictor in capturing the adverse effects of cumulative stress on ageing WM performance (Peavy et al., 2009; Dickinson et al., 2011).

Electrophysiological results for the N-back paradigm showed that in the high experienced stress group, young participants displayed higher levels of upper gamma synchronisation compared to elderly participants. Furthermore, elderly participants in the high experienced stress group showed a significant reduction of upper gamma ERS from the control to the demanding memory task. Both differences were observed

over the entire cortex. Furthermore, correlational analysis revealed that increased levels of upper gamma ERS over the entire cortical region were related to increased overall performance.

Gamma ERS during memory maintenance periods is commonly interpreted as the active binding and maintenance of a memory set (Roux & Uhlhaas, 2014). Contrary to the maintenance period of the Sternberg task, successful monitoring of an N-back sequence requires the engagement of numerous aspects of WM and entails on-going fast paced binding and updating of information. A significant age difference among individuals in the high stress group therefore indicates that experienced stress may have impacted on elderly participants' ability to maintain the continual active binding required for successful N-back task performance and could account for the observed reduction in performance displayed by elderly individuals with higher levels of experienced stress. The significant reduction of gamma ERS from the control to the memory demanding 2-back task among elderly participants in the high experienced stress group forms a further indication of impaired functioning. Inspection of group averages revealed that both young and elderly participants in the low stress group increased levels of gamma ERS from the control to the 2-back task which reflects heightened task demands. The reduction of gamma synchronisation among elderly participants in the high stress group may therefore suggest a breakdown of cortical activity once a task becomes too demanding and exceeds coping abilities. In keeping with this, a number of studies investigating age-related performance differences on the N-back task have reported that age differences only appear once demands require matching the current stimulus to the stimulus two positions back (Verhaeghen & Basak, 2005). Similar to the claim made by Babiloni and colleagues (2009), synchronous oscillatory activity in the gamma frequency

range has been argued to reflect hippocampal activation, indicating a dynamic interaction between the cortex and hippocampus (Wang & Buzsaki, 1996). The reduction of upper gamma ERS among high stress elderly participants may therefore form a further indication of damage sustained by the hippocampus through heightened levels of experienced stress.

Experiment 4: cumulative stress and Sternberg performance.

Corresponding to findings for the N-back paradigm, performance scores on the Sternberg task produced a significant difference among elderly and young individuals reporting high amounts of cumulative lifetime stress. As such, the detrimental effects of lifetime stress on old adults' WM performance are also apparent in a task which clearly distinguishes between different WM stages and does not require the co-ordination of multiple WM sub-processes to the same extent as the N-back task. Once again, behavioural results remained stable when controlling for perceived stress levels as well as prominent health factors that may have confounded earlier work. As such, our results provide convincing evidence that the sum total of stressful experiences acts as a reliable predictor for stress-induced WM impairments among elderly individuals and thus corresponds to the larger body of work on this issue (Peavy et al., 2009; Tschanz et al., 2013; Dickinson et al., 2011). Finding no cognitive impairments among young individuals reporting high amounts of experienced stress for both experiments indicates that it is not a large amount of experienced stress per se which causes cognitive WM impairment. Thus, results support the hypothesis that only long-term exposure to high amounts of cumulative stress experienced over the lifespan results in cognitive disability. Furthermore, failure to find an impact of perceived stress indicates that it is not the subjective feeling generated by the stressful life event but the experience of the event that has an

adverse effect on elderlies' cognitive performance. The behavioural findings of experiments 3 and 4 therefore indicate that the total amount of experienced stress sustained throughout the lifespan impacts on the rate of cognitive ageing in the domain of working memory.

For the Sternberg paradigm, EEG findings in the mid epoch of the retention period revealed a difference in high alpha ERS among young and elderly participants in the high experienced stress group: young participants were found to display increased alpha ERS compared to elderly over left central and right posterior cortical regions. Correlating high alpha activity with behavioural scores showed that the reduced alpha synchronisation displayed by elderly participants in the high stress group related to reduced performance on the Sternberg task.

Higher levels of alpha synchronisation during Sternberg maintenance periods have been ascribed to the successful inhibition of brain regions not necessary for memory maintenance (Klimesch, 2012) by, for example, reducing the level of potentially distracting information (Sauseng et al., 2009). A number of studies have reported an increase of activity in the alpha frequency range coupled with successful Sternberg task performance (Jensen et al., 2002). According to this interpretation, the reduced alpha ERS displayed by high stress group elderly participants could signify reduced ability to inhibit task-irrelevant cortical regions. Both right posterior and left central areas are involved in the visual uptake and encoding of new information. A reduced ability to inhibit these regions may therefore result in less focused stimulus maintenance coupled with increased vulnerability to distractors.

The reduction of upper alpha ERS among high stress elderly participants may also indicate an adverse effect of cumulative stress on areas of the hippocampus proposed by Sapolsky and Meaney (1986). The work of Babiloni and colleagues

(2009) reported that reduced hippocampal volume among elderly individuals coincided with a reduction in alpha power, therefore, these results may indicate increased damage to the hippocampus sustained by elderly participants in the high stress group.

Further directions and conclusion.

This study sheds an interesting light on the way cumulative experienced stress may impact on cognitive ageing in the domain of working memory. However, capturing the impact of mediating factors when aiming to assess a long-term impact using cross-sectional data is a great concern. Additional contributions to this area of research could therefore lie in accounting for further potential mediators such as measurement of participants' cortisol levels or life-style factors not assessed by the current study such as diet or living environment. Also, the current study used two different measures to assess cumulative experienced stress among elderly and young individuals which may have affected stress-related differences. However, employing two different measures was necessary to test the study's argument that experienced stress acts detrimentally to cognitive performance only in its cumulative form (as sustained over the lifespan). Moreover, by standardising cumulative stress scores within age groups, measures were taken to ensure differences resulting from the use of two different scales were kept to a minimum. Furthermore, we argue that even if the same scale had been used to ascertain experienced stress for both age groups, it would not be pertinent to compare this main effect. Compared to young individuals, elderly participants would necessarily obtain a higher stress score due to having lived longer. Furthermore, they might construe the scale differently or have a different outlook on their lives based on their viewpoint (looking back after having lived most of their lives, whereas young individuals have most of their time still ahead).

Therefore, different stress scores could manifest for a variety of different reasons and would not reliably reflect how stressful a life a young individual has led relative to an elderly counterpart. In order to circumvent this issue, the current study employed two different scales tailored to the different stressful experiences individuals of different age groups may experience. Also, we refrained from comparing main effects of experienced stress scores and focused instead on the interactive relationship between age and cumulative experienced stress which we argue provides more meaningful insight into the way cumulative stress impacts on cognitive performance. Finally, despite past studies successfully establishing links between oscillatory activity and the integrity of subcortical brain structures, this remains an indirect measure. Therefore, the current results provide an insight into the way stress affects the brain on a cortical level but cannot directly indicate how it may have affected the hippocampus. To study the effect of stress on subcortical areas of the brain, further research will need to utilise neuroimaging techniques able to investigate subcortical structural changes.

Findings of this study highlight the potentially adverse effect of cumulative experienced stress on age-related cognitive WM performance and provide insight into the way experienced stress may affect cortical oscillatory dynamics. Behavioural findings on both the Sternberg and N-back task demonstrate a clear association between higher experienced stress scores and reduced performance which was specific to elderly participants. In terms of electrophysiological data, cumulative experienced stress impacted on the upper alpha and gamma frequency ranges, resulting in a possible impairment of inhibitory upper alpha activity in the Sternberg task and a reduced capability in the upper gamma range to maintain a sequential memory set in the N-back task. Sternberg demands requiring the sustained 'static'

maintenance of stimuli produced differences in the upper alpha frequency range. Conversely, the continuous updating of the WM store required by the N-back task produced differences in the upper gamma band. This suggests cumulative stress may have a broad effect on WM and affect multiple aspects conducive to successful performance. Furthermore, both alpha and gamma ERS have been argued to index intact hippocampal functioning. Therefore, the reduction of event-related-synchronisation in both frequency bands forms a further indication of the adverse effect of cumulative experienced stress on the hippocampus and indicates how it may affect the brain on both cortical and subcortical levels. The present paper therefore constitutes further evidence that cumulative experienced stress should be considered as a possible risk factor for accelerated cognitive decline and highlights the merit in pairing behavioural with electrophysiological measures to gain a deeper insight into which underlying cognitive processes are affected by high levels of lifetime stress exposure.

Chapter 4: Cumulative Stress and Ageing Executive Control

Experienced Stress Produces Inhibitory Deficits in Old Adults Flanker Task Performance: First Evidence for Lifetime Stress Effects Beyond Memory

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Abstract

Reduced inhibitory performance among elderly individuals has been reported using a number of paradigms (e.g. the Stroop Task, the Simon Paradigm). However, discrepant results have been found regarding the inhibitory Flanker task. Past work has explained this discrepancy by hypothesising that elderly individuals make use of compensatory mechanisms advantageous to Flanker performance. The present study investigated these compensatory mechanisms, focussing on cumulative experienced stress as a factor that may impact on their successful execution. To this effect, thirty elderly and thirty young participants completed a modified version of the Flanker task. In order to gain more insight into possible cognitive mechanisms, behavioural data collection was paired with electroencephalographic recordings of the alpha frequency band, whose increased synchronisation is thought to index inhibitory processes. Findings revealed a general behavioural deficit among high stress elderly participants, producing increased reaction times for both incongruent and congruent stimulus arrays. Behavioural impairments among high stress elderly individuals correlated with alpha desynchronisation for congruent and incongruent stimulus categories which may indicate a deficit of inhibitory processing among low performing individuals rather than compensatory mechanisms engaged in by high performing elderly. Results of the present study provide further evidence for the detrimental effect of experienced stress on cognitive ageing and shed light on the controversy regarding ageing effects in Flanker task performance.

Introduction

Ageing is known to produce a progressive decline in multiple cognitive domains, resulting in impaired processing speed (Madden, 2001), a reduction of working memory capacity (Grady, 2000), impaired cognitive flexibility (Mayr, 2001) and an inability of top-down control processes to guard against the effects of distracting information (Kramer, Hahn & Gopher, 1999). Similarly, a number of studies report age-related changes in the ability to resist distractor interference (Mund, Bell & Buchner, 2012; Pettigrew & Martin, 2014). Reports of age-related inhibitory impairments, coupled with findings indicating that the prefrontal cortex is vulnerable to age-related cognitive decline, gave rise to theories such as the 'Frontal Hypothesis of Cognitive Ageing' (Dempster, 1992) and the 'Age-related Inhibitory Deficit Theory' (Lustig, Hasher & Zacks, 2007). Both theories posit that elderly individuals suffer from a general deficit in tasks measuring executive control as these rely on frontal areas of the cortex which are prone to decline with advancing age.

A further theory relating to ageing executive control states that inhibitory performance decrements are not abolished but merely delayed by normal ageing (Salthouse, 1996; Andres, Parmentier & Escera, 2006). Thus, shortcomings will be apparent if a timely response is elicited but will disappear if elderly individuals are given more time to engage attentional resources before responding. This idea was recently advocated by Gazzaley and colleagues (2008) who reported a direct link between neural processing speed and elderly individuals' ability to inhibit information at early processing stages. To further investigate this account, Wascher and colleagues (2012) recently paired an inhibitory suppression task with event-related potential (ERP) recordings of the N1pc and N2pc components, thus allowing them to explore distinct sub-processes of early stimulus processing, as well as

subsequent selection and control processes. The authors found evidence for both attentional slowing and increased early susceptibility to distracting information among elderly individuals, thus highlighting the wide-ranging changes advanced age produces in the domain of inhibitory control.

However, evidence from different inhibitory task paradigms demonstrates that age-related impairments are not selective to frontal areas of the cortex and indicate that inhibitory deficits in old age are not as general as originally assumed (Hsieh, Liang & Tsai, 2012). Whereas paradigms such as the Stroop (Kok, 1999) and the Simon task (Proctor, Pick, Vu & Anderson, 2005) consistently indicate elderly participants' enhanced susceptibility to distractors, research on the well-known Flanker task (Eriksen & Eriksen, 1974) has produced inconsistent results. As such, some studies indicate ageing deficits corresponding to those discovered in the Stroop and Simon task, namely that relative to young, elderly individuals show greater reaction time costs in interference compared to non-interference trials (Zeef & Kok, 1993; Zeef et al., 1996). However, a large body of research reports no age differences in Flanker interference (Nieuwenhuis et al., 2002; Wild-Wall, Falkenstein & Hohnsbein, 2008; Hsieh, Lang & Tsai, 2012).

The standard version of the Flanker paradigm was first introduced by Eriksen and Eriksen (1974) and consists of a five stimulus array: a central target stimulus (➔) requiring either a right or left hand response embedded within four flanking stimuli to either side. Task demands require an accurate and timely response to the central target while disregarding the flanking stimuli which can be congruent (➔➔➔➔➔) or incongruent (🡐🡐➔🡐🡐) to the central target. Common findings of this paradigm are increased reaction times (rt's) and error rates when comparing the incongruent to the congruent trials which, based on the nature of the task, are thought

to occur through motor interference (Coles et al., 1985; Eriksen & Eriksen, 1974). This interpretation has led to the hypothesis that ageing selectively affects different forms of inhibition, impairing performance on perceptual inhibition tasks such as the Simon and Stroop paradigm, while leaving Flanker performance which was thought to rely primarily on motor suppression largely unaffected (Kawai et al., 2012).

However, Hsieh and colleagues (2012) argue that the Flanker task contains aspects of both motor and perceptual interference. Investigating participants' performance patterns on a modified Flanker version distinguishing between both forms of interference, Van't Ent (2002) likewise concluded that both were inherent to the Flanker task.

Thus, discrepant age findings are unlikely to be the result of differing inhibitory demands among paradigms and have led to the hypothesis that elderly participants make use of a processing strategy which carries specific advantages for Flanker task performance (Hsieh & Fang, 2012). To this effect, Wild-Wall and colleagues (2008) suggested that elderly individuals place a strategic emphasis on performance accuracy which results in top-down enhanced processing of the central target and delayed information transmission from visual to motor areas of the cortex and manifests in increased reaction times to compensate for performance accuracy (Hoffmann & Falkenstein, 2011). Hsieh and colleagues (2012) tested age differences with Van't Ent's modified Flanker version and found no age differences in task performance. Thus, the authors likewise concluded that older adults maintained efficiency akin to that of young participants by employing enhanced top-down control strategies to compensate for deficiencies in task accuracy performance.

Attentional top-down control is a higher order cognitive performance largely carried out by frontal brain regions such as the dorso-lateral prefrontal cortex (dlPFC)

and the anterior cingulate cortex (ACC) (Wascher et al., 2012). In addition to age-related changes, frontal brain regions have also been highlighted as particularly vulnerable to the adverse effects of stress which are thought to occur through an increased number of micro lesions produced by heightened hypertonic strain (Rabbitt, 2005). Stress, especially in its chronic or cumulative form has also been shown to affect higher order cognitive processes such as working memory in old age. For example, recent longitudinal studies investigating the impact of experienced stress on cognitive ageing report that elderly individuals experiencing a greater amount of cumulative stressful incidents in the course of their lives display accelerated cognitive decline and perform worse on cognitive tasks (Pesonen et al., 2013). For example, Peavy and colleagues (2009) reported that higher amounts of cumulative stressful experiences over the course of three years resulted in decreased working memory performance among a sample of elderly individuals suffering from Mild Cognitive Impairment. Similar findings are reported by a number of cross-sectional studies which state that higher amounts of cumulative stressful events coincide with reduced working memory performance among elderly participants (Dickinson et al., 2011; Tschanz et al., 2013). Similarly, our own work presented in Chapter 3 established an inverse relationship between the amount of cumulative experienced stress and cognitive working memory performance among elderly individuals which was not present among young control participants (Marshall, Cooper, Segrave & Geeraert, 2015). Results advocating the adverse effects of stress on cognition among elderly but not young individuals, highlight the possibility of a cumulative impact of experienced stress which emerges late in life and causes cognitive impairments among the elderly. Memory has been the primary focus of studies investigating the effects of cumulative experienced stress on ageing, however, as impaired executive control has been found

to compromise memory performance (Hasher & Zacks, 1988), a reasonable extension to the field lies in investigating whether cumulative experienced stress impacts on related cognitive domains. As stress is also known to affect brain regions integral to the top-down compensatory mechanism elderly individuals are hypothesised to engage while completing the Flanker task, a further reasonable approach lies in investigating how this factor may affect compensatory Flanker performance.

The aforementioned work by Wascher and colleagues (2012) provides an edifying example of how investigations of electrophysiological recordings (in the form of oscillatory event-related activity or ERPs) can provide insight into underlying inhibitory mechanisms. As such, many studies interested in investigating underlying cognitive processing strategies have paired behavioural paradigms with electrophysiological recordings, indexing Event Related Potential (ERP) peak and latency or oscillatory activity in bandwidths associated with different processes conducive to successful cognitive performance. For example, in their investigation of Flanker age differences, Hsieh and colleagues (2012) surmised that no age differences occurred on the motor level as they had measured similar lateralised readiness potentials (an ERP component indexing motor planning) among both age groups. To gain insight into underlying processing strategies, a number of studies have paired the Flanker task with EEG recordings, many of which focus on the alpha bandwidth (8 - 12Hz). Oscillatory activity in the alpha band was traditionally associated with a lack of attention, however, more recent studies relate increased synchronous activity to functions such as working memory (Sauseng et al., 2009) and visual awareness (Romei et al., 2008a, 2008b) as well as inhibitory processes (Klimesch, Sauseng & Hanslmayr, 2007). In a recent review article, Fox and Snyder (2011) discussed a range of their own studies investigating functionality of alpha

band oscillations in light of an attention suppression mechanism. Reviewing studies on inter-sensory selective and feature-based attention over multiple sensory domains, the authors concluded that a central role of alpha oscillations relates to the attentional suppression of distracting stimulus features which have to be inhibited for successful task execution. Similarly, in their gating by inhibition theory, Jensen and Mazaheri (2010) implicate oscillatory alpha activity as one of the main mechanisms responsible for intact transmission of information between relevant neuronal assemblies by inhibiting task irrelevant brain regions. The inhibitory role of alpha has also been highlighted with respect to top-down sensorimotor control, in which alpha ERD is thought to indicate an activated brain region engaged in motor preparation, execution or imagery, whereas alpha ERS is thought to reflect a deactivated or inhibited cortical network. Alpha suppression of a task irrelevant region was illustrated by work undertaken by Neuper, Woertz and Pfurtscheller (2006), who demonstrated that mental imagery of foot movement led to an increase of the mu rhythm (alpha ERS expressed over the motor cortex) for the hand area. Similarly, Deiber and colleagues (2012) implicate alpha activity in higher-order motor control functions and conducted a study in which they convincingly demonstrated that motor preparation was accompanied by posterior alpha ERD (reflective of attentional engagement with respect to motor preparation) as well as mid parietal alpha ERS (indicative of inhibiting task irrelevant visual activity), thereby nicely demonstrating the interplay between the inhibitory and motoric roles attributed to the alpha band.

As such, alpha synchronisation observed during Flanker task performance has likewise been linked to task evoked inhibitory attentional and sensorimotor control processes (Hogan et al., 2013). For example, Compton and colleagues (2014) reported increased levels of alpha synchronisation over frontal and parietal as well as

motor regions following errors committed on a Flanker task, especially in motivational trials promising a monetary return. The authors therefore concluded that enhanced levels of alpha ERS reflected executive control processes, monitoring and constraining the motor response and perceptual interference from flanking stimuli. Similarly, Tang and colleagues (2013) found increased alpha ERS in widespread regions of the cortex in response to completing an inhibitory Stroop task. The authors likewise concluded that alpha band activity reflects a process of conflict control. Findings to this effect highlight that one possible compensatory mechanism engaged in by elderly individuals to keep up Flanker task performance might lie in devoting more cognitive resources towards inhibiting conflicting stimulus information, thus demonstrating higher levels of alpha ERS during incongruent Flanker task conditions in which misleading stimulus information needs to be supressed.

The present study aimed to investigate whether the adverse impact of cumulative experienced stress extended to elderlies' inhibitory performance both on a behavioural and electrophysiological level. In doing so, we are simultaneously pursuing our electrophysiological findings presented in Chapter 3 (experiment 4). Results of experiment 4 demonstrated that elderly high stress participants manifested reduced levels of alpha ERS during the maintenance period of a Sternberg WM task. These findings indicate that high levels of cumulative stress can modulate the alpha bandwidth and implicate impaired executive capabilities as a possible cause of WM impairments experienced by elderly (high stress) participants.

A further concern addressed by this study was to shed light on the controversy regarding age differences in the Flanker task, exploring whether cumulative experienced stress impacts on the proposed top-down compensatory processes engaged in by elderly individuals. We hypothesised that elderly high stress

participants would display reduced behavioural performance as indicated by higher error rates or reaction times in incongruent compared to congruent Flanker conditions when compared to young and elderly low stress counterparts. Furthermore, we hypothesised that elderly high stress participants would display reduced levels of alpha synchronisation relative to young and low stress elderly participants, indicating an impairment of inhibitory control strategies. On the other hand, elderly low stress participants were expected to manifest increased levels of alpha ERS, indicating compensatory efforts to keep up with young participants' task performance.

Experiment 5

Materials and Method

Participant selection.

The study consisted of 30 young (Mean age = 21.3, SD = 3.4; Range 18 - 30 years; 13 males) and 30 elderly (Mean age = 68.73, SD = 6.4; Range 60 – 82; 16 males) participants. Young participants were recruited from the University of Essex student population via e-mail advertising. Elderly volunteers were recruited via an advertisement in the local branch of the University of the 3rd Age newsletter. All participants were right-handed and healthy. Participants were screened for major medical conditions (e.g. diabetes, heart disease), major neurological damage (e.g. stroke), current diagnosis of a mental or psychiatric disorder (e.g. dementia, depression, anxiety disorder), use of psychoactive medication and a history of substance abuse. To further ensure against the presence of undiagnosed cognitive pathologies, all elderly participants completed the Mini Mental State Examination (Folstein, Folstein & McHugh, 1975), in which all scored full marks. Participants

provided written informed consent. The study was approved by the University of Essex Ethics Committee.

Preceding analysis, both age groups were split into high and low experienced stress groups based on the median split of scores from the Social Readjustment Rating scale for elderly (Median Split value 697) and the Student Life Events Scale for young (Median Split Value 606). Using independent-samples t-tests and the chi-square test for contingency tables for the nominal gender variable, no significant stress group differences emerged when comparing Mini Mental State performance, State/Trait anxiety scores, age, gender, educational attainment, cigarette/alcohol consumption or amounts of exercise ($p_s > .05$).

Stress and demographical measures.

This study focussed on the detrimental effect cumulative lifetime stress exerts on cognitive performance. Given that our elderly participants have on average three times the age of younger participants, they are likely to have experienced more and different stressful events. Thus, in order to assess prolonged stress exposure appropriate to each age group and make the argument that the long-term effects of cumulative stress exposure are responsible for behavioural shortcomings (not purely high amounts of immediate stress), different instruments were chosen for elderly and young participants. The amount of experienced stress was therefore assessed by the Social Readjustment Rating Scale (Holmes & Rahe, 1967) for elderly and the Student Life Events Scale (Clements & Turpin, 1996) for young participants. Both scales use a similar format to assess stressful experiences, consisting of a brief, self-administered scale (43 and 36 items respectively). Both scales contain incidents ranging from extremely stressful (i.e. 'Death of Spouse/Parent') to mildly stressful (i.e. 'Finding a part-time job'). Scores can range from 0 - 1466 for the Social

Readjustment Rating Scale and 0 - 1849 for the Student Life Events Scale. Higher scores reflect high amounts of experienced stress for both scales. In order to ensure values measured from different scales contributed equally to the analysis, the scores for each participant were standardised within age groups. The possible impact of stress tolerance and non-pathological levels of anxiety were assessed by the State-Trait-Anxiety Inventory (STAI) developed by Spielberger (1968). The STAI is comprised of two 20-item questionnaires, designed to assess respondents' general levels of trait anxiety and momentary levels of state anxiety. Items include statements such as 'I feel calm' or 'I feel nervous' which respondents are asked to answer both according to their current levels of anxiety as well as dependent on how they generally feel.

Further control measures included participants' gender, age, educational level, cigarette and alcohol intake, amount of physical exercise and whether participants suffered from a disability whose discomfort may impair performance on the task (units of measurement displayed in Table 4.1.).

Procedure and stimuli.

Before completing the Flanker task, each participant took part in an EEG eye-movement calibration session (Croft & Barry, 1998) which was followed by an eyes closed/resting EEG interval lasting two minutes.

Participants moved on to complete a modified version of the Eriksen Flanker task (Eriksen & Eriksen, 1974) programmed using Neuroscan Stim2 (Compumedics, Melbourne) software. Stimuli were developed after a template introduced by Fan and colleagues (2002; 2004) and consisted of five arrows embedded within the images of fish (see Figure 4.1.), displayed on a computer screen for congruent and incongruent conditions. Target and flanking stimuli were presented on screen simultaneously.

Table 4.1. Demographical information of elderly and young participants split by experienced stress group.

	Elderly		Young	
	Low Stress	High Stress	Low Stress	High Stress
Group Size	15	15	15	15
Age	67.8 (6.3)	68.6 (5.4)	21.9 (4.1)	20.7 (2.5)
Gender	8 ♂	8 ♂	6 ♂	7 ♂
Education	3.4	3.5	4.1	4.27
Cigarette Consumption	0	0	0	0.2 (0.6)
Alcohol Consumption	1.53 (1.5)	2.2 (1.7)	1.3 (1.7)	0.9 (1.0)
Presence of Physical Disability	2	3	0	1
Exercise	2.73 (1.1)	2.67 (1.1)	2.1 (1.0)	2.7 (1.0)
Mini Mental State Score	30	30	n.a.	n.a.
Trait Anxiety Score	35.53	35.8	39.87	37.87
State Anxiety Score	29.47	26.73	32.53	30.8
Experienced Stress Score	461.3*(142.7)	864.5* (94.5)	389.67*(112.5)	736.5* (109.0)

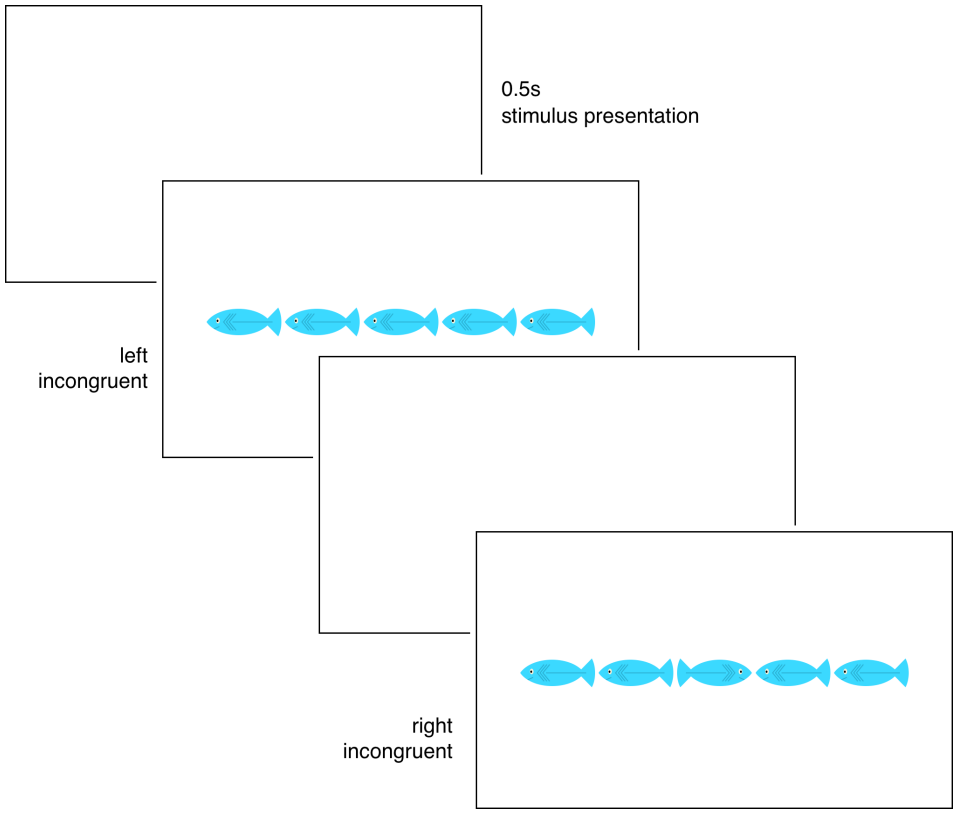
Note. Education ranging from 1 (lower than High School) – 6 (University PhD degree); Cigarette Consumption: cigarettes per day; Alcohol Consumption: units per week; Exercise: hours per week; *$p<.05$ represents significant stress group differences within age groups.

Stimuli were presented in blue against a white background on a 19inch computer monitor (refresh rate 100Hz). Participants were seated directly in front of the computer monitor (approximately 0.65m) and were asked to respond as quickly and as accurately as possible to the direction of the central target arrow by pressing

the corresponding response button (buttons on a response pad for left and right hand respectively).

Trials began with a blank screen presented for 500ms, after which the stimulus array appeared for a further 500ms (see Figure 4.1.). Stimulus congruency and direction were balanced equally across trials and varied pseudo-randomly between participants. Following a short block of practice trials, participants completed 2 blocks of 160 trials for a total of 320 trials. Participants were given the opportunity of a break between blocks.

Figure 4.1. Schematic representation of the Flanker task set-up.



Note. Participants were required to respond to the central target arrow while ignoring either congruent or incongruent flanking arrows to either side.

Electrophysiological recording and data preparation.

Electroencephalography (EEG) was recorded from 64 electrodes placed within a soft-cap according to the 10 - 20 method of electrode positioning. Recordings were referenced to a point midway between Cz and CPz. Impedances were lowered to below 10kΩ in all electrodes before acquisition. EEG signals were recorded and subsequently analysed using a Neuroscan Synamps2 system in conjunction with SCAN 4.5 software (Compumedics, Melbourne, Australia). Data was collected at a sampling rate of 1000Hz with a band-pass filter of 0.05 - 200Hz.

Data was visually inspected and noisy data blocks, general artefacts and bad electrodes were rejected. Principal components analysis was carried out on the eye-movement calibration data to obtain components reflecting saccades and blinks. These acquired components were subsequently rejected from the task data traces (Vigário, 1997; Vigário et al., 2000).

All data was re-referenced to a common average reference. In order to investigate the topography of possible age- and stress-related group differences, the 64 electrodes were averaged into nine brain regions: left (FP1, AF3, F7, F5, F3, F1, FT7, FC5, FC3, FC1), mid (FPz, Fz, FCz) and right (FP2, AF4, F8, F6, F4, F2, FT8, FC6, FC4, FC2) frontal; left (T7, C5, C3, C1, TP7, CP5, CP3, CP1), mid (Cz, CPz) and right (T8, C6, C4, C2, TP8, CP6, CP4, CP2) central; left (P7, P5, P3, P1, PO7, PO5, PO3, CB1, O1), mid (Pz, POz, Oz) and right (P8, P6, P4, P2, PO8, PO6, PO4, CB2, O2) posterior.

To calculate event-related synchronisation and desynchronisation (ERS/D), data segments for periods of Flanker monitoring were cut into 2000ms epochs (ranging from -1000 to 1000ms after stimulus onset). The first and last 500ms of the trials were trimmed to avoid filter warm-up artefacts, leaving a 500ms test (plus

500ms baseline reference before onset of the stimulus) interval for analysis. Only correct trials were used for electrophysiological analysis.

Using the Event-related-band-power transformation (SCAN 4.5 editing software), data underwent complex demodulation and concurrent filtering (zero phase-shift, 24dB roll-off, envelope computed) into the alpha (8 - 12Hz) bandwidth. Event-related activity was calculated as a percentage change between the active period and the reference period according to the following formula: [((reference – test)/reference)x100]. According to this method, developed by Pfurtscheller and Lopes da Silva (1999), positive values represent desynchronisation of the alpha frequency band, whereas synchronisation is indexed by negative values.

Results

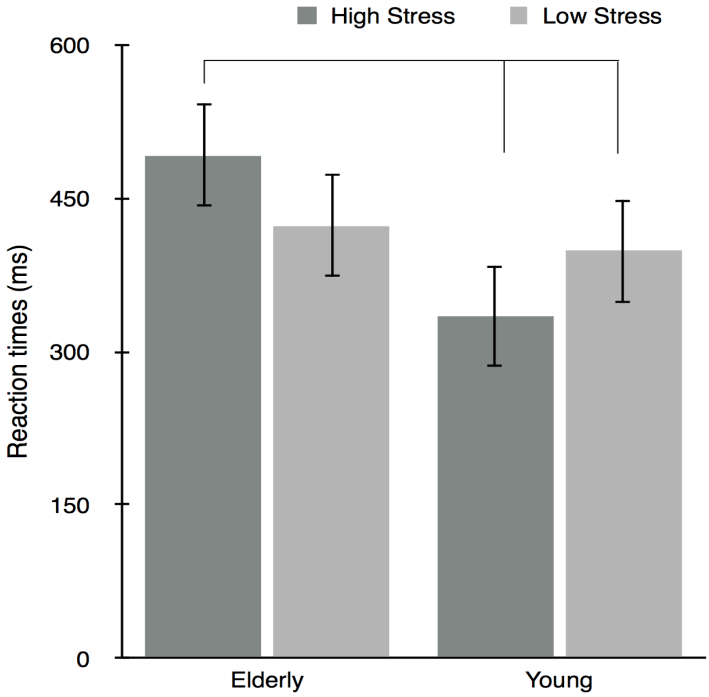
Behavioural results.

Error rates as well as reaction times were analysed by means of a 2 (Age: elderly vs. young) x 2 (Stress: high vs. low) x 2 (Congruency: incongruent vs. congruent) mixed measures ANOVA in which congruency acted as the within-subjects factor.

Analysis of error rates revealed a main effect of congruency ($F_{1\,56} = 4.18$, $p = .046$) which indicated that incongruent Flanker arrays elicited more errors than congruent ones. No further main effects or interactions reached significance ($p_s > .05$). Looking at reaction times next, a main effect of congruency emerged ($F_{1,56} = 7.16$, $p = .01$) indicating that participants took significantly longer to correctly respond to the target in incongruent (*M* = 437.2, *SD = 95.67)* compared to congruent (*M* = 396.7, *SD* = 93.39) trials. Results further revealed a main effect of age ($F_{1,56} = 9.21$, $p = .01$), indicating that elderly individuals took longer to respond (*M* = 457.7, *SD* = 70.18) than young (*M* = 387.3, *SD* = 85.7*)* participants. No further main effects

reached significance (all $p_s > .05$). However, the main effect of age was qualified by a significant age x experienced stress interaction ($F_{2,187} = 12.72$, $p = .001$).

Figure 4.2. Reaction time scores for both age and stress groups.



Note. Results indicate significantly longer reaction times of high stress elderly group members relative to young low and high stress participants. Error bars reflect SEM.

To decompose the interaction, differences between stress and age groups were compared by means of simple effects contrasts. In order to ensure against Type I error as a result of multiple comparisons, follow-up tests were Bonferroni corrected (adjusted p-value .008). These comparisons revealed a significant age difference among high stress group elderly and young participants ($F_{1,56} = 36.02$, $p < .001$) and between high stress elderly and low stress young individuals ($F_{1,56} = 38.71$, $p < .001$) indicating that elderly high stress participants ($M = 492.2$, $SD = 73.1$) took significantly longer to respond to both congruent and incongruent target stimuli when

compared to both young high (*M* = 334.5, *SD* = 50.6) and low stress counterparts (*M* = 398.0, *SD* = 64.15) (see Figure 4.2.). No further comparison points reached significance (all $p_s > .008$).

Electrophysiological results.

Electrophysiological data was analysed by means of a 2 (Age) x 2 (Stress) x 2 (Congruency) x 3 (Laterality: left vs. mid vs. right scalp regions) x 3 (Sagitality: frontal vs. central vs. posterior scalp regions) mixed measures ANOVA with repeated measures on the latter three factors.

Analysis found a main effect for congruency ($F_{1,56} = 4.37$, $p = .024$), indicating higher levels of alpha synchronisation in the incongruent relative to the congruent trials. Results further revealed an interaction of age x stress x laterality x sagitality ($F_{4,184} = 3.46$, $p = .037$). This interaction was decomposed by running two separate age x laterality x sagitality ANOVAs for high and low stress groups. For the low stress group, the model did not reach significance ($F_{4,88} = 1.3$, $p = .28$). The model for the high stress group showed a significant three-way interaction ($F_{4,88} = 3.26$, $p = .015$). To decompose this, simple effects comparisons were carried out comparing elderly and young high stress group participants across each of the nine brain regions (Bonferroni adjusted p-value .005). Results found a significant difference in alpha activity over the left central ($F_{1,24} = 8.77$, $p = .003$) and right posterior ($F_{1,24} = 7.65$, $p = .004$) scalp area (see Figure 4.3.), both indicating that whereas young high stress participants manifested synchronous alpha activity during responding, elderly high stress participants showed levels of event-related-desynchronisation to both congruent and incongruent flanker arrays. No significant differences were observed between elderly and young low stress individuals for either the left central ($F_{1,24} = 1.02$, $p=.149$) or right posterior ($F_{1,24} = 1.3$, $p =.081$) brain

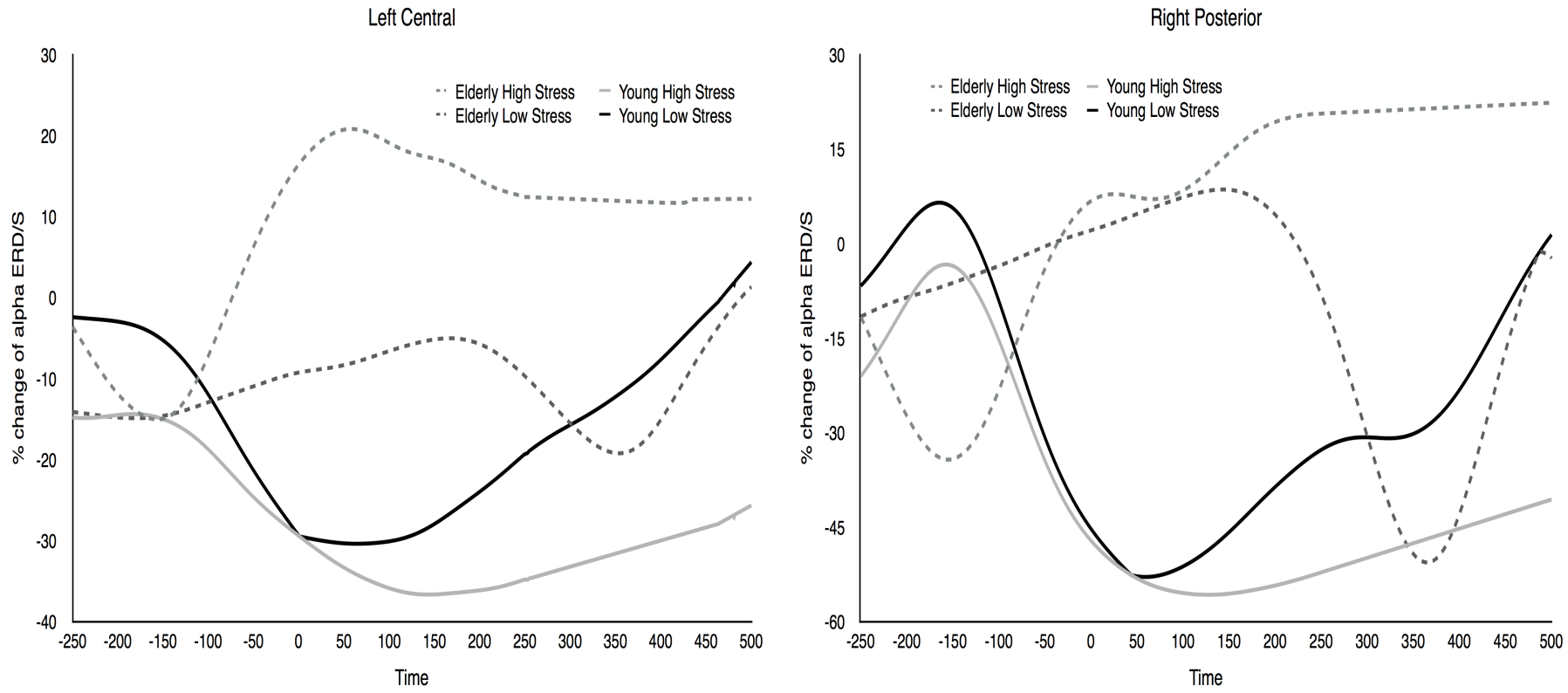
region, between high and low stress young for the left central ($F_{1,24} < 1$) and right posterior region ($F_{1,24} = 1.01$, $p = .138$) or between high and low stress elderly for the left central ($F_{1,24} = 2.07$, $p = .075$) or right posterior ($F_{1,24} = 1.89$, $p = .089$) region. In addition no significant differences emerged across any other scalp regions (all p's > .005) (see Figure 4.4. for a distribution of topographical effects)[7].

EEG and behavioural correlations.

Correlating behavioural performance (rt's) with alpha activity over the entire participant sample found a significant negative correlation between the level of alpha synchronisation and reaction times for the left central ($r = 0.32$, $p = .039$) and right posterior cortex ($r = 0.28$, $p = .042$), indicating that higher levels of alpha synchronisation corresponded to shorter rt's. This correlation was found to be stronger within the elderly participant sample: performing the correlation for both the young and elderly participants revealed non-significant results for young over both the left central ($r = 0.27$, $p = .054$) and the right posterior cortex ($r = 0.23$, $p = .072$) while demonstrating significant results among elderly participants for both the left central ($r= 0.37$, $p = .029$) and right posterior ($r= 0.36$, $p = .033$) cortical region.

[7] To investigate whether alpha findings are more applicable to the attentional or sensorimotor inhibitory domain, we re-ran the above ANOVA for both the lower and upper beta frequency range. This bandwidth has been explicitly linked to motor processes (Pfurtscheller et al., 2003). Should our findings be more applicable to the motor domain we would therefore expect to find corresponding age and stress effects in this frequency range. For the lower beta frequency, analysis revealed a sagitality x age interaction ($F_{2, 102} = 9.45$, $p < .001$) which found that elderly participants manifested higher levels of lower beta ERD over the central motor region. Results of the upper beta range similarly revealed a sagitality x age interaction ($F_{2, 102} = 5.04$, $p = .029$) for which, relative to young, elderly participants likewise displayed higher levels of upper beta ERD over frontal scalp sites. No further main effects or interactions reached significance (all $p_s > .05$).

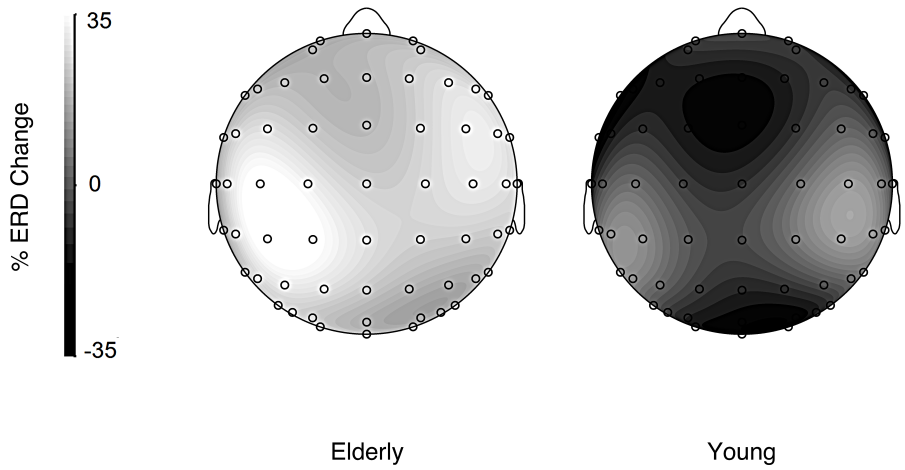
Figure 4.3. Grand average waveforms of the alpha frequency range computed for both stress and age groups over the left central and right posterior cortex.



Note. Elderly high stress participants show heightened levels of alpha ERD, which produces a significant difference relative to young high stress counterparts.

Results therefore highlight an association between the reduced ERS displayed by elderly high stress participants and their reduced performance on the Flanker task. It must be noted however that differences between correlation coefficients for elderly and young participant groups did not reach significance for either the left central ($z = 0.12$, $p = .91$) or the right posterior ($z = 0.15$, $p = .88$) region.

Figure 4.4. Topographical distribution of alpha activity for young and elderly individuals in the high experienced stress group.



Note. Elderly high stress participants show globally enhanced levels of alpha ERD (significant compared to young high stress individuals for left central and right posterior scalp regions). On the scale, negative values indicate alpha ERS while positive (lighter) values signify ERD.

Discussion

This study explored the impact of experienced stress on elderly participants' cognitive performance in domains related to memory. By choosing the Flanker task to measure inhibitory control, the study hoped to shed further light on the discrepant age-related performance differences reported in past papers using this paradigm. Behavioural findings indicated a general reaction time deficit among high stress

elderly relative to young high and low stress participants which extended to both congruent and incongruent stimulus arrays. These behavioural shortcomings were found to correlate with heightened levels of event-related-desynchronisation in the alpha frequency range manifested by high stress elderly participants over left central and right posterior regions of the cortex.

Behavioural findings.

Results discovered no age differences modulated by interference between young and elderly participants with low amounts of experienced stressful events. This finding is in line with previous work comparing elderly and young on the Flanker paradigm and reporting no increased interference effects for elderly individuals (Wild-Wall et al., 2008; Hsieh et al., 2011). However, both the aforementioned studies did report a general age-related slowing of response speed which is a common occurrence across multiple executive reaction time paradigms (Bashore et al., 2014) and which likewise manifested in our data set. Interestingly, this general age-related slowing was magnified when comparing elderly and young participants in the high experienced stress group. Findings to this effect indicate that Flanker task performance may vary between elderly participants and provide a possible explanation for the discrepant findings in the literature (Zeef & Kok, 1993; Hsieh et al., 2012). This highlights the importance of considering factors which may exacerbate ageing decline and provides evidence that the impact of experienced stress on ageing is not exclusive to memory, as evidenced by a number of past studies (Peavy et al., 2009; Dickinson et al., 2011), but extends to performance on executive control paradigms.

However, with respect to inhibitory control, elderly high stress participants' behavioural shortcomings diverge from those reported in previous papers, as no age

differences regarding the increase from congruent to incongruent conditions emerged, but a general deficit extending to both kinds of stimulus arrays. Past studies finding significant age differences reported that these manifested by elderly individuals displaying longer reaction times in the incongruent compared to the congruent condition, a difference which was less pronounced among young participants (Zeef & Kok, 1993; Zeef et al., 1996).

Two possible scenarios can account for this study's divergent behavioural findings. One interpretation given the observed behavioural data pattern is that rather than promoting inhibitory deficits among elderly participants, cumulative stress relates to increased sensorimotor decline, exacerbating the general age-related slowing normally found when comparing elderly to young individuals (Bashore et al., 2014). In line with this idea, a number of studies report that a breakdown of inhibitory performance is reflected in reduced accuracy rates rather than increased reaction times (Penades et al., 2007; Hutton & Ettinger, 2006), a difference which did not manifest for our data set. A second possibility is that cumulative stress does relate to impaired executive control, exacerbating general age-related slowing by adding an inhibitory deficit of irrelevant information processing. In this scenario, the performance pattern reported in this study may be the result of our Flanker task design. Similar to designs by Carrasco and colleagues (2013) and Hsieh, Liang & Tsai (2012), flanker and target stimuli in the current study appeared on screen simultaneously. As flanking stimuli did not precede the target stimulus, they did not guide attention in an either advantageous or misleading way. Therefore, they acted purely as distractors from the central target and since their appearance could not be used to obtain information ahead of target presentation, the best strategy may lie in screening out the flanking stimuli completely to focus accurately on responding to the

target. Behavioural deficits of elderly high stress participants may therefore be explained as an overall inability to shield against the flanking stimuli drawing attention away from the central target and may thus produce the observed increase in reaction times.

Electrophysiological findings.

Results revealed that elderly high stress individuals showed levels of alpha event-related desynchronisation (ERD). Inspection of group average waveforms revealed that elderly high stress participants were the only group to manifest desynchronisation, as both young and low stress elderly participant groups displayed enhanced levels of synchronous alpha activity during encounter of the flanker array. Increased levels of alpha synchronisation have been linked to both sensorimotor and attentional inhibitory control. With respect to sensorimotor involvement, alpha ERS is thought to indicate an inhibited or deactivated motor region, while ERD is thought to reflect an active brain region engaged in motor execution (Neuper, Woertz & Pfurtscheller, 2006; Deiber et al., 2012). In terms of attentional control, alpha ERS is linked to the successful inhibition of brain regions not necessary for stimulus processing or maintenance (Cooper et al., 2003; Klimesch, 2012), thereby facilitating the reduction of potentially distracting information (Sauseng et al., 2009). In line with these accounts, a number of Flanker studies report heightened levels of alpha synchronisation (Hogan et al., 2013; Compton et al., 2014). Similar to the behavioural findings, electrophysiological results can therefore be explained in two possible ways. Corresponding to the idea that cumulative stress relates to a sensorimotor deficit, the high levels of alpha ERD displayed by high stress elderly participants may highlight an over-activation of the motor system (which is successfully inhibited by ERS displayed by young and elderly low stress counterparts). This may lead to the

observed increase in reaction times due to response inhibition from conflicting non-motor (right posterior) and motor (left central) regions which should have been suppressed for optimal task performance. However, should our alpha findings be restricted to motor control and execution, we would have expected to find a corresponding pattern in the beta frequency range (12 - 30 Hz) (see footnote 1). Finding no age or stress effects in the beta range, which has been explicitly linked to planning and execution of movement (Pfurtscheller et al., 2003), detracts from this interpretation.

Conversely, if cumulative stress produces impairments regarding attentional inhibition, the increased levels of alpha ERS displayed by low stress elderly and young participants can be argued to reflect the successful inhibition of flanking distractors, an assumption which is further strengthened by the main effect of congruency, indicating higher alpha synchronisation towards the more distracting, incongruent stimuli. Coupled with the increased reaction times manifested by high stress elderly participants, their ERD may therefore indicate a breakdown of inhibitory control processes, thus leaving them more vulnerable to the distracting influence of the flanking stimuli. This interpretation corresponds to past work (Wascher et al., 2012; Gazzaley et al., 2008) which reports that elderly individuals do not suffer from impaired sensory/perceptual processing but suffer from an impaired as well as delayed top-down control mechanism responsible for reallocating attention in the face of distracting information. Current findings therefore extend results presented in experiment 4 of this thesis which likewise indicated that high levels of cumulative lifetime stress exert a negative influence on elderly individuals' executive cognitive control functions. Both experiments' results show that these shortcomings

manifest in the electrophysiological domain by elderly high stress participants demonstrating reduced levels of alpha ERS during task completion.

Conclusions and limitations.

This study provides a possible explanation for previous discrepant findings concerning age-related Flanker task differences, highlighting that performance may not homogenously decrease among elderly individuals but may relate to individual rates of cognitive decline as a result of multiple impacting factors. Thus, findings provide further evidence for the detrimental effect of cumulative stress on cognitive ageing, highlighting that impairments as a result of increased stress exposure are not exclusive to memory but extend to other cognitive domains. However, a number of questions still remain.

In terms of study design, we chose not to vary the inter-stimulus interval between the blank screen and onset of the flanker display. We adopted this approach after designs by Hsieh and colleagues (2012) as well as Wild-Wall and colleagues (2008) to make our findings compatible with their earlier reports. However, this may have resulted in anticipatory preparation processes which could have affected our electrophysiological results. Furthermore, we used two different measures to assess cumulative experienced stress among elderly and young participants which impacts on direct comparisons between both scales. For this reason, we refrained from comparing any main effects of experienced stress scores and focussed instead on the interactive relationship between age and experienced stress. We would further argue that even if the same scale had been used for both age groups, it would nevertheless not be pertinent to compare this main effect, as relative to young, elderly participants would necessarily obtain a higher stress score and might construe the scale differently based on their viewpoint (looking back after having lived most of their lives vs.

young individuals having most of their time still ahead). For this reason, we chose to use two different scales which were more appropriate for our different age groups. To ensure differences resulting from different scales were kept to a minimum, we further standardised cumulative stress scores within age groups.

With respect to our data pattern, our behavioural as well as our electrophysiological data can be explained with two different interpretations. As such, we are at this moment unable to conclude whether the adverse effect of cumulative stress extends to inhibitory shortcomings in the sensorimotor or attentional domain. While our behavioural data points to a sensorimotor impairment, finding no age and stress effects in the beta frequency range make our EEG results more compatible with an attentional interpretation. Further research should therefore extend this line of enquiry to determine which inhibitory domain is negatively affected by prolonged cumulative stress exposure. Past research has hypothesised that non-existent age-related performance differences may be the result of top-down compensatory control strategies engaged in by elderly individuals (Wild-Wall et al., 2008; Hsieh et al., 2012). These specify that elderly individuals may place greater emphasis on accuracy, maintaining error rates akin to those of young individuals at the cost of higher reaction times (Hoffmann & Falkenstein, 2011). In line with this speed-accuracy trade-off, we discovered a general slowing of reaction times among elderly individuals without any age differences concerning error rates. As increased reaction times were magnified among our high stress elderly participants, one could hypothesise that these individuals are engaging in compensatory mechanisms to a higher extent, possibly as a result of stress induced depletion of cortical processing resources. However, should this be the case, we would expect elderly high stress participants to display higher amounts of alpha ERS (signifying increased top-down

inhibitory control) and not the pronounced levels of alpha desynchronisation we observed. Therefore, rather than a compensatory strategy, the present results indicate an adverse change among low performing high stress elderly participants which can be interpreted as a breakdown of inhibitory functioning in the attentional or sensorimotor domain.

Interestingly, our topographical findings did not emerge over frontal scalp sites relating to cortical regions (dlPFC; ACC) which are integral to executive top-down control as well as vulnerable to the effects of cumulative stress and ageing. Instead, our group differences emerged for the left central and right posterior scalp regions. While the left central area relates to movement control over the motor cortex, the right posterior area is engaged in visual attentional domains, thus in light of both the sensorimotor as well as the attentional inhibition explanation, the increased alpha ERD displayed by high stress elderly individuals may signify an inability to shut-down brain regions either irrelevant or actively opposed to the screening of irrelevant information or execution of correct motor actions. What must be noted with respect to our topographical maps is that, compared to high stress young, elderly high stress participants display a widespread increase of alpha ERD which only reaches significance for the aforementioned two scalp regions. As such, elderly high stress individuals seem to have a global difficulty in constraining brain regions unconducive to task performance.

A final point of discussion concerns the relationship between cumulative stress and elderly high stress individuals' task performance. As our work assesses a longitudinal phenomenon, we are unable to manipulate this variable and therefore cannot make concrete claims about the direction of our proposed relationship (i.e. do higher levels of stress accelerate cognitive decline or do individuals with reduced

cognitive resources experience higher levels of stress due to impaired coping abilities). However, in-vitro cell work demonstrates that cumulative experienced stress causes direct damage to brain regions integral to cognitive performance (Sapolsky & Meaney, 1986; Rabbitt, 2005). Furthermore, longitudinal work undertaken by Pesonen and colleagues (2013) demonstrates that individuals reporting high levels of experienced stress show cognitive impairments in later life while no performance differences were apparent between these individuals during adolescence. Both lines of work advocate the interpretation that stress accelerates cognitive shortcomings in old age.

In conclusion, this study sheds light on multiple issues regarding cognitive ageing. Behavioural as well as electrophysiological results indicate that experienced stress is not only harmful to elderly participants' memory performance but extends to executive control processes in the form of inhibition. To the best of our knowledge, this paper is the first to widen the current literature regarding cumulative experienced stress and cognitive ageing in this manner. Furthermore, results provide a possible explanation for the discrepant age findings regarding Flanker task performance. Results therefore contribute to a deeper understanding of ageing cognitive processes and the factors or circumstances that may impact on them.

Chapter 5: Cumulative Stress and Aged Spatial Performance

The Impact of Experienced Stress on Aged Spatial Discrimination: Cortical Overreliance as a Result of Hippocampal Impairment

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Published

Hippocampus

Abstract

A large body of neuroscientific work indicates that exposure to experienced stress causes damage to both cortical and hippocampal cells and results in impairments to cognitive abilities associated with these structures. Similarly, work within the domain of cognitive ageing demonstrates that elderly participants who report experiencing greater amounts of stress show reduced levels of cognitive functioning. The present paper attempts to combine both findings by collecting data from elderly and young participants who completed a spatial discrimination paradigm developed by Reagh and colleagues (Reagh et al., 2013) to measure hippocampal-mediated cognitive processes. In order to investigate the effect of stress on the cortex and, indirectly, the hippocampus, it paired the paradigm with electroencephalographic (EEG) recordings of the theta frequency band, which is thought to reflect cortical/hippocampal interactions. Findings revealed that elderly participants with high levels of experienced stress performed significantly worse on target recognition and lure discrimination and demonstrated heightened levels of cortical theta synchronisation compared to young and elderly low stress counterparts. Results therefore provide further evidence for the adverse effect of experienced stress on cognitive ageing and indicate that impaired behavioural performance among high stress elderly may coincide with an over-reliance on cortical cognitive processing strategies as a result of early damage to the hippocampus.

Introduction

A substantial amount of research has indicated that the brain not only co-ordinates bodily responses to stress but also suffers from prolonged activation of physiological stress response systems such as the hypothalamic pituitary adrenal axis (HPA) and the sympathetic nervous system. Higher amounts of stress hormones such as adrenaline have been found to cause increased hypertonic strain on arteries and veins, which results in damage to the neocortex by producing an increased number of micro lesions (Rabbitt, 2005). Furthermore, past research has highlighted the hippocampus as particularly vulnerable to increased levels of glucocorticoid stress hormones (McEwen & Sapolsky, 1995). Responsible for the formation of declarative, episodic and spatial memories, the hippocampus contains a vast number of glucocorticoid receptors, whose short-term elevation facilitates the formation of strong, emotional memories. However, long-term exposure has been found to result in dendritic atrophy and an inhibition of neurogenesis, both of which have been attributed to glucocorticoids causing a prolonged reduction of glucose re-uptake into hippocampal cells (Sapolsky & Meaney, 1986).

A number of animal studies have since linked hippocampal damage sustained through prolonged glucocorticoid elevation (as a result of experienced stress exposure) to impaired cognitive functioning (Lupien & McEwen, 1997; McEwen & Sapolsky, 1995). For instance, investigating the impact of chronic psychosocial stress among male tree shrews over the course of 23 weeks, Ohl and colleagues (2000) discovered hippocampus-mediated spatial and episodic memory processes to be consistently impaired among the stressed rodent sample. They later found that these animals exhibited pronounced hippocampal atrophy compared to non-stressed controls. Similarly, Shao and colleagues (2015) reported that rats

subjected to high levels of stress through isolation rearing manifested pronounced oxidative damage in areas of the hippocampus and the prefrontal cortex.

Cognitive impairments as a result of long-term stress exposure have more recently been established among human elderly population samples. A number of longitudinal studies which focus on experienced life events as an index of stress have reported that elderly individuals experiencing higher amounts of cumulative stress suffer accelerated cognitive decline in old age (Peavy et al., 2009; Aggarwal et al., 2014). For example, Pesonen and colleagues (2013) reported that individuals separated from their parents during the Second World War showed accelerated cognitive decline at age 70 when compared to an age-matched control group, whereas no cognitive impairments were observed between groups at age 20. Findings to this effect suggest the possibility of a cumulative impact of stress, which emerges in later life, and results in accelerated cognitive decline among elderly individuals who have experienced high amounts of stress in the course of their life. This theory is further supported by a number of cross-sectional studies investigating the relationship between cumulative experienced stress and ageing. These studies likewise find that an increase in experienced stress reported by elderly individuals throughout their lifetime coincides with reduced cognitive performance when holding age and levels of education constant (Dickinson et al., 2011; Tschanz et al., 2013). For example, our own recent work in this respect demonstrated that elderly individuals who experienced high amounts of cumulative stress in the course of their lives performed significantly worse on two working memory tasks, whereas elderly individuals reporting low amounts of cumulative experienced stress showed no decline in performance (Marshall et al., 2015).

Given the great importance of discovering risk factors for accelerated cognitive decline faced with an ageing demographic, the above studies provide robust and highly important behavioural findings, indicating that cumulative experienced stress should be considered as a risk factor for cognitive ageing. However, based on the evidence that experienced stress can damage certain brain regions (Rabbitt, 2005; Sapolsky & Meaney, 1986), there is a shortage of work linking both domains to investigate how cumulative experienced stress has impacted on elderly individuals' brain structures. It is therefore imperative to devise strong behavioural paradigms which rely on the integrity of brain structures past research has identified as vulnerable to long-term stress exposure. Combining these paradigms with neuroscientific tools forms the next step towards gaining a deeper understanding of how stress may impact on the ageing brain.

One such paradigm was recently developed by Reagh and colleagues (2013). Aiming to investigate age-related changes in the ability to discriminate object locations, the authors devised a novel spatial task whose demands are thought to rely heavily on intact hippocampal performance (Yassa & Stark, 2011). To test their paradigm, the authors asked young and elderly participants to view a sequence of objects which were randomly presented on a computer monitor within a 5 x 7 grid invisible to participants. After a short retention period, participants viewed repeated object-location pairings, vertical or horizontal displacements of the objects by 1-, 2-, 3- or 4-grid spaces or maximal corner to opposite corner displacements. After each presentation, participants were asked to decide whether the object had remained in the same location or whether it had moved. The authors' design meant that task completion relied primarily on pattern separation; the process of distinguishing among similar inputs during recall of previously encoded material by using non-

overlapping representations. This process has been shown to take place in the hippocampal dentate gyrus and CA3 region (Marrone et al., 2014; McTighe et al., 2009; Bakker, Kirwan, Miller & Stark, 2008). Reagh and colleagues further subdivided their aged participants into individuals whose performance on the Rey Auditory Verbal Learning Test (RAVLT) was either impaired or unimpaired and proceeded to demonstrate that elderly individuals with performance deficits on the RAVLT likewise performed significantly below the young and the elderly RAVLT unimpaired participants on their spatial paradigm. The RAVLT is widely accepted as a test of declarative memory and is thought to be highly sensitive to hippocampal damage. Based on their findings, the authors concluded that, despite the limitation of not combining their behavioural results with neuropsychological data, their paradigm was able to capture hippocampal processes and showed promise for distinguishing early forms of hippocampal impairment among the elderly.

Cortico-hippocampal interactions have long been assumed to facilitate the retrieval and storage of previously encoded material (Young & McNaughton, 2009). Past studies investigating this relationship have placed particular focus on the medial prefrontal cortex, which receives both monosynaptic excitatory and plastic input connections from the hippocampus and the medial temporal lobes connecting to the entorhinal cortex which is thought to form the main informational bridge between hippocampus and cortex (Battaglia et al., 2011). However, electrophysiological studies have indicated that hippocampal cortical connections extend to far wider areas of the neocortex, with neurons many synapses removed from the hippocampus in sensory and associative areas of the cortex manifesting a propensity to be entrained by slow wave oscillations originating from the hippocampus (Sirota et al., 2008). One of the core activities hippocampal-cortical pairing is thought necessary for is the

conversion of short-term memories formed by the hippocampus into long-term ones stored within the greater capacity of the neocortex (Battaglia et al., 2011).

One of the frequency bands thought to be indicative of hippocampal cortical interactions is the theta band, a slow wave frequency oscillating between 4 - 6Hz. Activity within the hippocampus is most prominently represented by theta oscillations, however, these also appear over cortical regions and have been posited to regulate informational exchange between cortex and hippocampus. For example, Takehara-Nishiuchi and colleagues (2012) discuss an inverse relationship of theta synchronisation taking place between the hippocampus/entorhinal cortex and medial prefrontal/entorhinal cortex of rats undergoing a conditioning paradigm, thus highlighting that oscillations in the theta band are reflective of hippocampal-cortical interactions during the process of memory consolidation. Over the course of learning an eyeblink-conditioning paradigm, the authors observed continuously decreased synchrony of theta oscillations between the hippocampus and entorhinal cortex of rats that were forming reliable associations. Reduced synchrony between these two brain regions was mirrored by a corresponding increase of theta synchrony between the medial prefrontal and entorhinal cortex. Findings to this effect suggest that changing theta oscillations in the hippocampus and cortex index the transition of newly encoded memories into long-term items stored in the neocortex. Takehara-Nishiuchi and colleagues' findings thereby correspond to the widely held view that the hippocampus is involved in the encoding of new memories and shows strong activation during the retrieval of recently encoded items (Takashima et al., 2009), whereas long-term memories and conditioned associations rely on an increasing neocortical role over time (Maviel et al., 2004). Increased cortical theta synchronisation (especially over the frontal-midline) has been reported by a number

of electroencephalographic (EEG) studies investigating the neural correlates of memory (Burgess & Gruzelier, 1997; Enriquez-Geppert et al., 2014; Mizuhara et al., 2015). For example, Shi, Gao and Zhou (2015) reported increased frontal-midline theta synchronisation among high performing individuals completing an emotive memory span task (relative to a neutral control task), whereas highly anxious participants whose performance declined in the emotive memory task showed reduced levels of frontal-midline theta synchronisation. However, increases of cortical theta synchronisation have also been linked to decreased memory performance when they are observed over widespread cortical regions. For example, Vogel, Broverman & Klaiber (1968) suggested that a global increase of cortical theta may index a more resource sparing but less effective memory processing strategy which may result in performance decrements. This theory is in line with the findings of Doppelmayr and colleagues (1998). Comparing cortical theta activation patterns between good and bad performers on an episodic memory task, the authors reported that bad performers did not show hemispheric localisation of theta activity but manifested a widespread pattern of theta event-related synchronisation over the entire scalp.

Given the promising findings of Reagh and colleagues, indicating their paradigm is able to determine hippocampal damage among the elderly, the present study asked 30 elderly and 30 young participants to complete their task, aiming to investigate the effect of long-term experienced stress on neocortical and hippocampal damage sustained by elderly individuals. In order to explore how experienced stress impacts on the relationship between the neocortex and hippocampus and extend the findings of Reagh and colleagues, the present study paired the behavioural task with EEG recordings to gain further insight into how stress affects vulnerable areas of the

brain. Based on past literature addressing the impact of experienced stress on cognitive ageing, elderly participants with high levels of experienced stress were predicted to display reduced levels of behavioural performance. With respect to the EEG data, two scenarios were hypothesised. Should the effects of stress be restricted to cortical areas and not affect the hippocampus directly, elderly high stress participants were hypothesised to display reduced theta synchronisation in frontal and temporal regions, thus indicating impairments to hippocampal-cortical interactions from a cortical standpoint. However, should large amounts of experienced stress result in direct hippocampal damage, elderly high stress individuals were hypothesised to manifest a widespread increase of cortical theta synchronisation relative to young and low stress elderly participant groups. Past work asserts that early forms of memory processing involve a large amount of hippocampal activity which declines over time to be replaced by higher amounts of cortical theta synchronisation (Takehara-Nishiuchi et al., 2012). In line with this, the latter scenario is thought to reflect a change of processing strategy, demonstrating an over-reliance on cortical processing resources due to compromised hippocampal functioning. Given that different forms of stress have been shown to cause considerable damage to areas of the hippocampus (McEwen & Sapolsky, 1995), the latter scenario is hypothesised to be the more likely outcome.

Experiment 6

Materials and Method

Participant selection.

Thirty young adult participants (Mean age = 21.3, SD = 3.4; Range 18 - 30 years; 13 males) were recruited from the University of Essex student population via

institutional e-mail advertising. A second group of 30 elderly participants (Mean age = 68.73, SD = 6.4; Range 60 - 82 years; 16 males) were recruited via an advertisement placed in the local branch of the University of the 3rd Age newsletter. All participants were right-handed and healthy. Exclusion criteria specified in the advertisement included major medical conditions (i.e. diabetes, heart disease), major neurological damage (i.e. stroke) and a current diagnosis of a mental or psychiatric disorder (dementia, depression or anxiety disorder), as well as the use of psychoactive medication and a history of substance abuse. In order to ensure against undiagnosed cognitive pathologies, all elderly participants completed the Mini Mental State Examination (Folstein, Folstein & McHugh, 1975) in which all scored full marks. All participants provided written informed consent. The study was approved by the University of Essex Ethics Committee. Participants completing experiment 6 consisted of the same individuals presented in Chapter 4 who completed experiment 5 and 6 in counter-balanced order during the same testing session.

Stress and demographical measures.

This study investigated the impact of cumulative stressful experiences on cognitive ageing. However, given that our elderly participants were on average three times the age of younger participants, they are likely to have experienced more stressful events. Additionally, stressful experiences are likely to be different for both populations. To therefore assess prolonged experienced stress exposure appropriate to each age group and test the argument that the long-term effects of cumulative stress exposure cause performance impairments rather than purely high amounts of immediate stress, different instruments had to be used for both age groups. The amount of experienced stress was therefore assessed by the Social Readjustment Rating Scale (Holmes & Rahe, 1967) for elderly and the Student Life Events Scale

(Clements & Turpin, 1996) for young participants. Both scales were chosen as they comprise a similar format to assess stressful life experiences, consisting of a brief, self-administered scale (43 and 36 items, respectively). Scales contain incidents ranging from extremely stressful (i.e. 'Death of Spouse/Parent') to mildly stressful (i.e. 'Finding a part-time job'). Scores can range from 0 - 1466 for the Social Readjustment Rating Scale and 0 - 1849 for the Student Life Events Scale. Higher scores reflect high amounts of experienced stress for both scales. In order to ensure values measured from different scales contributed equally to the analysis, the scores for each participant were standardised within age groups.

In order to control for the possible impact of anxiety, this was further assessed by the State-Trait-Anxiety Inventory (STAI) developed by Spielberger (1968). The STAI comprises two 20-item questionnaires, designed to assess respondents' general levels of trait anxiety and momentary levels of current anxiety. Positively worded items are reverse scored for both questionnaires so that higher scores on either correspond to heightened levels of state and trait anxiety.

Further measured background demographics are displayed in Table 5.1.. As this is a cross-sectional data set, these additional variables were obtained to control for the possible impact of factors known to affect cognitive ageing. No stress or group differences emerged for any of the demographical variables (see Table 5.1.).

Procedure and spatial mnemonic discrimination task.

Before progressing to the spatial task, each participant completed an eye-movement calibration session (Croft & Barry, 1998) which was followed by an eyes closed/resting EEG interval lasting two minutes. EEG data gathered from the eye-movement calibration session was subsequently used to filter out electrical activity reflecting eye-movements and blinks.

For the spatial discrimination task, the same one hundred and forty images of common objects (Brady et al., 2008) employed by Reagh and colleagues (2013) were used. Images were presented on a widescreen monitor (23 inches) divided into a 5 x 7 grid (35 grid spaces) which remained invisible to participants.

Table 5.1. Demographical information of elderly and young participants split by experienced stress group.

	Elderly		Young	
	Low Stress	High Stress	Low Stress	High Stress
Group Size	15	15	15	15
Age	67.8 (6.3)	68.6 (5.4)	21.9 (4.1)	20.7 (2.5)
Gender	8 ♂	8 ♂	6 ♂	7 ♂
Education	3.4	3.5	4.1	4.27
Cigarette Consumption	0	0	0	0.2 (0.6)
Alcohol Consumption	1.53 (1.5)	2.2 (1.7)	1.3 (1.7)	0.9 (1.0)
Presence of Physical Disability	2	3	0	1
Exercise	2.73 (1.1)	2.67 (1.1)	2.1 (1.0)	2.7 (1.0)
Mini Mental State Score	30	30	n.a.	n.a.
Trait Anxiety Score	35.53	35.8	39.87	37.87
State Anxiety Score	29.47	26.73	32.53	30.8
Experienced Stress Score	461.3*(142.7)	864.5* (94.5)	389.67*(112.5)	736.5* (109.0)

Note. Education ranging from 1 (lower than High School) – 6 (University PhD degree); Cigarette Consumption: cigarettes per day; Alcohol Consumption: units per week; Exercise: hours per week; *$p < .05$ represents significant stress group differences within age groups

The spatial discrimination task consisted of an encoding and retrieval phase. During the encoding phase, participants were presented with a sequence of 140 objects appearing at randomly assigned grid locations for 2500ms.

To ensure continued attention during the encoding phase, a rating screen asking participants to decide whether the encountered object was more likely to appear indoors or outdoors in a real life setting followed each presented object. Participants responded with their right or left index finger (corresponding to an indoors or outdoors judgment) and proceeded to the next object location screen after each rating. This modification of Reagh and colleagues' paradigm ensured that EEG activity corresponding to the motor response was distinct from activity during encoding and later retrieval intervals.

After a five-minute resting delay, participants completed the retrieval phase during which they encountered a sequence of the same objects previously encoded (again presented for 2500ms). Objects appeared either in the same grid location as before or had moved to another space on the grid. Participants were asked to decide whether the object had been displaced or remained in the same location and provide their answer on the rating screen, which followed each object presentation. Following Reagh and colleagues' design, 40 of the 140 objects remained in the same grid space, acting as targets. The remaining 100 images were divided evenly into five different lure-types (20 per category): objects displaced horizontally or vertically by 1-, 2-, 3- or 4-grid spaces, plus objects performing a maximal move from one side of the grid into the opposite corner. Reagh and colleagues designed their task to allow parametric comparisons across levels of mnemonic interference, ranging from minimal to low for corner- and 4-grid moves to high for 1-grid moves, varying only the spatial locations in regard to the original position. The sequence of trials was randomly

assigned for each participant and direction of lure displacement was balanced across trials so that all grid spaces during encoding and retrieval phases were used equally, given the amount of presented images. Therefore, each grid location was equally likely to contain an object (except corners in which only corner lures appeared) and vertical and horizontal displacements were equally likely in both phases. No diagonal displacements were used. The task was programmed using E-prime presentation software (Schneider et al., 2002).

Electrophysiological recording and data preparation.

Electroencephalography (EEG) was recorded from 64 electrodes placed within a soft-cap according to the 10 - 20 method of electrode positioning. Recordings were referenced to a point midway between Cz and CPz. Impedances were lowered to below 10kΩ in all electrodes before acquisition and re-checked in the interval between encoding and retrieval. EEG signals were recorded and subsequently analysed using a Neuroscan Synamps2 system in conjunction with SCAN 4.5 software (Compumedics, Melbourne, Australia). Data was collected at a sampling rate of 1000Hz with a band-pass filter of 0.05 - 200Hz.

Acquired data was visually inspected and noisy data blocks, general artefacts and bad electrodes subsequently rejected. Principal components analysis was performed on the acquired eye-movement data to obtain components reflecting saccades and blinks. To carry out ocular artefact rejection, the acquired components were subsequently rejected from the task data traces (Vigario, 1997; Vigario et al., 2000). All data was re-referenced to a common average reference. In order to investigate the topographical aspects of age- and stress-related group differences in response to completing the mnemonic spatial task, the 64 electrodes were averaged into nine brain regions: left (FP1, AF3, F7, F5, F3, F1, FT7, FC5, FC3, FC1), mid

(FPz, Fz, FCz) and right (FP2, AF4, F8, F6, F4, F2, FT8, FC6, FC4, FC2) frontal; left (T7, C5, C3, C1, TP7, CP5, CP3, CP1), mid (Cz, CPz) and right (T8, C6, C4, C2, TP8, CP6, CP4, CP2) central; left (P7, P5, P3, P1, PO7, PO5, PO3, CB1, O1), mid (Pz, POz, Oz) and right (P8, P6, P4, P2, PO8, PO6, PO4, CB2, O2) posterior.

In order to calculate event-related synchronisation and desynchronisation, data segments for both encoding and retrieval periods were cut into 4000ms epochs (ranging from -1000 to 3000ms after stimulus onset). The first and last 500ms of the trials were trimmed in order to avoid filter warm-up artefacts, leaving a 2500ms test interval and a 500ms reference period (-500ms before onset of the next stimulus) for subsequent analyses. For the electrophysiological analyses of displaced lures, corner moves were disregarded and lures moved by 1- and 2-grid spaces were combined into a high interference condition, whereas lures displaced by 3- and 4-grid spaces were combined into a low interference condition. This procedure ensured an adequate and equal amount of epochs for each condition (40 each in unmoved trials, high interference lures, low interference lures). Only correct trials for targets and lures were used.

Using the Event-related-band-power transformation (SCAN 4.5 editing software), data underwent complex demodulation and concurrent filtering (zero phase-shift, 24dB roll-off, envelope computed) into the theta (4 - 6Hz) bandwidth. Event-related activity was calculated as a percentage change between the active period and the reference period according to the following formula: [((reference – test)/reference)x100]. According to this method (Pfurtscheller & Lopez da Silva, 1999), positive values represent desynchronisation (ERD) of the theta frequency band, whereas negative values indicate synchronisation (ERS).

Results

Behavioural analysis.

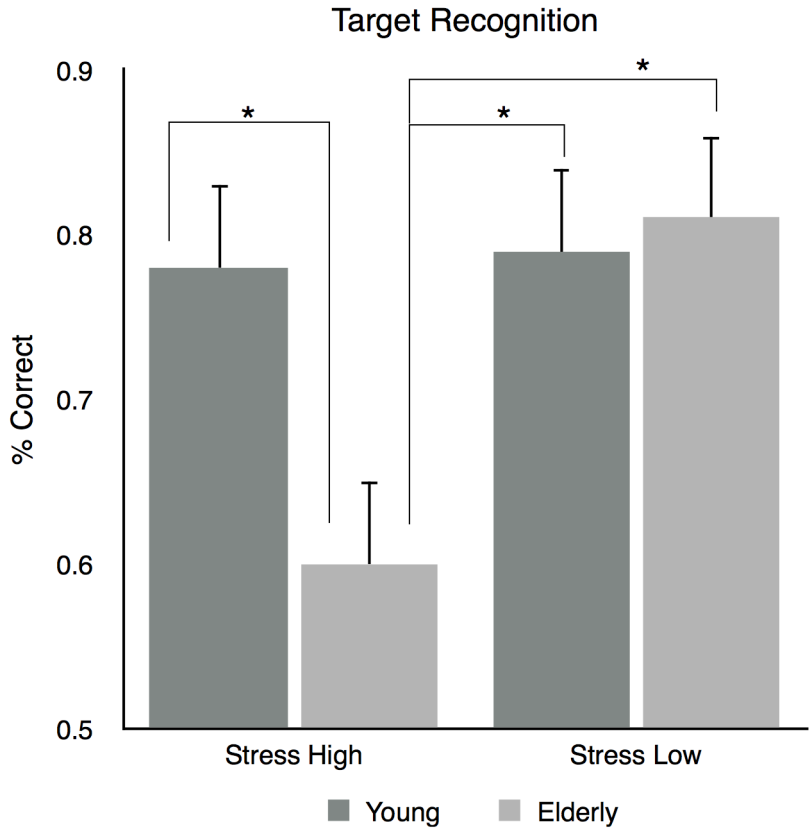
In an extension of Reagh and colleagues (2013), both age groups were split into high and low stress scorers based on the median split of scores from the Social Readjustment Rating Scale for elderly (Median Split value 697) and the Student Life Events Scale for young participants (Median Split value 606). No significant group differences in Mini Mental State performance, State/Trait anxiety scores, age, gender, educational attainment, cigarette/alcohol consumption or amounts of exercise were observed between stress groups (all $p_s > .05$). The present study thus ensured equal sample sizes and hoped to gain more insight into the way experienced stress had impacted on performance. Following the steps undertaken by Reagh and colleagues (2013), target detection, lure discrimination and performance increases at each lure interference level (i.e. increase in % correct from 1- to 2-grid moves etc.) were investigated by three ANOVAs with Bonferroni corrections for the follow-up comparisons.

Target recognition.

For target recognition, correct judgments were calculated as p (No Move/Target). The target recognition was analysed by means of a 2 (Age: old vs. young) by 2 (Experienced Stress: high vs. low) full factorial ANOVA. The analysis revealed a main effect of age ($F_{1,57} = 4.8$, $p = .033$), indicating that elderly participants ($M = 0.72$, $SD = .16$) performed worse overall compared to young participants ($M = 0.79$, $SD = .13$) (see Figure 5.1.). Results further revealed a main effect of experienced stress group ($F_{1, 57} = 14.72$, $p < .001$), highlighting that individuals in the high stress group ($M = 0.69$, $SD = .14$) performed worse at target recognition relative to low stress group counterparts ($M = 0.81$, $SD = .13$). However,

these main effects were qualified by an interaction between age and experienced stress ($F_{1, 57} = 12.51$, $p = .001$). No other main effects or interactions reached significance (all $p_s > .05$). The age x experienced stress interaction was parsed by conducting corrected pairwise comparisons (corrected p-value .008). Findings revealed that elderly participants with high levels of experienced stress performed significantly below elderly participants in the low experienced stress group ($t_{28} = 4.26$, $p < .001$) and young participants in both the high ($t_{28} = 3.67$, $p < .001$) and low ($t_{28} = 3.15$, $p < .001$) experienced stress group (see Figure 5.1.). No other group differences reached significance (all $p_s > .008$).

Figure 5.1. Target detection scores for both age groups split into high and low experienced stress scorers.



Note. Findings show significantly reduced accuracy of high stress elderly participants compared to elderly low stress and both young stress groups. Error bars represent SEM.

Lure displacement.

For lure displacement, correct judgments were calculated as p (Move/Target). Performance on lure displacement trials were subsequently analysed by a 2 (Age) x 2 (Experienced Stress) x 5 (Lure Displacement: 1 vs. 2 vs. 3 vs. 4 vs. corner moves) mixed measures ANOVA. Similar to target recognition, analysis of lure displacement revealed a main effect of age ($F_{1, 57} = 5.37$, $p = .024$) which highlighted that elderly participants ($M = 0.64$, $SD = .11$) performed significantly below young participants ($M = 0.70$, $SD = .10$) on correctly identifying object displacements. Analysis also found a main effect of experienced stress group ($F_{1, 57} = 6.14$, $p = .016$), indicating that members of the high experienced stress group performed worse ($M = 0.63$, $SD = .11$) on lure displacement trials relative to low experienced stress group counterparts ($M = 0.70$, $SD = .09$). Results further revealed a significant main effect of lure displacement ($F_{4, 220} = 132.47$, $p < .001$). Simple effects contrasts of this main effect (corrected p-value .005) indicated significant increments in performance at all levels apart from 4-grid to corner displacements ($p > .05$). This highlights that the task became progressively easier as the distance between the original target and the presented lure became more apparent. Analysis also revealed a significant age x lure ($F_{4, 220} = 4.71$, $p = .001$) and a significant age x stress x lure displacement interaction ($F_{4, 220} = 3.3$, $p = .012$). No further interactions or main effects reached significance (all $p_s > .05$). Simple effects contrasts of the age x lure interaction (corrected p-value .005) showed that young participants outperformed elderly counterparts on moderate (3-grid moves) ($t_{28} = 3.14$, $p = .004$) and low interference trials (4-grid moves) ($t_{28} = 5.52$, $p < .001$), thus replicating the findings by Reagh and colleagues (2013) (see Figure 5.2.). No further simple main effects reached significance for this interaction (all $p_s > .005$).

Simple effects contrasts of the age x stress x lure displacement interaction (corrected p-value .0016) revealed that for moderate interference trials (3-grid moves), elderly high stress participants performed significantly below elderly low stress participants ($t_{28} = 3.4$, $p = .001$) and both young high ($t_{28} = 4.06$, $p < .001$) and young low ($t_{28} = 4.23$, $p < .001$) stress group participants. Similarly, for low interference trials (4-grid moves), elderly high stress participants' performance was significantly below that of elderly low stress participants ($t_{28} = 6.05$, $p < .001$) and both young high ($t_{28} = 6.15$, $p < .001$) and young low stress group participants ($t_{28} = 5.4$, $p < .001$) (see Figure 5.2.). No further simple main effects reached significance (all $p_s > .002$). Results therefore indicate that age differences seem primarily driven by the decreased performance of high stress elderly group members whose performance falls significantly below that of all other groups in moderate to low interference trials in which object relocation was more easily determined[8].

[8] The analysis was re-run with a 2 (Age) x 2 (Experienced Stress) x 3 (Stimulus: unmoved vs. low interference vs. high interference) ANOVA, thus matching the EEG analysis strategy to ensure compatibility of results. Results revealed a ME of stimulus ($F_{2,110} = 244.59$, $p < .001$), as well as a main effect of age ($F_{1,55} = 8.25$, $p = .006$) and experienced stress group ($F_{1,55} = 10.16$, $p < .002$). Simple effect contrasts of the main effect of stimulus (corrected p-value .017) indicated that performance differed between all stimulus types and was lowest for unmoved target detection ($M = 0.61$, $SD = .016$), followed by high interference lures ($M = 0.76$, $SD = .26$) and was highest for low interference lures ($M = 0.86$, $SD = .029$) (all $p_s < .010$). The main effect of age revealed that elderly participants ($M = 0.67$, $SD = .026$) performed significantly below young individuals ($M = 0.76$, $SD = .021$). The main effect of experienced stress found that high stress group members ($M = 0.64$, $SD = .026$) performed worse than low stress group members ($M = 0.77$, $SD = .024$). MEs were qualified by an age x stimulus ($F_{2,110} = 6.77$, $p = .002$) as well as an age x stimulus x experienced stress group ($F_{2,110} = 4.26$, $p = .037$) interaction. No further interactions or main effects reached significance (all $p_s > .05$). Simple effects contrast of the age x stimulus interaction (corrected p-value .017) showed that young participants outperformed elderly counterparts for unmoved targets ($t_{28} = 6.80$, $p = .012$) and for low interference lures ($t_{28} = 19.01$, $p < .001$). These findings mirror the age effects reported for the earlier analyses of both target detection and lure displacement. Simple effects contrasts for the three-way interaction (corrected p-value .008) revealed that high stress elderly participants performed significantly below members of the young high stress group for both unmoved target detection ($t_{28} = 16.70$, $p < .001$) and low interference lures ($t_{28} = 33.57$, $p < .001$). Similarly, elderly high stress participants performed significantly worse than elderly low stress participants for unmoved target detection ($t_{28} = 27.66$, $p < .001$) and low interference lures ($t_{28} = 25.08$, $p < .001$). The three-way interaction thus reproduces the age and stress effects found for the earlier target detection and lure displacement analysis and demonstrates that analysing behavioural data in the same manner as the subsequent electrophysiological analysis yields the same findings.

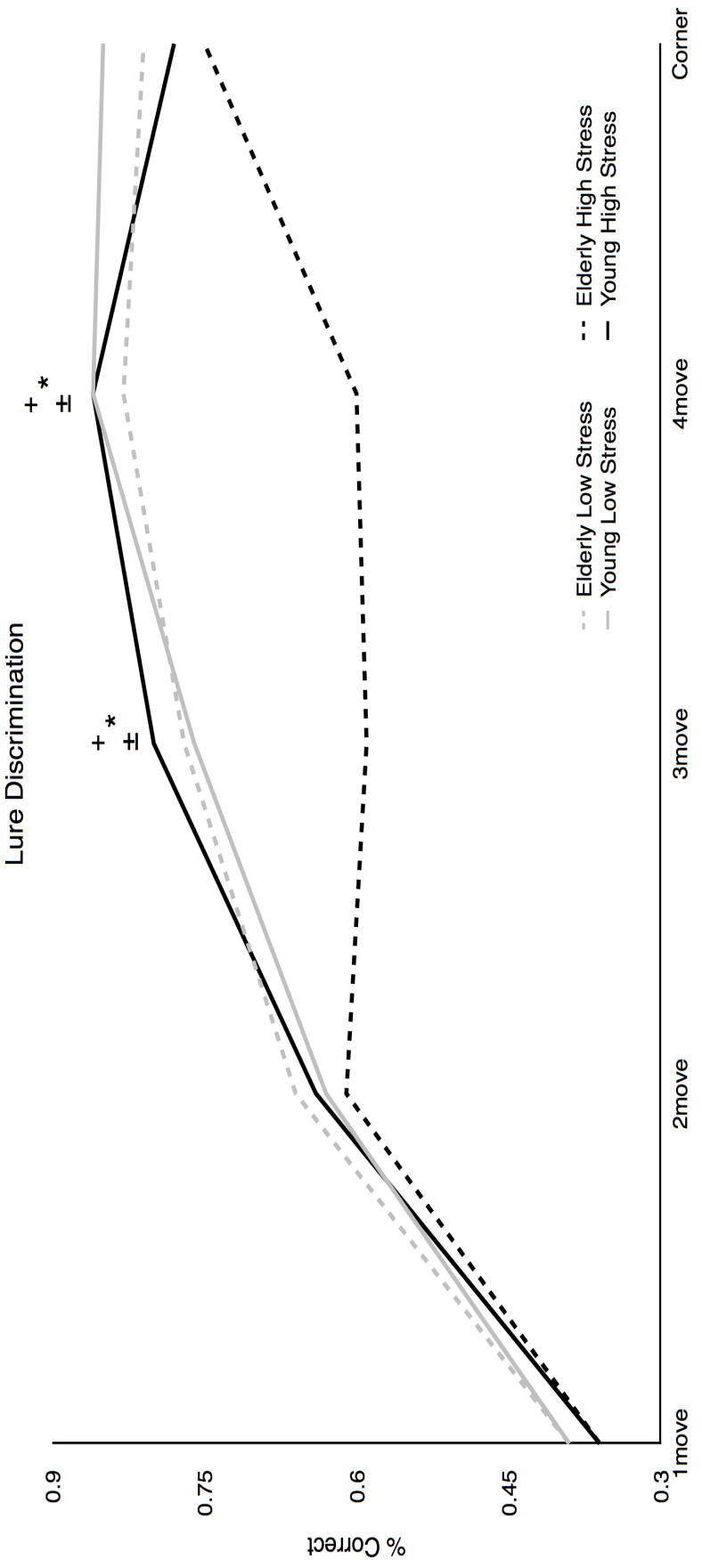


Figure 5.2. Lure discrimination scores at each level of mnemonic interference for both age and stress groups

Note. Results indicate reduced performance among High Stress Elderly participants compared to to High and Low Stress Young and Low Stress Elderly participants at moderate to low levels of interference (3- and 4-grid moves). Young High Stress > Elderly High Stress(*); Young Low Stress > Elderly High Stress(+); Elderly Low Stress > Elderly High Stress(±).

Performance increases at each lure interference level.

The percentage of performance increase at each level of lure displacement was analysed using a 2 (Age) x 2 (Stress) x 4 (Slope Increase: 1 - 2 vs. 2 - 3 vs. 3 - 4 vs. 4 - corner) mixed measures ANOVA. Analysis of the difference scores between each interference level revealed a main effect of slope increase ($F_{3,165} = 23.82$, $p < .001$). Simple effects contrasts of this main effect (corrected p-value .008) indicated that performance rose sharply from high to easier lower interference trials (1 - 2, 2 - 3; $p_s < .008$) and plateaued for moderate to low levels of interference (3 - 4, 4 - c; $p_s > .008$). Results further indicated a significant age x slope increase interaction ($F_{3, 165} = 4.27$, $p = .006$) and a significant age x stress x slope increase ($F_{3, 165} = 3.42$, $p = .019$) interaction. No further main effects or interactions reached significance (all $p_s > .05$). Simple effect contrasts of the age x slope interaction (corrected p-value .006) once again replicated the findings of Reagh and colleagues (2013), indicating that relative to young, elderly participants displayed a reduced increase in performance from high to moderate interference levels (2 - 3; $t_{57} = 2.14$, $p = .004$) but showed a steeper performance increase than young from low to very low interference trials (4 - c; $t_{57} = 3.1$, $p = .003$). No further simple main effects reached significance for this interaction ($p_s > .006$).

Simple effects contrasts of the age x stress x slope increase interaction (corrected p-value .003) revealed that elderly high stress individuals showed less performance increases on low to moderate interference trials (2 - 3) compared to both young high ($t_{28} = 2.51$, $p = .002$) and low stress group members ($t_{28} = 2.73$, $p = .002$ A steeper performance increase could be observed among elderly high stress group members from low to very low interference trials (4 - corner) relative to both young high ($t_{28} = 4.57$, $p < .001$) and young low ($t_{28} = 4.27$, $p = .001$) stress group members

and elderly low stress group members ($t_{28} = 3.14$, $p = .002$). No further simple main effects reached significance ($p_s > .003$). Results to this effect indicate that elderly participants reporting high amounts of experienced stress were less able to capitalise on moderately favourable interference conditions (2 - 3 grid moves) compared to young high and low stress groups. The steeper performance slope displayed by elderly high stress individuals relative to all other groups from four to corner move displacements indicates that they were able to catch up with other participant groups once interference had reached very low levels. Similar to results on lure displacement, age differences in the age x slope interaction seem primarily driven by the reduced performance of high stress group elderly participants.

Electrophysiological analysis.

Electrophysiological data of the spatial discrimination task was analysed by means of a factorial ANOVA, utilising the median split of both age groups into high and low experienced stress scorers as detailed above. In order to assess the temporal specificity of task-related theta activity, the 2.5s encoding and retrieval periods were split into early and late intervals (each lasting 1250ms). As this paper is the first to adapt this novel paradigm for use with EEG, time windows were determined through inspection of the grand average waveform collapsed across all participant groups. This revealed a larger amount of evoked electrophysiological activity at early stages of stimulus encoding as well as stimulus retrieval which changed to a larger proportion of invoked activity during later periods of encoding and retrieval. This observation highlighted the importance of dividing the data into early and late time periods. Data for the encoding period was subsequently analysed using a 3 (Sagitality: frontal vs. central vs. posterior cortical regions) x 3 (Laterality: left vs. mid vs. right cortical regions) x 2 (Age: young vs. old) x 2 (Experienced Stress: high

vs. low) mixed measures ANOVA, which was run separately for both early and late intervals. Data for the retrieval period was analysed by means of a 3 (Sagitality) x 3 (Laterality) x 2 (Age) x 2 (Experienced Stress) x 3 (Stimulus: unmoved vs. low interference vs. high interference) ANOVA which was run separately for early and late periods of stimulus retrieval.

Encoding early interval (0 – 1250ms).

Analysis revealed a significant main effect of age ($F_{1,45} = 16.87$, $p < .001$) indicating that elderly participants displayed higher levels of theta ERS during early periods of stimulus encoding compared to young counterparts. No further main effects or interactions reached significance (all $p_s > .05$).

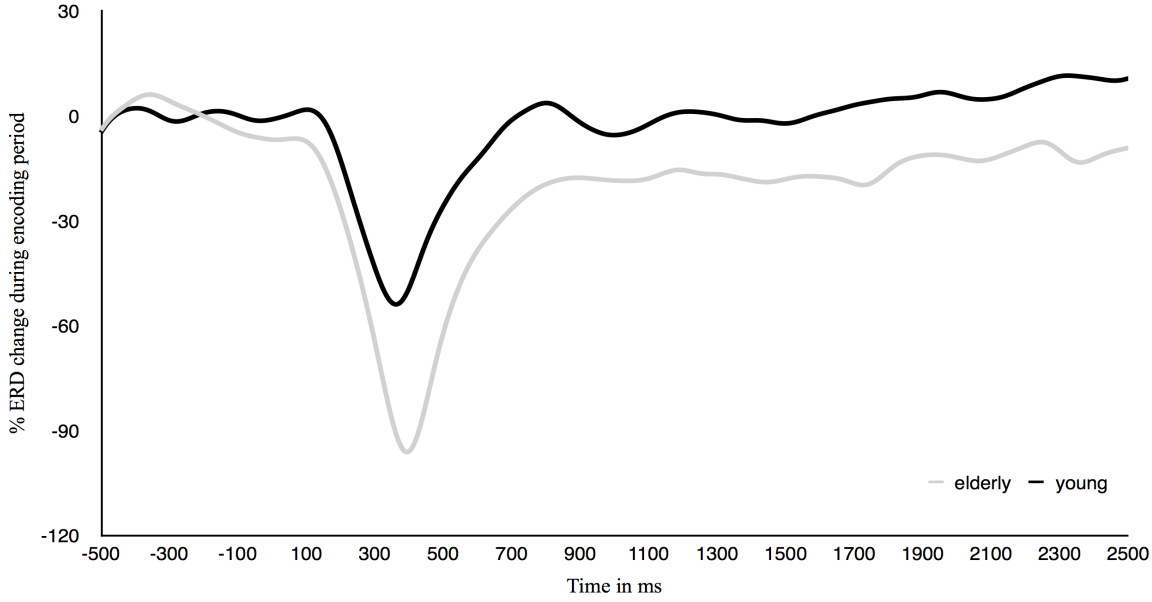
Encoding late interval (1250 – 2500ms).

Similar to the early epoch, analysis of the late interval found a significant main effect of age ($F_{1,45} = 9.91$, $p = .003$), indicating that elderly participants show higher levels of theta ERS in late periods of stimulus encoding compared to young participants (see Figure 5.3.). No further main effects or interactions reached significance (all $p_s > .05$).

Retrieval early interval (0 – 1250ms).

Analysis of the early interval of retrieval produced a main effect of age ($F_{1,45} = 11.46$, $p = .001$), once again indicating that elderly participants exhibited higher levels of theta ERS compared to young participants. Furthermore, analysis revealed a significant laterality x age x stress x stimulus interaction ($F_{4,180} = 4.89$, $p = .022$). To decompose the interaction, four relevant group differences for the three stimulus categories were analysed for each of the three lateral cortical regions by means of simple effect contrasts.

Figure 5.3. Grand average waveforms over the entire cortex during encoding of the original stimulus location.



Note. Graph displays ME of age, indicating that elderly participants display increased theta ERS during encoding of the original object location relative to young individuals.

A Bonferroni corrected p-value (.001) was employed to correct for multiple comparisons. Simple effects contrasts revealed that among individuals with high levels of experienced stress, elderly participants showed significantly higher levels of theta ERS over left lateral ($F_{1,45} = 14.78$, $p < .001$), mid lateral ($F_{1,45} = 13.82$, $p < .001$) and right lateral ($F_{1,45} = 8.54$, $p = .013$) cortical regions when retrieving object locations in the low interference category (see Figure 5.4a.). No other main effects or interactions reached significance (all $p_s > .05$).[9]

[9] EEG results were re-run with different time windows to more accurately balance these with respect to evoked activity prominent in the early time window (0 - 600ms) and induced activity prominent in the later time frame (600 - 2500ms).
Encoding early interval (0 - 600ms). Results found a ME of age ($F_{1,45} = 18.13$, $p < .001$) indicating that elderly participants displayed higher levels of theta ERS during early periods of stimulus encoding relative to young counterparts. No further main effects or interactions reached significance (p's > .05).
Retrieval early interval. Analysis revealed a ME of age ($F_{1,45} = 13.11$, $p < .001$) once again highlighting that elderly participants showed higher levels of theta ERS relative to young counterparts. Results also found a significant laterality x age x stress x stimulus interaction ($F_{4,180} = 5.63$, $p = .013$). A Bonferroni corrected p-value (.001) was employed to correct for multiple comparisons. Follow-up analyses revealed that relative to young high stress group members, elderly high stress participants manifested significantly higher levels of theta ERS across electrodes summed over the left cortical

Retrieval late interval (1250 – 2500ms).

Analysis of the late retrieval period once again produced a main effect of age ($F_{1,45} = 25.44$, $p < .001$). This main effect indicated that elderly participants showed higher levels of theta event-related synchronisation in late periods of stimulus retrieval when compared to young counterparts. Analysis further discovered a four-way laterality x age x stress x stimulus interaction ($F_{4,172} = 3.46$, $p = .021$). To parse the interaction, four relevant group differences over the three stimulus categories (unmoved vs. low interference vs. high interference) were analysed for each of the three lateral cortical regions (Bonferroni corrected p-value .001). This was done by means of simple effects contrasts. These revealed that, compared to young participants in the high experienced stress group (who showed theta ERD), elderly high stress individuals displayed high levels of theta ERS over left lateral ($F_{1,45} = 14.78$, $p < .001$), mid lateral ($F_{1,45} = 21,59$, $p < .001$) and right lateral ($F_{1,45} = 13.45$, $p < .001$) cortical regions when retrieving the locations of objects in the high interference category (see Figure 5.4b).

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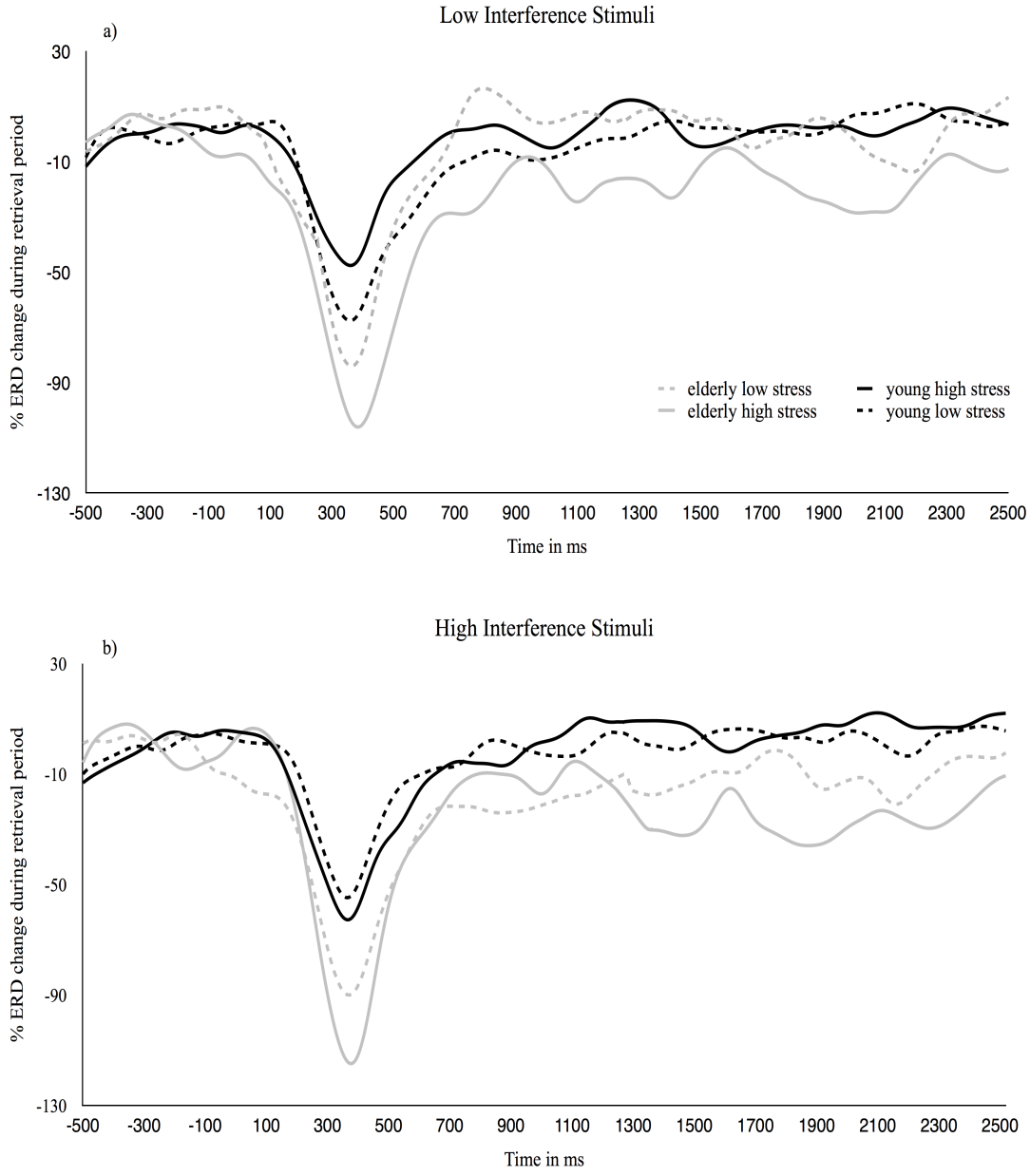
region (left lateral) ($F_{1,45} = 17.66$, $p < .001$), the central cortical region (mid lateral) ($F_{1,45} = 15.32$, $p < .001$) and the right cortical region (right lateral) ($F_{1,45} = 10.54$, $p < .001$) when retrieving the locations of objects in the low interference category.

Retrieval late interval (600 - 2500ms). Once again, analysis revealed a ME of age ($F_{1,45} = 21.36$, $p < .001$) which demonstrated that elderly participants manifested higher levels of theta ERS compared to young individuals. Akin to earlier results, analysis further discovered a significant laterality x age x stress x stimulus interaction ($F_{4,172} = 2.97$, $p = .032$). This interaction was again decomposed using simple effects contrasts for the four relevant group comparisons over each of the three stimulus categories (Bonferroni corrected p-value .001).

Comparisons once again revealed that relative to young high stress group participants, elderly individuals of the high stress group exhibited significantly higher levels of theta ERS over left ($F_{1,45} = 12.33$, $p < .001$), mid ($F_{1,45} = 19.48$, $p < .001$) and right ($F_{1,45} = 11.83$, $p < .001$) lateral cortical regions when retrieving the locations of objects in the high interference category.

With one exception (finding no main effect of age in the late time window for stimulus encoding), reanalysis of EEG data thereby replicates the original analyses, thus demonstrating that the previously used time windows of equal length accurately capture manifesting age and stress differences.

Figure 5.4. Grand average waveforms computed over the entire cortex during retrieval of original object location.



Note. a) Increased theta ERS of high stress elderly participants during early periods of stimulus retrieval. b) Increased theta ERS of high stress elderly participants during late periods of stimulus retrieval.

Discussion

The current study explored the way experienced stress impacts on elderly participants' cognitive performance in a task thought to depend on hippocampal integrity. Behavioural findings indicated that experienced stress negatively impacted on elderly participants' performance. Furthermore, these behavioural shortcomings coincided with enhanced theta oscillations manifested by elderly high stress participants over widespread cortical regions.

Behavioural results.

Investigating general age differences in spatial discrimination performance revealed that young participants were significantly better at correctly retrieving original object locations when mnemonic interference was moderate to low (3- & 4-grid moves). Enhanced performance among young participants, as a result of conditions favourable to pattern discrimination, was further highlighted by steeper performance increases from 2- to 3- and 3 to 4-grid moves. Splitting young and elderly participant samples into high and low stress groups revealed that the general age difference is primarily driven by reduced performance among the high stress elderly participant sample. Results revealed that elderly high stress participants performed significantly worse in moderate to low interference conditions (3- & 4-grid moves), as well as unmoved target detection, compared to all three other groups, whereas no differences in performance were observed among young and elderly low stress participants. No behavioural differences were observed for objects with high mnemonic interference (moved by 1- or 2-grid spaces) or for objects with very low mnemonic interference (moved from corner to opposite corner). Within the high interference conditions, performance of all four groups remained at chance level, indicating that all participants (regardless of stress or age group) were unable to make

informed decisions about object displacements on high interference trials. Whereas the performance of high stress elderly remains below that of young participants in the very low interference condition, elderly high stress individuals were able to significantly increase their accuracy once interference from lures became negligible, thus making the object displacement very apparent.

Our behavioural findings therefore replicate the results published by Reagh and colleagues (2013) who discovered similar age differences. Akin to results of this study (when comparing elderly high stress individuals to the performance of young and elderly low stress counterparts), Reagh and colleagues reported more pronounced differences when comparing the performance of elderly participants who had scored low on a test of hippocampal integrity to that of young and elderly high scorers. Based on these authors' conclusion that their paradigm reliably indexed early forms of hippocampal impairment, our results indicate that experienced stress may have impacted on the hippocampal integrity of elderly high stress participants and resulted in corresponding behavioural impairments. Our results thereby extend both longitudinal (Peavy et al., 2009; Pesonen et al., 2013) and cross-sectional work (Dickinson et al., 2011), reporting that higher levels of experienced stress result in reduced cognitive performance among elderly individuals, as well as in-vitro studies detailing the adverse effects of stress on the hippocampus (Sapolsky & Meaney, 1986).

Electrophysiological results.

The electrophysiological findings of the present study provide a further indication that experienced stress may have impacted on hippocampal function, particularly the interactions between the cortex and hippocampus during the recall of original object locations. In keeping with the second hypothesis, elderly high stress

participants were found to display globally higher levels of theta ERS (in relation to a pre-stimulus baseline) for retrieval in the low interference condition (objects moved by 3- or 4-grid spaces), compared to young high stress counterparts. Results for the high interference condition revealed similar findings, indicating that elderly high stress participants continued to display widespread theta ERS compared to young high stress group participants who showed theta ERD during the retrieval of objects displaced by 1- or 2-grid moves.

The main purpose of the interaction between the hippocampus and cortex (as partially indexed by synchronous theta activity) is thought to be the conversion of new memories, recently encoded by the hippocampus, into long-term remembrances stored within the cortex. As such, the hippocampus has been found to show increased activation during the encoding and retrieval of novel material (Takashima et al., 2009), whereas recall of long-term memories, learned associations and conditioned responses tends to elicit an increased neocortical response (Maviel et al., 2004). As original object locations were only presented to participants once, they represent newly formed memories and as such should be primarily processed in the hippocampus. In keeping with this, small to moderate amounts of cortical activation (as indexed by synchronous theta activity) were found among most participant groups. Investigating grand average waveforms for high and low stress young and low stress elderly participant groups revealed that, apart from an early increase of theta ERS when the stimulus was first encountered, theta activity remained relatively close to baseline, with both young participant groups manifesting theta suppression in later stages of the demanding high interference condition. However, elderly high stress participants were found to differ from this pattern, manifesting pronounced levels of widespread theta synchronisation during the retrieval of original object

locations in both the high and low interference condition. In light of the proposed interactive role between hippocampus and neocortex with regard to memory consolidation, one would expect small to moderate amounts of theta activity localised to specific parts of the cortex that form direct connections to the hippocampus. As such, the global increase of theta synchronisation manifested by elderly high stress individuals does not seem indicative of intact cortical-hippocampal interactions but rather points to a different way by which elderly high stress group members process task demands. Based on work detailing that cortical theta activity is low during the formation of newly encoded memories (Maviel et al., 2004) and increases over time in conjunction with a decrease of hippocampal theta activity (Takashima et al., 2009), one possible explanation could be that elderly high stress participants placed an increased reliance on neocortical processes of memory retrieval due to stress-induced hippocampal damage, recruiting cortical resources as a compensatory attempt. In such a scenario, reduced hippocampal resources may thus have forced elderly high stress participants to rely on cortical processing resources as a substitute but less effective mechanism whose necessitated use resulted in the observed behavioural impairments among this participant group. The idea that a widespread increase of theta ERS over the cortex may reflect engagement in less effective but more resource sparing strategies was originally raised by Vogel and colleagues (1968). These authors proposed that a global increase of theta ERS may reflect a change from more reflective, involved forms of stimulus processing towards a more resource sparing approach normally used for learned associations and automated processes. This theory therefore corresponds to the idea that neocortical processing resources which are commonly employed for the retrieval of automated associations formed over a prolonged period of time may be employed instead of more elaborate forms of

stimulus recall (in this case hippocampal processing resources) in situations where these are not accessible or functional. The necessitated use of a mechanism commonly used for the retrieval of previously learned material may not be as effective at retrieving novel stimuli and may thus give rise to the behavioural shortcomings observed among elderly high stress participants. In concordance with this idea, global activation of theta activity has been linked to pronounced working memory impairments (Doppelmayr et al., 1998).

However, as the present study obtained no direct hippocampal measures, it remains unclear which underlying processes are reflected by the increased cortical theta activity displayed by elderly high stress participants. However, paired with the study's behavioural findings, high levels of theta synchronisation seem indicative of a shortcoming in the process of correctly retrieving the original spatial location of stimuli, which in turn is thought to rely strongly on hippocampal integrity.

A further striking characteristic of the electrophysiological findings is that significant differences between age and stress groups during retrieval manifested for low interference lures during analysis of the early time window, whereas the same difference manifested for high interference lures in the later time window. The paradigm devised by Reagh and colleagues (2013) involves two cognitive processes, both of which have been linked to hippocampal involvement: spatial memory of the object's original location and a pattern separation process which involves matching the memory trace to the newly encountered location in the face of conflicting information (overlapping representations between the memory trace and lure). Based on these two cognitive components, the observed pattern of results may be due to theta activity in the early time window reflecting memory retrieval processes, whereas activity in later time window indicates processes related to pattern

separation. Arguably, low interference stimuli place reduced demands on the system with respect to pattern separation, whereas high interference lures place heightened demands on the system to achieve this process. Thus, differences observed in the early time window for low interference lures may indicate increased cortical reliance by elderly high stress individuals to retrieve the stored location from memory, whereas the same activity in the later time window for high interference lures indicates increased cortical processing to achieve the pattern separation process. As pattern separation has been shown to depend on hippocampal activity (Yassa & Stark, 2011; Leutgeb et al., 2007; Hunsaker et al., 2008), little global theta activity would be expected to occur over the cortex. As such, the event-related desynchronisation close to baseline displayed among young participant groups reflects the expected intact cortical processing pattern, whereas the increased cortical theta synchronisation displayed among elderly participants may again indicate increased reliance on cortical processing resources based on reduced hippocampal integrity with advancing age which is exacerbated among elderly individuals who have been subjected to high amounts of cumulative stress.

Further directions and conclusions.

The present paper provides further insight into the way experienced stress impacts on cognitive ageing and broadens previous work, highlighting the hippocampus as particularly vulnerable to the adverse effects of stress hormones by investigating hippocampal-cortical interactions. However, since no imaging techniques were employed which could have investigated hippocampal activation directly, the electrophysiological and behavioural findings presented here remain an indirect measure and therefore any direct claims about hippocampal damage as a result of long-term stress exposure cannot be made. To adequately capture presumed

hippocampal impairment, further research would need to utilise neuroimaging techniques able to capture the subcortical impact of stress. A further possibility to gage whether increased cortical theta activity coincided with less employment of hippocampal resources would be for animal research to obtain both cortical and depth-electrode recordings of electrophysiological activity in the hippocampus, thus investigating whether increased cortical theta activity during memory recall was mirrored by decreased theta activity in the hippocampus among highly stressed rodents.

The findings of the current study provide further evidence for the adverse effect of long-term experienced stress exposure on cognitive ageing. More specifically, they highlight the potentially damaging effect of long-term stress exposure towards hippocampal brain structures and hippocampal-cortical interactions necessary for intact cognitive performance. The behavioural findings from a paradigm thought to rely heavily on hippocampus-mediated processes, in the form of pattern separation and spatial memory, indicate that high levels of experienced stress selectively impact on elderly participants' performance, producing pronounced impairments on low and moderate interference trials as well as target detection. Behavioural shortcomings of high stress elderly participants coincided with increased levels of cortical theta ERS which may indicate a corresponding decrease of early stage hippocampal involvement necessary for the successful retrieval of newly encoded memories. The results of the present study therefore bring together multiple aspects of research (relating longitudinal work assessing the impact of stress on ageing cognition with in-vitro studies exploring how stress impacts on hippocampal cells), to arrive at a fuller understanding of how cumulative experienced stress affects ageing cognition.

Chapter 6: Cumulative Stress and Resting State Power Changes

Increased Vulnerability to Cognitive Pathologies among Aged Individuals with High Levels of Stress Exposure: An Investigation of Resting-state EEG Dynamics

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Manuscript in preparation

Abstract

The investigation of resting state EEG dynamics is widely held to provide an accurate estimation of the underlying cognitive state. As such, it is used to investigate cognitive integrity among both normally ageing individuals as well as elderly patients suffering from age-related cognitive pathologies (i.e. Alzheimer's Disease and Mild Cognitive Impairment). The adverse impact of cumulative experienced stress on cognitive ageing has been demonstrated by cross-sectional and longitudinal work as well as our own investigations addressed in the above chapters. The present study therefore aimed to explore whether the electrophysiological changes manifested by high stress elderly individuals during the completion of cognitive tasks (when compared to low stress elderly and low/high stress group young participants) were also apparent in the system at rest. To this effect, resting state power changes in the delta, theta, alpha, beta and gamma frequency ranges were obtained from 56 young and 55 elderly participants during a 2-minute eyes-closed resting EEG recording. Findings revealed significantly elevated levels of delta power among elderly individuals reporting high levels of experienced stress compared to elderly participants with low levels of experienced stress and young individuals with high and low amounts of experienced stress exposure. As increased levels of delta activity have been linked to the emergence of diseases such as Alzheimer's Disease and Mild Cognitive Impairment, these findings suggest that large amounts of cumulative stress exposure may increase the risk of developing age-related cognitive pathologies in later life.

Introduction

One of the prime challenges facing ageing research is to develop a better understanding of the neurobiological mechanisms that result in or mediate cognitive decline and its associated cognitive pathologies. As such, the discovery of neurocognitive markers, which are able to index the emergence of age-related cognitive decrements, is of increasing importance (Albert et al., 2011; Braak & Braak, 1991; Dubois et al., 2007; Nestor, Scheltens & Hodges, 2004). The discovery of such indicators, preferably ones which are easy to administer, offers large potential to efficiently address age-related cognitive decline using earlier and more targeted interventions. One marker receiving increased scientific acclaim is the recording of resting-state eyes-closed electroencephalographic (EEG) rhythms (Rossini et al., 2007). The recording of resting state EEG activity as a marker of elderly individuals' cognitive integrity offers a number of advantages, as it is low in cost, non-invasive and easy to administer, relying on equipment which is widely available to both researchers and clinicians (Babiloni et al., 2015). Abnormalities in the power spectra of different frequency ranges have been linked to altered cerebral blood flow, impaired cognitive functioning as well as reduced structural integrity of associated brain regions (Rodriguez et al., 1999a, 1999b; Sloan et al., 1995; Babiloni et al., 2013) and have gained widespread credibility as an indicator of age-related cognitive change. As such, a number of studies have used this approach to investigate differences in resting state power among healthy elderly and elderly individuals suffering from either Alzheimer's Disease (AD) or Amnesic Mild Cognitive Impairment (MCI – a clinically intermediate state between normal ageing cognition and AD) (Dierks et al., 1993; Huang et al., 2000; Ponomareva et al., 2003).

A consistent finding when comparing the resting state power of ageing individuals suffering from AD or MCI to that of healthy ageing individuals is an increase in delta (0.5 - 4Hz) power coupled with a reduction of posterior alpha (8 - 12Hz) power (Babiloni et al., 2015; Koenig et al., 2005; Jeong, 2004). Further resting-state power changes, which co-occur with either pathology, have been reported as an increase of theta and a decrease of beta power (Brenner et al., 1986; Giaquinto & Nolfe, 1986) which have been found to correlate with the severity of the disease (Kowalski et al., 2001). This picture is complemented by a number of longitudinal studies (Rae-Grant et al., 1987; Soininen et al., 1989) which likewise indicate that the EEG resting power spectra among elderly AD patients exhibit significantly increased delta and theta power in conjunction with severely reduced alpha and beta power over a follow-up period ranging from 2.5 - 5 years.

Investigations into resting state EEG power spectra have also been employed to explore changes accompanying healthy ageing (Jeong, 2004; Torres et al., 1983). Reports to this effect highlight a reduction of alpha power, particularly over temporal regions of the cortex (Busse et al., 1956) and a steady decline of individual alpha peak frequency which highlights a general age-related slowing of the alpha rhythm (Klimesch, 1999). The decrease of individual alpha peak frequency is thought to proceed in a linear fashion and was conceptualised as a 0.053 Hz decrease with each advancing year after puberty by Kropruner and colleagues (1984). Additionally, Finnigan and Robertson (2011) reported that resting theta power (4 - 6.5Hz) significantly correlated with measures of memory, attention and executive function in a sample of 73 healthy older adults. To dissociate their findings from reports that higher amounts of theta power are indicative of cognitive decline, the authors suggested the possibility of two forms of theta power: one reflecting ‘true’ theta

network activity which indicates healthy cognitive ageing; the other comprised of slowed alpha activity which has dropped into the theta frequency range and indicates cognitive impairment. Further age-related power changes among healthy elderly participant samples were reported by Babiloni and colleagues (2006) who aimed to investigate whether normal ageing produced a dominant trend in cortical EEG rhythms across the delta (0.5 - 4Hz), theta (4 - 6Hz), alpha1 (8 - 9Hz), alpha2 (10 - 12Hz), beta1 (12 - 20Hz) and beta2 (20 - 30Hz) frequency ranges. Comparing the power spectra of 108 young and 107 elderly participants, the authors reported a significant reduction of occipital delta power in old compared to young participants which coincided with a significant reduction of alpha1 and alpha2 power over parietal, occipital and temporal cortical regions. Both alpha and delta activity negatively correlated with age which led the authors to conclude that these frequencies show a decreasing trend with advanced healthy ageing.

A further branch of the ageing literature concerns itself with the effects certain impact factors have on the progression and severity of cognitive decline experienced in old age. One factor which has only recently been found to impact on the rate of cognitive ageing is cumulative experienced stress. Since then, however, cross-sectional as well as longitudinal work has demonstrated that large amounts of cumulative life stress produce pronounced behavioural shortcomings among elderly participants completing cognitive tasks (Dickinson et al., 2011; Peavy et al., 2009; Pesonen et al., 2013). The adverse effects of cumulative experienced stress on cognitive ageing have largely been the focus of our own work detailed in the above chapters. As such, we have demonstrated in a series of experiments that large amounts of cumulative life stress result in impaired performance to working memory (Chapter 3), executive control (Chapter 4) and spatial memory (Chapter 5) among

elderly but not young participants. Pairing each of our tasks with EEG recordings of oscillatory activity in frequencies related to the execution of the specific cognitive task, we were able to demonstrate that elderly individuals with high levels of cumulative stress manifested alterations in the theta, upper alpha and upper gamma frequency ranges which complemented the behavioural results and likewise indicated that cumulative stress had impacted on the successful execution of processes necessary for intact memory and inhibitory performance.

The present study aimed to investigate whether these changes in electrophysiological processing activity during task execution are mirrored by altered power differences at rest. To this effect, the two-minute resting-state EEG recordings obtained from participants (60 elderly and 60 young) before completing experiments 3, 4, 5 and 6 were analysed with regard to power spectrum differences in the delta, theta, alpha1, alpha2, beta1, beta2, gamma1 and gamma2 frequency ranges. Should the detrimental effects of cumulative experienced stress we observed in earlier studies likewise be apparent in the system at rest, significant power spectrum differences were expected to manifest for high stress elderly when compared to low stress elderly and both low and high stress young counterparts. Specifically, reductions of alpha and beta power as well as increased power in the theta frequency range were expected. Should stress exposure have resulted in increased vulnerability towards contracting age-related pathologies, an increase in delta power was hypothesised. Conversely, if the detrimental effects of cumulative stress only manifest when the system is cognitively tasked, elderly high stress participants were not expected to differ from any of the three other participant groups.

Experiment 7

Materials and Method

Participant characteristics.

Data from previous experiments was screened to determine participants who had taken part in multiple data collection sessions. Excluding data from repeating participants resulted in 56 young adult participants (Mean age = 22.3 (3.9); Range = 18 - 30 years; 28 males) and 55 elderly participants (Mean age = 68.1 (4.7), SD = 2.3; Range = 60 - 85 years; 30 males). All elderly participants scored full marks on the Mini Mental State Examination (Folstein, Folstein & McHugh, 1975) and were screened for major medical conditions (i.e. diabetes, heart disease), major neurological damage (i.e. stroke), diagnosis of a mental or psychiatric disorder (dementia, depression or anxiety disorder) and current use of psychoactive medication. Data from the same participants has been previously reported in Thesis Chapters 3, 4 and 5.

Stress and demographical measures.

The amount of cumulative stress experienced throughout the lifespan was assessed by the Social Readjustment Rating Scale (Holmes & Rahe, 1967) for elderly and the Student Life Events Scale (Clements & Turpin, 1996) for young participants. A detailed description of both scales as well as a justification for choosing both has been reported in Chapters 3, 4, and 5.

In order to account for certain factors known to affect cognitive ageing, further background information was obtained on participants' age, level of education, their amount of cigarette and alcohol consumption, their levels of exercise as well as whether they were suffering from a physical disability whose discomfort may impact on their sense of well-being at the present moment. Demographics and units of

measurement can be viewed in Table 6.1.. No stress or age differences emerged for any of the demographical variables.

Table 6.1. Pooled demographical information (experiments 3, 4, 5 & 6) of elderly and young participants split by experienced stress score.

	Elderly		Young	
	High Stress	Low Stress	High Stress	Low Stress
Group Size	27	28	28	28
Age	68.3	67.9	21.9	22.6
Gender	16 ♂	14 ♂	15 ♂	13 ♂
Education	3.25	3.57	4.07	4.25
Cigarette Consumption	0	0.7	0.32	0.06
Alcohol Consumption	2.88	2.36	2.21	2.97
Presence of Physical Disability	6	4	0	0
Exercise	2.44	2.54	2.52	2.17
Mini Mental State Score	30	30	n.a	n.a
Experienced Stress Score	899.1* (103.4)	473.6* (97.7)	351.7* (89.2)	730.4* (93.7)

Note. Education ranging from 1 (lower than High School) – 6 (University PhD degree); Cigarette Consumption: cigarettes per day; Alcohol Consumption: units per week; Exercise: hours per week; *$p < .05$ represents significant stress group differences within age groups.

Procedure.

The data for this chapter were obtained from two separate testing sessions (reported in Chapters 3, 4, & 5). Across both sessions and for all participants, 2-minute recordings of resting-state EEG activity were obtained before participants completed either of the cognitive tasks or were instructed about task specifics. Each

resting state recording was proceeded by an eye-movement calibration session (Croft & Barry, 1998).

For the purpose of this study, the resting-state condition is defined as a mode of brain activity unrelated to visual processing, task demands or goal-oriented cognitive operations (planning, problem solving or expectancies about personal matters or tasks). As such, participants were instructed to close their eyes, not to sleep and not to engage in any specific goal-oriented activity for the duration of the 2-minute recording.

Electrophysiological recording and data preparation.

Electroencephalography (EEG) was recorded from 64 electrodes placed within a soft-cap according to the 10 - 20 method of electrode positioning. Recordings were referenced to a point midway between Cz and CPz. Impedances were lowered to below 10kΩ in all electrodes before acquisition. EEG signals were recorded and analysed using a Neuroscan Synamps2 system in conjunction with SCAN 4.5 software (Compumedics, Melbourne, Australia). Data was recorded at a sampling rate of 1000Hz with a band-pass filter of 0.05 - 200Hz.

Acquired data was visually inspected and noisy data blocks, general artefacts and bad electrodes were subsequently rejected.

Principal components analysis was performed on the acquired eye-movement data to obtain components reflecting saccades and blinks. To carry out ocular artefact rejection, the acquired components were rejected from the resting-state data trace (Vigario, 199; Vigario et al., 2000). All data was re-referenced to a common average reference and was subsequently divided into the delta (0.5 - 4Hz), theta (4 - 6Hz), alpha (8 - 12Hz), lower alpha (8 - 9Hz), upper alpha (10 - 12Hz), lower beta (12 - 20Hz), upper beta (20 - 30Hz), lower gamma (31 - 42Hz) and upper gamma (43 -

80Hz) frequency range by means of a digital Fast Fourier Transform-based spectrum analysis (frequency domain, cosine windowing function).

To investigate the topographical aspects of the proposed impact of cumulative stress on elderly participants' resting state power, the 64 electrodes were then averaged into nine brain regions: left (FP1, AF3, F7, F5, F3, F1, FT7, FC5, FC3, FC1), mid (FPz, Fz, FCz) and right (FP2, AF4, F8, F6, F4, F2, FT8, FC6, FC4, FC2) frontal; left (T7, C5, C3, C1, TP7, CP5, CP3, CP1), mid (Cz, CPz) and right (T8, C6, C4, C2, TP8, CP6, CP4, CP2) central; left (P7, P5, P3, P1, PO7, PO5, PO3, CB1, O1), mid (Pz, POz, Oz) and right (P8, P6, P4, P2, PO8, PO6, PO4, CB2, O2) posterior which were used for the subsequent analyses.

Results

Preliminary analysis.

In order to investigate the impact of cumulative experienced stress on resting EEG activity among elderly and young participants, both age groups were split into high and low stress scorers based on the median split of scores from the Social Readjustment Rating Scale for elderly (Median Split value 659) and the Student Life Events Scale for young participants (Median Split value 598). A preliminary analysis was carried out to investigate the impact of individual alpha frequency (IAF) peak on results. The IAF peak is defined as the frequency associated with the strongest EEG power at the extended alpha range of 6 - 14Hz (Klimesch, 1999). As ageing is known to produce a significant drop of individual alpha peak (Klimesch, 1999), it is necessary to investigate its contribution when comparing the power spectra of different age groups. The mean IAF peak was found to be 9.37 (± .74 SD) for low stress elderly, 8.89 (± .92 SD) for high stress elderly and 10.13 (± .99 SD for low; ± 1.07 for high) for both low and high stress young participant groups. A 2 (Stress: high

vs. low) x 2 (Age: young vs. old) ANOVA found a significant main effect of age ($F_{1,106} = 28.9$, $p < .001$) which indicated that IAF was higher in young relative to elderly participants. However, no main effect for stress and crucially no stress by age interaction reached significance ($p_s > .05$), therefore indicating that IAF will not have impacted on any stress by age effects in the further EEG analysis.

Electrophysiological analysis.

The effects of cumulative experienced stress on resting state EEG activity was subsequently analysed by means of a factorial ANOVA using the median split of both age groups into high and low stress scorers as detailed above. Data were therefore analysed by a 3 (Sagitality: frontal vs. central vs. posterior cortical regions) x 3 (Laterality: left vs. mid vs. right cortical regions) x 2 (Age: young vs. old) x 2 (Experienced Stress: high vs. low) mixed ANOVA in which the first two factors acted as the within-subjects components. A separate model was run for each of the nine frequency bands under investigation.

Delta power.

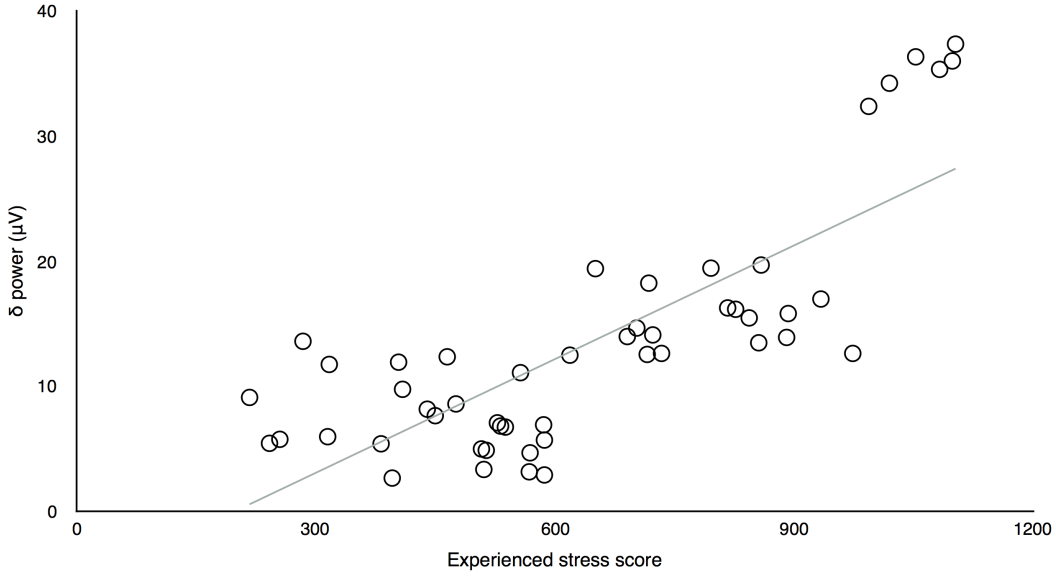
For the delta frequency range, analysis revealed a significant main effect of age ($F_{1,107} = 10.47$, $p = .002$) which indicated that elderly participants manifested higher levels of delta power compared to young individuals. Results further revealed a main effect of stress ($F_{1,107} = 8.46$, $p = .005$) which demonstrated that high stress group participants showed higher levels of delta power at rest compared to low stress counterparts. Both main effects were qualified by a significant age by stress interaction ($F_{1,107} = 4.54$, $p = .036$). To decompose this interaction, four relevant group comparisons with corrections (Bonferroni adjusted p-value 0.01) were undertaken. These indicated significant differences when comparing high stress elderly and high stress young participants ($F_{1,107} = 13.42$, $p < .001$) and for

comparisons between high stress elderly and low stress elderly ($F_{1,107} = 11.67$, p= .001). In both instances, elderly high stress participants were found to manifest significantly higher delta power over the entire scalp (see Figure 6.2.). No further follow-up comparisons reached significance ($p_s > .05$).

While investigating the distribution of scores highlighting the magnitude of delta power among participant groups a number of outliers became apparent. In order to objectively discern these outliers, a criterion was defined using Tukey's method (Tukey, 1977). This procedure specifies a range using the lower (Q1; 25th percentile) and upper quartile (Q3; 75th percentile), as well as the interquartile range (interval between Q1 and Q3) in the following formula to determine the lower boundary: Q1 – (r x IQR) and the upper boundary: Q3 – (r x IQR). Common r factors have been reported as 1.5 and 2.2 (Hoaglin, Iglewicz & Tukey, 1986; Marques de Sá, 2007). Using the r factor of 2.2, the current study identified six outliers among the high stress elderly participant group (see Figure 6.1.). However, investigating the raw experienced stress scores of these six individuals found that all had exceptionally high experienced stress scores, all of which fell well into the upper fourth quartile (Mean high stress group 899.1, Mean of outliers 1004).

Therefore, the large amounts of delta power may not be atypical of the participant sample but rather the result of increased damage due to excessively high amounts of cumulative stress exposure. Therefore, the six participants were included in the current analysis.

Figure 6.1. Correlation between raw experienced stress scores and eyes-closed resting state delta power.



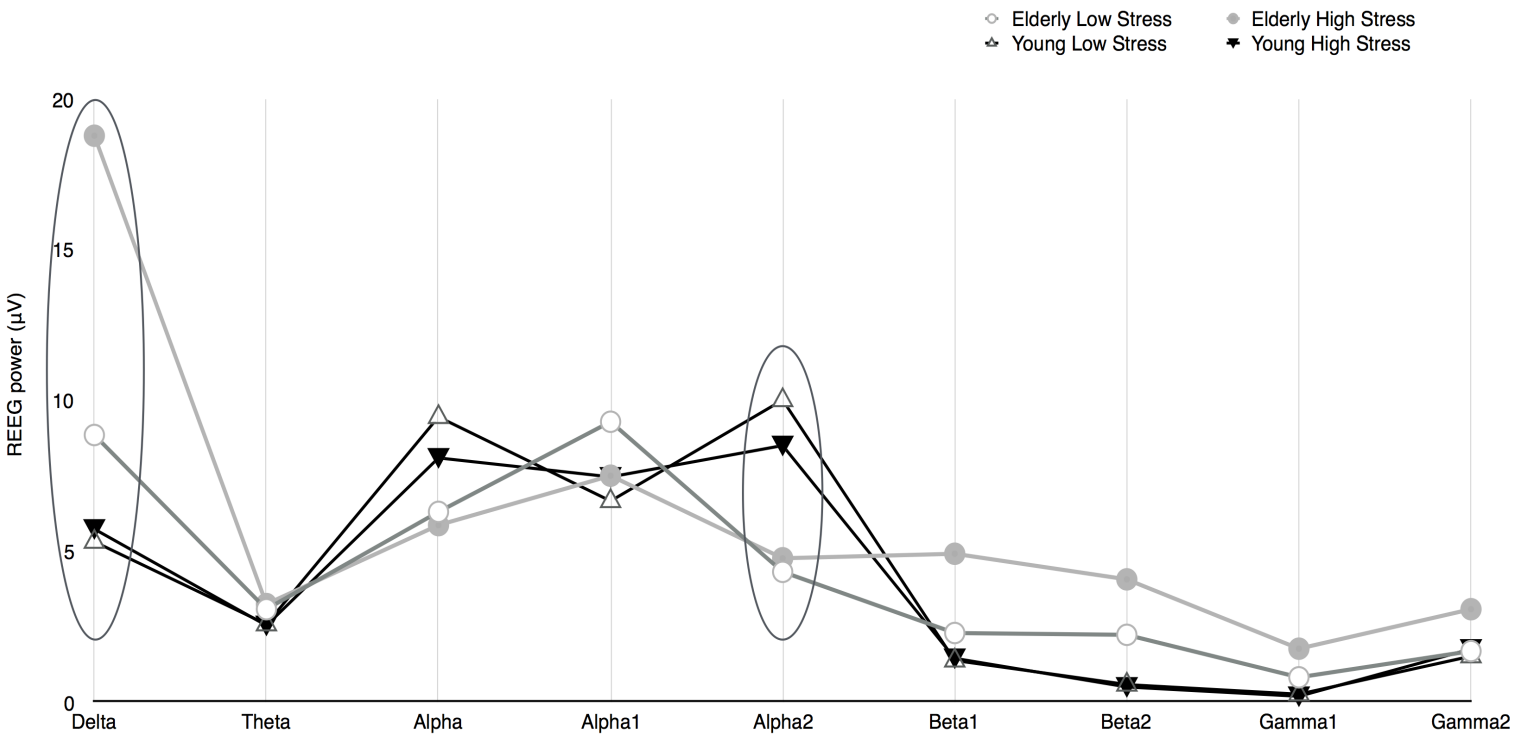
Note. Trend line indicates a moderate positive correlation between raw experienced stress scores and resting delta power.

Upper alpha power.

Results of the upper alpha frequency range revealed a main effect of age ($F_{1,107} = 8.99$, $p = .003$) which indicated that elderly participants showed significantly lower upper alpha power when compared to young counterparts (see Figure 6.1.). No further main effects or interactions reached significance ($p_s > .05$).

Furthermore, no main effects or interactions reached significance for any of the other frequency bands.

Figure 6.2. Eyes-closed resting-state power distributions among elderly and young stress groups for each of the nine frequency bands of interest.



Note. Results indicated a main effect for the upper alpha frequency (elderly < young) and a stress by age interaction for the delta frequency which demonstrated that elderly high stress individuals showed significantly higher levels of delta power compared to all other groups.

Discussion

The present chapter explored whether the age differences occasioned by high amounts of cumulative experienced stress we observed in earlier studies were likewise present in the system at rest. To this effect, the two-minute resting-state recording sessions obtained for earlier studies were investigated for power changes in the delta, theta, upper /lower alpha, beta and upper/lower gamma frequency ranges.

Results produced a main effect of age for the upper alpha frequency range, highlighting that, relative to young participants, elderly individuals manifested globally reduced levels of alpha power. Findings further revealed a significant age by stress interaction, demonstrating that elderly high stress participants manifested significantly higher levels of delta power over the entire cortex at rest when compared to both low stress elderly and high stress young participant groups.

Findings respecting the upper alpha range are in line with past investigations into both healthy (Busse et al., 1956) and pathological (Babiloni et al., 2015; Koenig et al., 2005) cognitive ageing, both of which report decreases of resting alpha power among elderly individuals. As such, the present alpha results correspond to reports about the general slowing of the EEG, of which a reduction of resting state alpha power is a common characteristic (Klimesch, 1999).

Conversely, the increase of resting delta power observed among high stress elderly individuals is not what one would expect to find when investigating healthy ageing individuals. As such, past work has reported that normally ageing individuals exhibit a linear decrease of delta power with advancing years which is significantly reduced when compared to young participants (Babiloni et al., 2006). Increases of resting state delta power are, however, a prominent occurrence among elderly individuals suffering from age-related cognitive pathologies such as Alzheimer's

Disease (AD) or Mild Cognitive Impairment (MCI) (Rae-Grant et al., 1987). For example, Soininen and colleagues (1989) found that among a subset of elderly patients suffering from AD, the progression of the disease over the course of one year was associated with significant increases of resting state delta power. At this stage, it is important to note that among individuals suffering from mid to early stages of either pathology, increases of resting delta power often coincide with impaired global cognitive function as evaluated by the Mini Mental State Examination (MMSE; Jeong, 2004; Rodriguez et al., 1999a). As this thesis investigates the effect of cumulative life stress on healthy ageing, all elderly participants were screened against the presence of undiagnosed cognitive pathologies by completing the MMSE. Pre-screening allowed us to determine that all participants scored full marks on the test. Taking this into consideration, the elevated levels of delta power manifested by high stress elderly participants are unlikely to signal the presence of a fully developed cognitive pathology. However, it could be interpreted as an indication of early stages of pathological development or, in line with one of our hypothesis, as a marker indexing increased vulnerability towards contracting age-related pathologies. As such, present findings highlight that the adverse effects of high cumulative life stress exposure are also apparent in the brain's resting-state activity and form a further indication of the detrimental impact high levels of cumulative stress exert on cognitive ageing. This is in line with both cross-sectional and longitudinal studies reporting the adverse effects of cumulative stress on cognitive performance among elderly individuals (Dickinson et al., 2011; Peavy et al., 2009) as well as our own work discussed in earlier chapters which indicates that, as well as cognitive shortcomings, large amounts of stress exposure affect the underlying electrophysiological processing patterns associated with the successful execution of

cognitive tasks. Moreover, it corresponds to past work relating experienced stress to cognitive pathologies (Magri et al., 2006). For example, Daulatzai (2014) relates the experience of stress to an increased risk of developing Alzheimer's Disease via a mechanism of peripheral neuroinflammation which induces stress and depression via a complex neurochemical interplay within the central nervous system. According to the author, stress and depression in turn lead to neuronal dysfunction and apoptosis which enhance the individual's vulnerability to contracting this particular cognitive pathology.

Conclusions and limitations.

The present study sheds further light on the way cumulative stress exposure impacts on ageing cognition. Results complement findings discussed in earlier empirical chapters by further highlighting the adverse effects large amounts of lifetime stress exert on cognitive integrity in old age. Investigating age- and stress-related changes in the system at rest explores this topic from a different angle and thereby adds to the picture emerging in previous chapters by demonstrating that elderly members of the high experienced stress group manifest electrophysiological resting state patterns which are widely taken as indicators of, or increased susceptibility towards, developing cognitive pathologies common to ageing individuals (Soininen et al., 1989; Rae-Grant et al., 1987).

What must be noted at this point is that the significant stress by age interaction observed for the delta frequency range was in part driven by six elderly members of the high stress participant group who showed very high levels of resting delta power when compared to the larger body of group members. Applying an objective statistical procedure to screen for the presence of outliers placed these six values outside of the specified range. However, investigation of the raw experienced

stress scores revealed that these participants' high levels of delta power were mirrored by exceptionally high experienced stress scores. Further investigating responses made by these individuals highlighted that their scores were largely due to these participants experiencing profoundly traumatic and stressful incidents such as the 'Death of a spouse or close family member' or 'Experiencing a major personal injury or illness' as well as incidents which occasion a high amount of prolonged stress and worry such as 'Major monetary trouble', each of which carries a high individual stress score. We would therefore argue that rather than being atypical of the high stress participant group, these six individuals may be manifesting increased damage sustained by excessively high levels of cumulative stress exposure.

Findings to this effect highlight the importance of extending investigations to include aged individuals who have suffered from the experience of severely stressful traumatic events or have been subjected to high levels of chronic stress for a prolonged period of time. The increased symptoms, which may possibly be displayed by these individuals, would provide further support for the detrimental effect stress exerts on the ageing organism and deepen our understanding of the domains which are primarily affected. The present thesis refrained from taking into account chronic and traumatic stressful experiences, as past evidence linking stress to cognitive ageing decline has reported this for cumulative life stress. A further consideration lay in the high co-occurrence of traumatic and chronic stress with conditions such as post-traumatic stress disorder (PTSD) and reduced bodily health which would make it harder to dissociate the impact of stress on cognitive integrity from the shortcomings produced by the above disabilities. However, present results indicate that investigating the symptoms produced by highly impactful stressful experiences (in

the form of chronic and traumatic stress) may add to our understanding of the way in which stressful experiences affect cognitive integrity and cognitive ageing.

In conclusion, this study complements and extends earlier findings by indicating that high amounts of cumulative stress exposure may occasion a predisposition among elderly individuals towards developing cognitive pathologies. The present findings therefore add to previous work advocating the detrimental impact of cumulative lifetime stress and further highlight the effectiveness of resting state power as a means to investigate ageing cognitive decline and the impact of environmental factors that may accelerate it.

Chapter 7: General Discussion

General Discussion

This final chapter will summarise the research presented in chapters 2 to 6 of this thesis as well as highlight the methodological and theoretical contributions of this work to the field of ageing cognition and stress research. Limitations, practical implications as well as future directions highlighted by this body of work will likewise be discussed and will form the concluding comments of this thesis.

Summary of Research

The experimental work conducted in the scope of this PhD programme was presented across five chapters (2 through 6). Apart from the 2nd experimental chapter, each of these was conceptualised and written with the intent to submit them to appropriate peer-reviewed journals for publication. Each chapter therefore constitutes and independent piece of research, contributing to the relevant body of the wider literature.

Chapter 2 was designed to explore the different states of acute stress reactivity among elderly and young participants. Across two studies, age differences in behavioural (experiment 1) and electrophysiological (experiment 2) performance markers, manifesting during exposure to acutely stressful situations, were compared between age groups in order to reliably dissociate these from later exploration into the effects of long-term cumulative stress exposure. In Chapter 3, which was recently published in the Journal Neurobiology of Aging (Marshall, Cooper, Segrave & Geeraert, 2015), the impact of lifetime cumulative stress exposure on elderly individuals' performance in the domain of working memory (WM) was investigated. To this effect, oscillatory and behavioural responses among elderly and young participants were compared in a task that required the simultaneous co-ordination of

multiple aspects relating to working memory (experiment 3) as well as a task measuring the same WM stages in isolated, serial fashion (experiment 4).

Chapter 4 extends the working memory findings offered by the 3rd chapter into the domain of executive control (experiment 5), investigating whether high cumulative stress exposure exacerbates behavioural shortcomings in inhibitory control known to manifest among ageing individuals (Mund et al., 2012; Pettigrew & Martin, 2014). Chapter 5, which was recently published in the Journal Hippocampus (Marshall, Cooper& Geeraert, in press) follows-up on findings highlighting the structural damage chronic and cumulative stress have been shown to produce in certain areas of the hippocampus by exploring elderly and young individuals' behavioural performance on a spatial memory paradigm designed to capture hippocampal impairment (experiment 6). In order to gage hippocampal involvement, cortical theta oscillations during task execution were measured, as these have been shown to reflect the extent of hippocampal-cortical interactions during memory formation (Takehara-Nishiuchi et al., 2012). The 6th chapter complements the above work by investigating whether electrophysiological differences produced by high levels of cumulative stress exposure among elderly individuals during the performance of cognitive tasks, were likewise apparent when the system is at rest. Experiment 7 therefore pooled the data from a resting EEG recording session collected from participants completing experiments 3 to 6 in order to analyse the way in which stress affected the expression of absolute power spectra among elderly and young individuals at rest. The work presented across these 5 empirical chapters offers a number of methodological and theoretical contributions to the field of cognitive ageing and stress research. These will be discussed in the following sections.

Methodological Contributions

The core methodological contribution from research presented in this thesis comes from our choice to pair behavioural measures with cortical, electrophysiological recordings. As highlighted in the introduction, the impact of stress on ageing cognition has only recently captured scientific interest. Thus, so far, work exploring the impact of stress on elderlies' cognitive performance has remained on a behavioural level. Within the neuroscientific domain, pairing the execution of cognitive paradigms with measures of the cortical oscillatory patterns they produce or modulate has had a profound impact on our understanding of which processes in the brain facilitate cognitive navigation of our general surroundings and specific tasks (Berger et al., 2014; Enriquez-Geppert et al., 2014). Conversely, this knowledge also allows us to approach the interplay between cognitive oscillatory processes and behaviour from the opposite angle: knowledge of which cognitive process is facilitated by a particular oscillatory pattern in the brain enables inferences about the way behaviour is affected or compromised based on the change observed in the oscillatory response. Since the EEG was first discovered in humans by Hans Berger in the 1920s (Berger, 1929), vast amounts of research have been undertaken into how oscillations in the different frequency bands relate to performance on various cognitive tasks. Despite a constantly developing literature and remaining controversy as to the cognitive contributions of certain frequency bands, a large and stable reference body has been established in subsequent decades which span nearly a century. As such, it is possible to relate, for example, increased oscillatory expression in the alpha band to cognitive control processes (Klimesch, 2012) or an increase of gamma activity in conjunction with theta to memory binding mechanisms (Sauseng et al., 2009; Roux & Uhlhaas, 2014). Pairing both aspects in this body of work has

therefore enabled us to move beyond simply determining a general behavioural deficit. Instead, we were able to pinpoint specific cognitive executions that have been compromised among elderly high stress individuals. For example, we were able to demonstrate that in a task that clearly distinguishes between different memory stages, large amounts of stress impact on elderlies' ability to shield memory traces from task-irrelevant information during the maintenance phase (Chapter 3) which was indexed by reduced upper alpha activity during this particular memory period.

A second methodological aspect, which we necessarily had to address, based on our use of EEG was our choice of behavioural paradigm. Thus far, the behavioural implications of heightened stress exposure on ageing cognition have been assessed with established cognitive test batteries such as the Mini Mental State Examination (MMSE) (Folstein, Folstein & McHugh, 1975), the CERAD cognitive test battery (Morris et al., 1989) or the Wechsler Memory Scale (Wechsler, 1955) (Dickinson et al., 2011; Tschanz et al., 2013). Such test batteries usually involve the completion of various cognitive tasks spanning category fluency, verbal learning and numerous short sub-tests of memory and inhibitory control which are usually administered in pen and paper format in a one-on-one test scenario between the experimenter and the participant. This set-up involves relatively few trials for any particular task and a multiple-choice response system in which participants are able to take their time before answering (Pesonen et al., 2013). In order to arrive at meaningful electrophysiological data, we required tasks that spanned a large number of trials with distinctly separated time periods which could further be completed independently by the participant. We therefore chose tasks which assessed the cognitive aspects implicated by previously used psychometric tests but also corresponded to the format we required for our electrophysiological data collection. As such, work presented in

chapters 3 through 5 demonstrates that paradigms with a fast-paced, continuous response format produce findings akin to the ones established by previously used cognitive test batteries and can be used effectively to study the impact of cumulative stress exposure on cognitive ageing. Our work therefore broadens the repertoire of paradigms which produce the desired stress by age effect and, most importantly, advocates the use of neuroscientific tools to gain a deeper understanding of the detrimental effects of cumulative stress.

Theoretical Contributions

This thesis offers a number of theoretical contributions which will be addressed in the following section according to the chapters in which they occur.

With respect to Chapter 2, our investigations into the way effects of acute stress exposure differ with advancing age highlight that the increased vulnerability to acute stress attributed to elderly individuals may not be universal to the entire ageing population. To date, researchers investigating the effects of acute stress in advanced age have pointed out exacerbated performance impairments among elderly individuals completing immediate declarative memory tasks (Kukolja et al., 2008; Hidalgo et al., 2014). Our behavioural as well as our EEG findings presented in Chapter 2 do not correspond to this literature, as we find no change to performance and only limited electrophysiological occurrences which are modulated by both acute stress and age. Conversely, our results support work exploring age differences to acute stress sensitivity in the domain of long-term memory where for example work by Pulopulos and colleagues (2013) has likewise found no performance differences between elderly and young individuals modulated by acute stress exposure. Similarly, the same group of researchers report that acute stress does not affect the executive component of working memory in older participants (Pulopulos et al., 2015).

Therefore, the relationship between age and acute stress vulnerability may not be as straightforward as originally assumed. Our findings thus add to this emerging picture by indicating that high performing elderly participants may differ from low performing counterparts by demonstrating intact resistance to the adverse effects of acute stress exposure. Elderly participants volunteering for the work conducted throughout this thesis stem from a cohort of individuals with high levels of education who keep both physically and mentally active (recruited from University of the 3rd Age and exercise groups). Their high performance is apparent in discovering only a marginal main effect of age for one set of memory scores in experiment 1, thus showing that elderly participants' performance was only slightly reduced compared to young individuals on a moderately demanding memory task (no ceiling effects). Our findings thus highlight the possibility that the increased acute stress vulnerability among elderly participants may in fact be selective to low performing elderly individuals.

Chapter 3 addresses a number of controversies within the small but expanding literature relating high levels of cumulative life stress to working memory (WM) impairments in old age. Within this domain, there is an on-going debate as to whether the sum total of stressful events is the best predictor of ageing cognitive decline or whether only certain stressful experiences exacerbate cognitive deficits in old age (Comijs et al., 2011). To this effect, Rosnick and colleagues (2007) have argued that certain stressful events may have an enhancing effect on cognitive performance, while others have a debilitating influence. The authors thus argue that the aggregate score of stressful experiences will result in events cancelling each other out, thereby negating the effect. A similar line of debate relates to whether the experience of a stressful event per se has detrimental consequences for ageing

cognition or whether the subjective experience of the event's gravity and impact is more meaningful in this respect (Sands, 1981). A final point to note respecting the existing studies into the effects of cumulative stress and age-related working memory impairments is that, while past cross-sectional studies have accounted for educational level, they have not controlled for a number of health behaviours which have been shown to affect the rate of cognitive decline in old age, such as for example alcohol and cigarette intake (Kalmijn et al., 2002) or physical exercise (Kimura, Yasunaga & Wang, 2013). We addressed all of these issues in the 3rd chapter by investigating the impact of cumulative stress on ageing working memory performance while controlling for the five most prominent factors implicated in the ageing literature as well as participants' perceived stress reactivity. Thus, we were able to establish that the aggregate score of stressful experiences acted as a significant predictor of elderlies' WM impairments when controlling for compromising factors as well as individuals' subjective stress appraisal. Findings therefore support the general body of work (Dickinson et al., 2011; Peavy et al., 2009) highlighting that the sum total of experiences, regardless of subjective appraisal have a negative impact on the age-related rate of WM decline while ruling out prominent factors that could have confounded earlier findings.

Chapter 4 carried two main theoretical objectives. Firstly, it extended the findings regarding stress and aged WM performance into the domain of executive inhibitory control. Intact inhibitory performance is known to play a key role for successful WM execution (Hasher & Zacks, 1988). Based on this and on our EEG findings from Chapter 3, which indicate that reduced levels of inhibitory alpha are related to elderly high stress participants' impaired WM performance, we believed investigating whether cumulative stress also affected elderlies' executive functioning

formed a worthwhile endeavour. Our findings in this regard indicate that high levels of cumulative life stress seem to produce a general inhibitory deficit among elderly individuals extending either to the attentional or sensorimotor domain. Our results are hereby the first to show that high levels of stress can encroach on more cognitive domains and capabilities than previously demonstrated. We were hereby able to offer a meaningful extension to the developing literature concerning stress and cognitive ageing. The second objective of Chapter 4 was to address an on-going debate about age differences manifesting for the Flanker paradigm (Eriksen & Eriksen, 1974). Age-related shortcomings in executive control are an established phenomenon and a stable finding across multiple executive paradigms (Kok, 1999; Proctor et al., 2005). However, with regard to the Flanker task, findings are mixed (Zeef et al., 1996; Nieuwenhuis et al., 2002; Hsieh, Liang & Tsai, 2012) and have been attributed to elderly peoples' compensatory mechanisms such as a reduced attentional field and increased focus on the specified target location which may carry particular advantages for a Flanker task set-up (Wild-Wall et al., 2008). The experiment presented in Chapter 4 aimed to bring more clarity to this issue and indeed, within our data, we found a sub-group of elderly individuals (low levels of stress) whose performance on the task did not decline, whereas that of a second elderly sub-group (high levels of stress) showed considerable performance decrements in the form of increased reaction times. Paired with our electrophysiological data demonstrating a break-down of inhibitory alpha activity among the low performing elderly participant group, this indicates that rather than compensatory mechanisms employed by high performing elderly individuals, discrepant findings are due to certain sub-groups of elderly participants experiencing increased rates of inhibitory impairments that extend to domains in which ageing inhibitory performance usually remains unaffected. Our

findings were hereby able to provide a possible explanation for controversial findings within the ageing inhibition literature, which we suggest form a further step towards resolving this discrepancy.

Turning to the research presented in Chapter 5, we aimed to combine the theoretical knowledge about the adverse effects of stress offered by multiple scientific domains. To this effect, we drew on two main research findings: the first stems from in-vitro cell studies demonstrating that stress exposure results in significant cell damage to neurons residing in areas CA3 and the dentate gyrus of the hippocampus (Miller & O'Callaghan, 2003); the second is firmly rooted in the behavioural domain and indicates that in aged humans, higher levels of stress exposure coincide with reduced cognitive capabilities (Peavy et al., 2009; Dickinson et al., 2011). To the best of our knowledge, these two approaches have not yet been combined and merging them constitutes a significant advancement towards understanding the way in which stress impacts on the cognitive integrity and well-being of the human organism. The findings offered by this chapter highlight that high stress elderly individuals manifest behavioural impairments on a paradigm known to rely on hippocampal integrity while displaying cortical electrophysiological markers (excessively heightened levels of theta synchronisation), indicating impaired hippocampal functioning. Our measure of hippocampal involvement remains an indirect marker in this instance but nevertheless, our method as well as our findings demonstrate the merit of integrating both approaches. In general, combining the neuroscientific with the cognitive behavioural approach to study the interplay between life stress and cognitive ageing has been the overarching aim of the work presented in this thesis. Merging theoretical knowledge of this issue offered by both domains constitutes a significant progression in our understanding of this phenomena and we hope that following publication, this

work will inspire future research to approach the way in which stress impacts on cognitive ageing from a multi-disciplinary background, drawing on tools and approaches from cognitive/behavioural, biological as well as neuroscientific domains.

In a similar vein, research presented in the final 6th chapter once more highlights the merit of exploring the impact of life stress on cognitive ageing using neuroscientific tools. Up to this point, the neurophysiological markers of damage occasioned by high levels of cumulative stress have remained unexplored. Our findings, indicating that high stress elderly individuals manifest aberrant electrophysiological activity both at rest and when cognitively taxed, provide the first theoretical indication that studying the impact of life stress with neuroscientific measures offers meaningful insight into the way stress affects the human ageing process.

Limitations

The experiments introduced in this thesis provide consistent and stable results, indicating that cumulative experienced stress acts as a viable risk factor for accelerated cognitive decline in old age. However, a number of potential caveats need to be discussed in relation to the presented work. These will be introduced in the following section.

A primary concern to note is that the work undertaken in the course of this PhD investigates a longitudinal phenomenon (the impact of experienced stress on cognition as it accumulates over the course of a lifespan), using cross-sectional data sampling. From our method, it is thus impossible to infer a direct line of causation or account for the possible influence of all mediating factors (known & unknown) which impact on cognitive ageing. As such, despite carefully considering the prominent impact factors we wished to control for in our experiments (see Chapter 3), a number

of mediators, such as diet or living environment, were not assessed and could have influenced the reported findings.

A further point to highlight is that the questionnaires we used to measure cumulative experienced stress sum stressful experiences over a pronounced time span based on the assumption that the impact of events is constant over each time point. However, stressful events during childhood, adolescence or old age, in which coping resources are not fully developed or depleted (Lupien et al., 1997), may have a more formative or detrimental effect compared to experiences encountered during middle age. On a similar note, both questionnaires used to assess cumulative experienced stress are biased towards events taking place from young adulthood (i.e. 'Failing a University course') to old age (i.e. 'Death of spouse') and do not capture stressful events occurring in childhood and early adolescence. Given the promising findings of our work so far, possible extensions thus lie in sampling events over the entire lifespan and exploring whether the times at which they are encountered affect their impact on cognitive health. This work would strengthen the argument that the effects of experienced stress increase steadily and consistently over the course of human life.

With regard to the electrophysiological data, research into the way stress affects the brain has been prolific in highlighting its adverse effect on the hippocampus (Lupien & McEwen, 1997; Sapolsky & Meaney, 1986; Miller & O'Callaghan, 2003). Given these findings, this has been addressed by the current thesis in Chapter 3 and more specifically in Chapter 4. However, despite indications that oscillatory activity recorded over the scalp surface in the alpha (Babiloni et al., 2009), gamma and theta (Bastiaansen & Hagoort, 2003) frequency ranges is reflective of hippocampal-cortical interactions, and can thus provide insight into the way stress affects hippocampal integrity, this remains an indirect measure. As such, we are

unable to make any definite claims about the subcortical effects of prolonged exposure to experienced stress in our work. In order to directly address the effects of cumulative stress on the hippocampus and link this to the pronounced behavioural impairments observed across our experiments, subsequent investigations will need to utilise neuroimaging tools to capture the detrimental effects of stress on a subcortical level.

On a similar note, another limitation associated with EEG is that of source localisation. Described as the inverse problem (Gramfort et al., 2013), source localisation issues relate to the difficulty of capturing the spatial source of an EEG signal which is supposedly generated by a vast number of cortical pyramidal neurons outnumbering the recording EEG sensors on a large-scale basis. In a mathematical sense, the signal captured by the EEG sensors is therefore ill-posed and underdetermined (Nummenmaa et al., 2007; Grech et al., 2008), a problem which is further exacerbated by the signal dispertion produced by passing through the various conductive tissues (e.g. the brain, cerebro-spinal fluid, meninges and skull; Dickter & Kieffaber, 2014) before reaching the EEG sensors. Given our argument in Chapter 4 that frontal and temporal theta activity is indicative of hippocampal-cortical communication, this limitation must be noted, despite past studies highlighting the EEG's validity as a tool for localising cognitive functions (Burgess & Gruzelier, 1997). Our argument in this regard is qualified by a chain of reasoning which rests on a number of in-vitro cell and animal studies demonstrating that hippocampal neurons oscillate predominantly at the theta frequency range (Hansen, Nedergaard & Andreasen, 2014; Tsutajima et al., 2013) and have the propensity to entrain cortical cells to the hippocampal theta rhythm (Sirota et al., 2008). Additionally, manifestation of theta oscillations over distinct cortical regions has been linked to

enhanced memory performance on tasks believed to highly depend on hippocampal involvement (Shi, Gao & Zhou, 2015). However, once again, the use of neuroimaging equipment such as fMRI (possibly in conjunction with EEG recordings) could lend additional weight to the argument made in Chapter 4.

Practical Implications

The research findings presented in the scope of this thesis have very clear practical and applied implications. Results of four empirical chapters identify cumulative life stress as a risk factor which accelerates the rate of cognitive ageing and increases the vulnerability of aged individuals toward contracting age-related cognitive pathologies. Over the last century, the expected lifespans of western individuals have been steadily increasing. Indeed, the current average age of a British individual is estimated at 79 years for a male and 82.8 years for a female by the UK office for national statistics (2012). This steady increase of population ageing has had profound implications for our healthcare and welfare systems, as well as producing an ever growing proportion of individuals, whose well-being and independence will benefit from identifying factors which can lead to reduced cognitive and bodily health in later years. As such, it is imperative for ageing research to identify ways in which individuals can preserve their bodily and cognitive health in order to retain their independence into the high old age we have come to expect. While it is of course not always feasible to avoid stressful experiences, in certain situations it is possible to choose a course of action which carries less potential for stressful encounters. As such, we hope that the results presented in this thesis will enable individuals on a personal level to make better-informed decisions about how to weight their priorities when making decisions about which lifetime goals to pursue. Certainly, on a corporate as well as an educational level, the present results advocate the importance

of promoting less competitive and stressful working and learning environments, as these will not only impact on individuals' present mental well-being, but may also produce long-term damaging effects on cognitive health in later life.

Future Directions

Having identified the detrimental impact cumulative life stress exerts on ageing cognition, the next logical step lies in exploring possible ways by which we can protect against its damaging effects. In this regard, two avenues seem particularly worth exploring. One lies in the intrinsic way with which individuals approach a stressful situation. A large body of scientific work has been undertaken with regard to identifying different coping strategies and within the stress literature, a clear distinction is drawn between two specific approaches: coping directed towards managing or altering the problem causing distress and coping geared towards regulating the emotional response to the problem. These two major styles have been recognised by a number of researchers (Kahn et al., 1964; Mechanic, 1962; Murphy, 1974) and have been termed problem-focussed and emotion-focussed coping respectively (Lazarus & Folkman, 1984). Emotion focused coping is thought to cover a wide range of approaches, the largest area encompassing cognitive processes directed towards lessening experienced distress. These include strategies of avoidance, minimisation, distancing and selective attention and seem to derive from a shared basis of defensive processes. Conversely, problem focused coping often reflects efforts aimed at defining the problem, generating alternative solutions or weighing cost and benefit to determine a course of action. However, strategies can also be of an inward nature, encompassing motivational or cognitive changes such as altering aspiration levels and finding alternative means of gratification (Kahn et al., 1964). Since their discovery, a number of reports (Aldwin & Revenson, 1987;

McCrae & Costa, 1986) have identified problem-focussed coping as the more adept strategy, as in the majority of situations, approaching the problem 'head on' is the more effective approach towards erasing a disquieting element and restoring equilibrium. As such, employing a problem-focussed approach coincides with increased levels of well-being, whereas a more emotion-focussed style leads to increased reports of behavioural and psychological problems among both adults and children (Compas et al., 1988; Chang, 2002). Given these findings, it would be worthwhile to investigate whether individuals who employ a more problem-focussed coping style when dealing with stressful situations suffer less from the adverse effects of stress exposure in old age, as they were more adept at effectively dealing with the stressful situation when it arose. In a similar vein, exploring whether intervention programs such as stress-management courses or meditation programs targeted at alleviating stress and training individuals towards a calmer, more balanced approach to stressful encounters are an effective way of reducing or counter-acting the adverse effects of stress on cognitive ageing. Should either of these approaches produce promising findings, this would open up exciting possibilities for future research as well as carry a high applied value towards promoting the well-being of individuals.

A further avenue of this research that warrants further exploration is a more detailed look at the nature of stressful life experiences, possibly differentiating the way in which they affect cognitive integrity in old age. The work presented in this thesis has produced promising findings using the aggregate score of stressful experiences. While our results certainly do not indicate that using the sum total of stressful experiences negates their effect on cognitive capabilities (Rosnick et al., 2007), it must be noted that within the stress literature the perceived controllability and personal relevance (Miller, 1979) of the event are one of the key aspects that

determine the gravity of a stressful event. Additionally, in recognition of the fact that both positive as well as negative events can produce stress, the Social Readjustment Rating Scale (Holmes & Rahe, 1967) as well as the Student Life Events Scale (Clements & Turpin, 1996) include both types of items. Unfortunately, the amount of positive items in both scales is too limited to allow a contrasted analysis of how the aggregate score of positive stressful experiences compares against the effects of the aggregate score of negative experiences. However, a useful way of extending the current findings would lie in undertaking such a comparison while also taking into account participants' perceived gravity and controllability of each stressful event. This could be achieved by including two further rating scales for each event or by considering the use of semi-structured interviews. The two possibilities for future research, highlighted in this section, form only a subset of avenues which could be further explored. For example, we hope that our methodological choice will inspire much future research into the neurocognitive markers of the effects of stress on cognitive ageing.

Conclusion

The work detailed in above chapters has substantially advanced the to date concise body of work investigating the effects of cumulative life stress on ageing cognition. It has done this by providing a significant number of theoretical and methodological contributions to this field.

Empirical findings across five experiments highlight the detrimental consequences that high levels of cumulative stress exposure have for cognitive performance in old age. Our findings thus strengthen existing work, demonstrating that the aggregate score of experienced stressful events significantly impairs elderly individuals' working memory performance. In addition, our results advance findings

in this domain by being the first to demonstrate that the performance impairments associated with high levels of cumulative stress in old age extend to the domains of executive inhibitory control as well as spatial memory. The latter findings are hereby the first to provide an empirical link between in-vitro cell and animal studies, investigating the impact of stress on the hippocampus, and cognitive work exploring behavioural impairments on hippocampus-dependent memory tasks. Furthermore, our results indicate that cumulative stress may form a risk factor for contracting age-related cognitive pathologies. The work presented in this thesis thus highlights that high amounts of cumulative stress exposure can both impair cognitive operations in healthy elderly populations as well as result in increased vulnerability to contracting age-associated cognitive diseases.

Our work was furthermore the first to pair behavioural investigations with EEG recordings. Our findings in this regard demonstrate that the effects of cumulative stress are apparent in the underlying cortical operations facilitating cognitive performance and strengthen behavioural findings by demonstrating that impaired performance scores coincide with changes to frequency bands associated with their successful execution.

Research presented in this thesis therefore has the potential to further scientific discussion on the impact cumulative stress exerts on ageing cognition and inspire future research. Our findings advocate the use of cross-disciplinary measures (using neuroscientific tools in conjunction with psychometric and cognitive measures) to study ageing phenomena and provide a number of avenues for future research to explore. These need to be investigated and broadened in order to arrive at a detailed understanding of how stress affects our well-being and cognitive health in

old age. Based on this, we can begin to devise informed approaches with which to protect ourselves from its detrimental impact.

Final Remarks

I would like to conclude this thesis by saying it is my hope that the work I have undertaken in the course of this PhD and which I have presented in this thesis will inspire and promote future research into the way in which lifetime experiences shape our cognition and influence the way in which our brain develops and changes. In so many ways, we still stand at the beginning of unravelling the brain's many mysteries and I hope that my work signifies a small but meaningful step in the right direction. When I first heard about the plasticity of the brain, I found the idea that we are actively shaping the neural pathways that translate into the person we are as inspiring as I found it incredible, and so I would like to conclude with some favourite words which came to my mind at the time I first heard about this:

"Alas, I shall be telling this with a sigh, some day ages and ages hence
Two roads diverged in a wood and I, I took the one less travelled by
And that has made all the difference"
− Robert Frost

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Appendix

Items for demographics questionnaire

age

gender
(male, female)

education
(< high school, high school, trade school, bachelor degree, master degree, PhD)

exercise
(hours per week: 0-2, 3-4, 5-6, 7+)

cognitive training tasks
(hours per week: : 0-2, 3-4, 5-6, 7+)

alcohol consumption
Units per week: 0, 1-2, 3-4, 5-6, 7-8, 10+)

cigarette consumption
(number in typical day: 0, 1-10, 11-20, 21-30, 31+)

physical disability
(yes, no)

Items for mini mental state examination	Maximum score
what is the year/season/date/day of the week/ month?	5
in/on which country/county/	5

town/building/floor are we?	
count backwards from 100 by 7s five times (93, 86, 79, 72, 65) or spell WORLD backwards	5
repeat the names of the three things I told you before starting the test (rabbit, book, candle)	3
point to two simple objects and ask the person to name them	2
Repeat the phrase: 'No ifs, ands, or buts.'	1
'take the paper in your right hand, fold it in half, and put it on the floor' (examiner hands person a piece of blank paper)	3
'please read this and do what it says' (written instruction is 'close your eyes')	1
'make up and write a sentence about anything' (sentence must contain a noun and a verb)	1
please copy this picture (all 10 angles must be present and two must intersect): 	1

Items for perceived stress scale (over last month how often…)	Scale (0 = never – 4 = very often)
have you been upset because of something that happened unexpectedly?	
have you felt that you were unable to control the important things in your life?	
have you felt nervous and stressed?	
have you felt confident in your ability to handle personal problems? [R]	
have you felt that things were going your way? [R]	
have you found that you could not cope with all the things that you had to do?	
have you been able to control irritations in your life? [R]	
have you felt that you were on top of things? [R]	
have you been angered because of things that were outside of your control?	

have you felt difficulties piling up so high that you could not overcome them?

Five sample items for state-trait anxiety inventory (constrained by copyright)	State scale (1 = not at all – 4 = very much so)
(at this moment I feel/am)	
calm [R]	
at ease [R]	
upset	
nervous	
worried	
(in general I feel/am)	Trait scale (1 = almost never – 4 = almost always)
nervous and restless	
satisfied with myself [R]	
like a failure	
calm, cool and collected [R]	
a steady person [R]	

Items for the social readjustment rating scale	Weights
death of spouse	100
divorce	73
marital separation	65
jail term	63
death of a close family member	63
personal injury or illness	53
marriage	50
fired at work	47
marital reconciliation	45
retirement	45
change in health of family member	44
pregnancy	40
sex difficulties	39
gain of a new family member	39
business readjustment	39
change in financial state	38

death of a close friend	37
change to different line of work	36
change in number of arguments with spouse	35
high mortgage	31
foreclosure of mortgage or loan	30
change in responsibilities at work	29
son or daughter leaving home	29
trouble with in-laws	29
outstanding personal achievements	28
wife/husband begins/stops work	26
begin or end school	26
change in living conditions	25
revision of personal habits	24
trouble with boss	23
change in work hours or conditions	20
change in residence	20
change in school	20
change in recreation	19
change in religious activities	19
change in social activities	18
low mortgage or loan	17
change in sleeping habits	16
change in number of family get-togethers	15
change in eating habits	15
vacation	13
holidays	12
minor violations of laws	11

Items for student life events scale	Weights
death of parent	100
death of your best or very good friend	91
jail term (self)	80
pregnancy (either yourself or being the father)	78
major car accident	77
major personal injury or illness	75
break-up of parents' marriage/divorce	70

getting kicked out of college/school	68
major change of health in close family member	68
break-up with boy/girlfriend	65
major and/or chronic financial problems	63
parent losing a job	57
losing a good friend	57
failing a number of courses	56
seeking psychological or psychiatric consultation	56
seriously thinking about dropping college	55
failing a course	53
major argument with boy/girlfriend	53
major argument with parents	48
sex difficulties with boy/girlfriend	48
beginning and undergraduate program at University	47
moving away from home	46
moving out of town with parents	44
change of job	43
minor car accident	42
switch in program within same college or university	37
getting an unjustified low mark on a test	36
establishing new steady relationship with partner	35
minor financial problems	32
losing a part-time job	31
vacation with parents	27
finding a part-time job	25
family get-together	25
minor violation of the law	24
getting your own car	21
vacation alone/with friends	16

Note. R = reversed item