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

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Stress and Aged Spatial Performance

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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 aging 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, Z. et al., Hippocampus 2013; 24:303-314) 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 synchronization compared to young and elderly low stress counterparts. Results therefore provide further evidence for the adverse effect of stress on cognitive aging and indicate that impaired behavioral performance among high stress elderly may coincide with an overreliance 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 coordinates 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 elevation 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 reuptake 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 & Sapolski, 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 aging. 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., 2012). 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 aging demographic, the above studies provide robust and highly important behavioral findings indicating that cumulative experienced stress should be considered as a risk factor for cognitive aging. 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 behavioral 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 aging 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 5x7 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, 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). 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 behavioral results with neurobiological 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 widespread 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 synchronization 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 synchronization (especially over the frontal-midline) has been reported by a number of electroencephalographic (EEG) studies investigating the neural correlates of memory (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 synchronization have also been linked to decreased memory performance when they are observed over widespread cortical regions. For example, Vogel and colleagues (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. Impaired memory performance in conjunction with global activation of theta activity was further demonstrated by 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 ERS 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 behavioral 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 aging, elderly participants with high levels of experienced stress were predicted to display reduced levels of behavioral 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 participants 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 synchronization (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 as the more likely outcome.

Materials and Method

Participant selection

Thirty young adult participants (17 females; Mean age = 21.3, SD = 3.4; Range 18-30 years) were recruited from the University of Essex student population via institutional e-mail advertising. A second group of 30 elderly participants (14 females; Mean age = 68.73, SD = 6.4; Range 60-82 years) 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 in which all scored full marks. All participants provided written informed consent. The study was approved by the University of Essex Ethics Committee.

Stress and Demographical Measures

This study investigated the impact of cumulative stressful experiences on cognitive aging. 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 background demographics included participants' age, gender, educational level, cigarette and alcohol intake, amount of physical exercise and whether respondents suffered from a disability whose discomfort may compromise performance on the task (for units of measurement refer to Table 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 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 5x7 grid (35 grid spaces), which remained invisible to participants.

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 colleague's 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 analyzed 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 artifacts 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 artifact 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 synchronization and desynchronization, 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 artifacts, leaving a 2500ms test interval and a 500ms reference period (-500ms before onset of the next stimulus) for subsequent analysis. For the electrophysiological analysis 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, hard lures, easy 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 event-related desynchronization (ERD) of the theta frequency band whereas negative values indicate event-related synchronization (ERS).

Results

Behavioral 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, see Table 1). 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 analyses revealed a main effect of age ($F_{1,57}$ = 4.8, p = .033), indicating that elderly participants (*M* = 0.72 , *SD* = 0.16) performed worse overall compared to young participants (*M* = 0.79, SD = 0.13) (see Figure 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* = 0.14 performed worse at target recognition relative to low stress group counterparts (*M* = 0.81, *SD* = 0.13. 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 0.008). 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 2). No other group differences reached significance (all p's >.008).

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: 1,2,3,4, 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* = 0.11) performed significantly below young participants (*M*= 0.7, *SD* = 0.1) 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* = 0.11) on lure displacement trials relative to low experienced stress group counterparts (*M* = 0.7, *SD* = 0.09). 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 0.005) 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 0.005) 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 1). No further simple main effects reached significance for this interaction (p's >.005).

Simple effects contrasts of the age x stress by lure displacement interaction (corrected p-value 0.0016) 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 3). No further simple main effects reached significance (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.

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, 2-3, 3-4, 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 0.008) 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 0.006) 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_{28}= 2.14, p = .004) but showed a steeper performance increase than young from low to very low interference trials (4-c; t_{28}= 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 0.003) 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/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 by 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 and retrieval which changed to a larger proportion of invoked activity during later periods of encoding and retrieval and thus highlighted the importance of dividing the data into early and late time periods. In order to establish whether event-related activity in the early (0-1250ms) and later time window (1250-2500ms) reflected meaningful electrophysiological data, the combined cortical ERD/S activity across all four participant groups was compared against the value of zero for both the retrieval and encoding periods. Results demonstrated that for both time windows electrophysiological activity manifested in response to all three stimulus types differed significantly from zero (all p's < .003), thus qualifying both time windows for further analysis (see supplementary materials for detailed analysis).Data for the encoding period was subsequently analysed using a 3 (Sagitality: frontal, central and posterior cortical regions) x 3 (Laterality: left, mid and right cortical regions) x 2 (Age: young and old) x 2 (Experienced Stress: high and low) mixed 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, low interference, 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= 0.003) indicating that elderly participants show higher levels of theta ERS in late periods of stimulus encoding compared to young participants (see Figure 4). 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= 0.001) 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 ($F_{1,45}$ = 4.89, p= 0.022). 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. A Bonferroni corrected p-value (0.001) was employed to correct for multiple comparisons. Follow-up comparisons revealed that among individuals with high levels of experienced stress, elderly participants showed significantly higher levels of theta ERS across electrodes summed over the left cortical region (left lateral) ($F_{1,45}$ = 14.78, p<.001), the central cortical region (mid lateral) ($F_{1,45}$ = 13.82, p<.001) and the right cortical region (right lateral) ($F_{1,45}$ = 8.54, p < .001) cortical regions when retrieving the locations of objects in the low interference category (see Figure 5a). No other main effects or interactions reached significance (all p's >.05).

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) indicating that elderly participants showed higher levels of ERS in late periods of stimulus retrieval compared to young counterparts. Analysis further discovered a four-way laterality x age x stress x stimulus interaction ($F_{4,172} = 3.46$, $p = 0.021$). To parse the interaction, four relevant group differences over the three stimulus categories were analysed for each of the three lateral cortical regions (Bonferroni corrected p-value 0.001) 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 ($F_{1,45} = 14.78$, $p < .001$), mid ($F_{1,45} = 21.59$, $p < .001$) and right ($F_{1,45} = 13.45$, $p < .001$) lateral cortical regions when retrieving the locations of objects in the high interference category (see Figure 5b).

Discussion

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

Behavioral 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 behavioral 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 for 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 (difference non-significant, see Figure 3), 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 behavioral 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 behavioral 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 (see Figure 5). 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 synchronization 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 aging 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 behavioral 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. On a similar note, we propose that localised theta observed during completion of the spatial memory task is indicative of hippocampal-cortical interactions. However, we would like to acknowledge that this interpretation is based on EEG data manifesting over the scalp surface and is as such limited by well-documented source localisation issues (Gramfort et al., 2013). Described as the inverse problem, 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 . 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. However our argument 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 (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). As a possible means to address the above issues and adequately capture presumed hippocampal impairment, further research would need to utilize 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 aging. 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 behavioral 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. Behavioral 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 aging cognition with in vitro studies exploring how stress impacts on hippocampal cells), to arrive at a fuller understanding of how cumulative experienced stress affects aging cognition.

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Figures: (NB, these are not as edited in final manuscript)

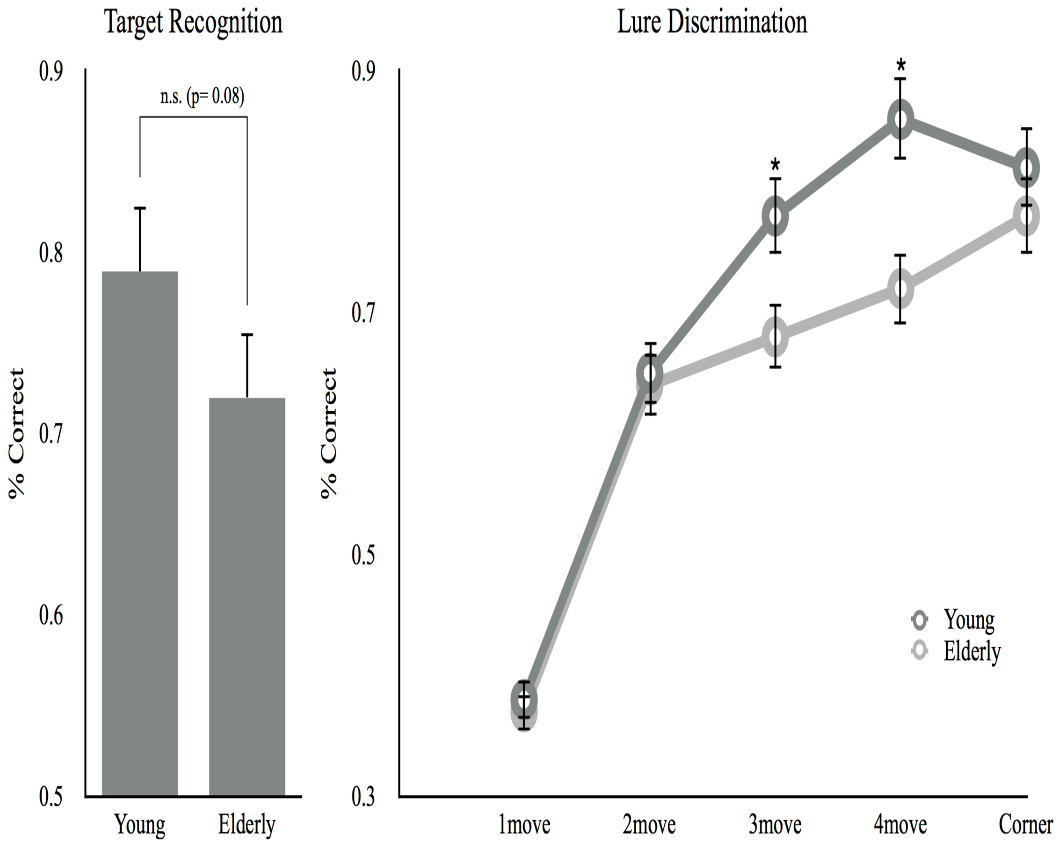

Figure 1: Performance scores on both target recognition and lure displacement at each level of mnemonic interference. No significant age difference emerged for target detection. Results for lure displacement indicate reduced levels of elderly participants when levels of interference are moderate to low. Young>Elderly (*); not significant (n.s.).

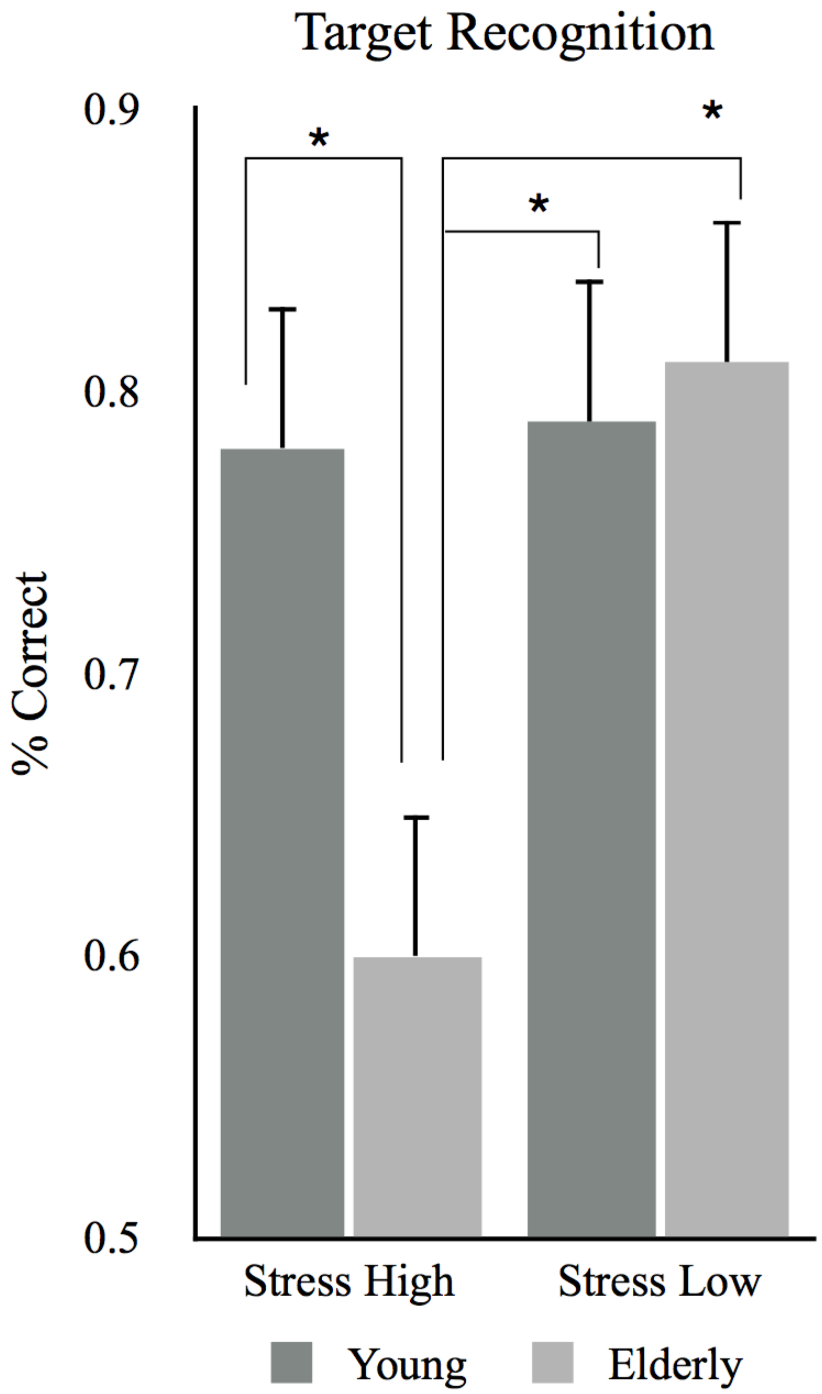

Figure 2: Target detection scores for both age groups split into high and low experienced stress scorers. Findings show significantly reduced accuracy of High Stress Elderly participants compared to all elderly low stress and both young stress group. Young Low/Young High/Elderly Low Stress>Elderly High Stress(*).

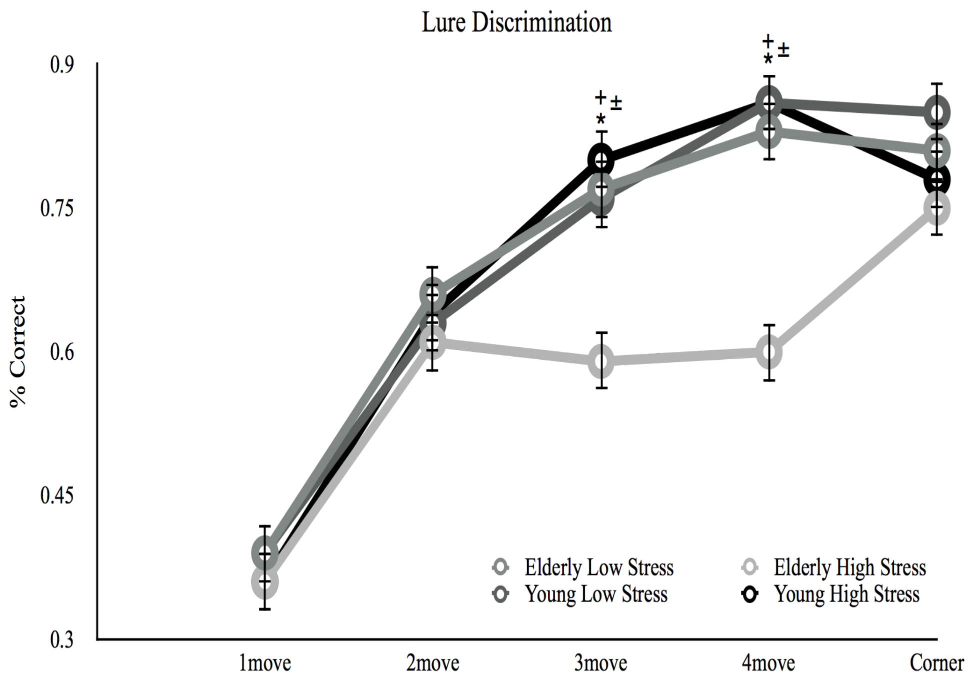

Figure3: Lure discrimination scores at each level of mnemonic interference for both age and stress groups. Results indicate reduced performance among High Stress Elderly participants compared to High and Low Stress Young and Low Stress Elderly participants when levels of interference at 3- and 4-grid moves (moderate to low levels of interference). Young High Stress>Elderly High Stress(*); Young Low Stress>Elderly High Stress(+); Elderly Low Stress>Elderly High Stress(±).

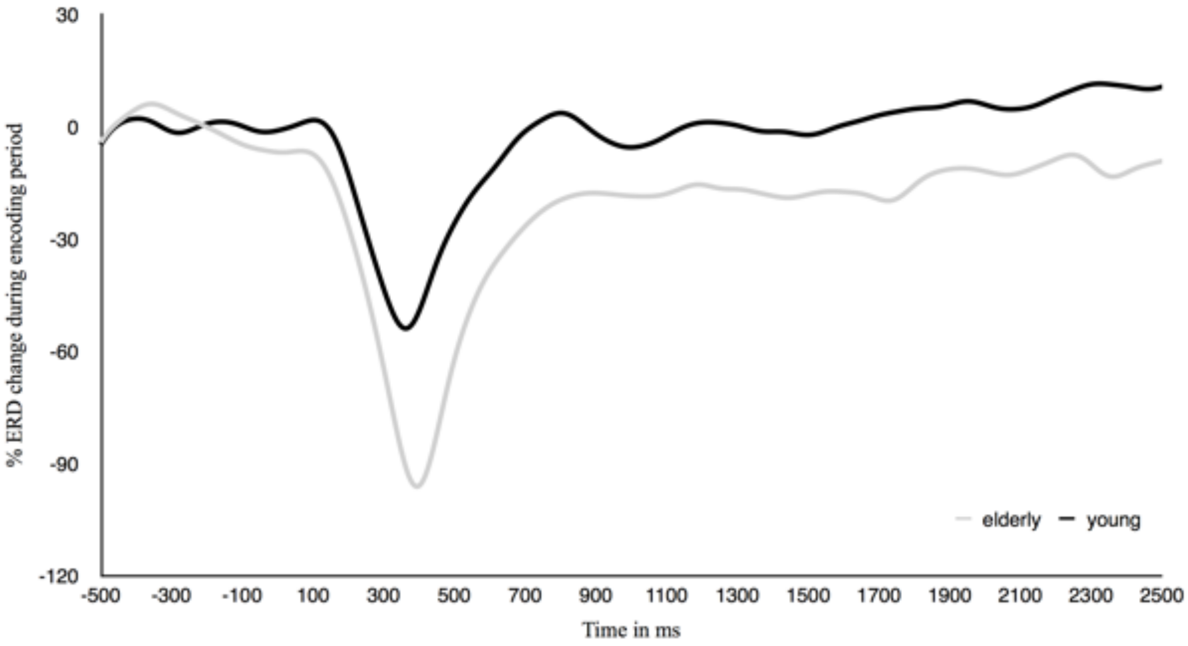

Figure 4: Grand average waveforms for the theta frequency range computed over the entire cortex during encoding of the original object location. Elderly participants demonstrate higher levels of theta ERS relative to young individuals.

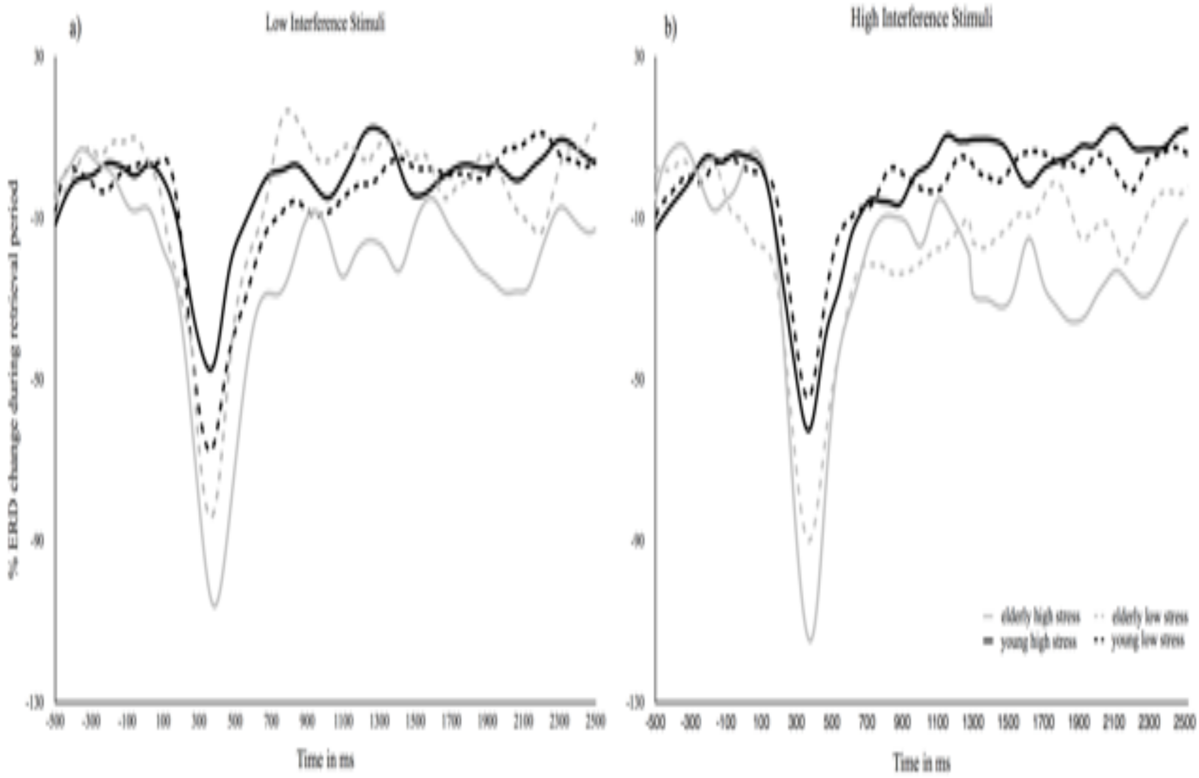

Figure 5: Grand average waveforms for theta frequency range computed over the entire cortex during retrieval of original object location in the face of conflicting information. a): Retrieval of low interference stimuli: Increased theta ERS of High Stress Elderly participants during early periods of stimulus retrieval (0-1250ms). Difference reaches significance compared to the Young High Stress participant sample. b): Retrieval of high interference stimuli: Increased theta ERS of High Stress Elderly participants during late periods of stimulus retrieval (1250-2500ms). Once again the difference is significant compared to the Young High Stress participant group.