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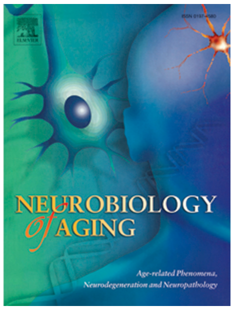

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Stress-related deficits of older adults' spatial working memory: An EEG investigation of occipital alpha and frontal-midline theta activity

Running Title:

Stress-related deficits of older adults' spatial WM

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Abstract

Studies highlight cumulative life stress as a significant predictor of accelerated cognitive aging. This study paired electrophysiological with behavioral measures to explore how cumulative stress affects attentional and maintenance processes underpinning working memory retention. We collected electroencephalographic (EEG) recordings from 60 individuals (30 older, 30 younger) reporting high or low levels of cumulative stress during the performance of a spatial Sternberg task. We measured mid-occiptial alpha (8 – 12 Hz) and frontal-midline theta (4 – 6 Hz) as indicators of attentional and maintenance processes. Older, high stress participants' behavioral performance lay significantly below that of younger adults and low stress older individuals. Impaired task performance coincided with reduced event-related synchronization in alpha and theta frequency ranges during memory maintenance. Electrophysiological findings suggest that older adults' reduced performance results from a stress-related impact on their ability to retain a stimulus in working memory and inhibit extraneous information from interfering with maintenance. Our results demonstrate the wide-ranging impact of cumulative stress on cognitive health and provide insight into the functional mechanisms disrupted by its influence.

Keywords: alpha; cognitive aging; cumulative stress; EEG; theta

1. Introduction

Deficits of cognitive functioning are an established co-occurrence of aging (Salthouse & Babcock, 1991; Hahn et al., 2011; Vasquez, Binns & Anderson, 2014; Colino et al., 2017). However, age-related cognitive decline is not uniform as several biological and environmental factors have been shown to influence its trajectory. These range from genetic make-up (Stessman et al., 2005; Bis et al., 2012) to certain lifestyle choices such as physical activity and dietary intake (Chang & Etnier, 2009; Tedesco et al., 2000). A further determining factor highlighted by past work is the amount of stressful experiences individuals encounter during their lifetime. The impact of stress on cognitive aging has only recently gained scientific interest. However, since then several studies have demonstrated that cumulative life stress has a significant impact on cognitive integrity in old age (Dickinson et al., 2011; Pesonen et al., 2013; Munoz et al., 2015). This is not surprising as prolonged exposure to the stress hormone cortisol (glucocorticoids) results in pronounced oxidative damage to areas of the hippocampus and neocortex (Ohl et al., 2000; Shao et al., 2015), brain structures integral for intact executive functioning and memory performance. Stress-induced hippocampal damage has been attributed to glucocorticoids causing a prolonged reduction of glucose reuptake into hippocampal cells (Sapolsky & Meaney, 1986) which results in dendritic atrophy and an inhibition of neurogenesis. Frontal damage is thought to be sustained by an increased number of micro lesions produced by stress induced hypertonic strain on arteries and veins (Rabbitt, 2005).

Correspondingly, our own work comparing older and younger participant groups with high and low levels of cumulative stress demonstrates stress- and age-related behavioral deficits in the realms of inhibitory control and working memory (Marshall et al., 2015; Marshall et al., 2016a). For working memory (WM), we demonstrate that behavioral shortcomings among older high stress adults coincide with aberrant patterns in the alpha (8 – 12 Hz) and theta (4 – 6 Hz) frequency ranges. Specifically, studying WM with a standard version of the Sternberg paradigm (Sternberg, 1966) revealed significantly reduced alpha event-related activity across the parieto-occipital scalp regions of older high-stress adults during periods of memory maintenance (Marshall et al., 2015), highlighting that stress may impact on older adults' ability to successfully inhibit task irrelevant brain regions. Our work thus suggests that, among older adults, cumulative stress has a detrimental impact on oscillatory processes contributing to the successful retention of stimulus material. Findings to this effect highlight the efficacy of pairing behavioral with neurophysiological markers of cognitive functions as the latter provide an insight into the cognitive mechanisms affected by lifetime stress exposure. We extended this work by introducing a spatial component to the WM process by means of an object location memory task (Reagh et al., 2014). This revealed a global change of theta activity during the recall of stimulus material which was specific to older adults with high amounts of lifetime stress (Marshall et al., 2016b). However, this spatial paradigm did not afford the opportunity to investigate theta activity during WM maintenance. As our past work shows that cumulative stress compromises the maintenance period, this constitutes a necessary extension to investigating the effects of stress on spatial WM. In the current study, we thus explored stress- and age-related changes to the alpha and theta bands during encoding and maintenance periods of a spatial Sternberg paradigm. In addition to extending our work, this also afforded the opportunity to replicate the observed effect of stress on cognitive aging. The impact of stress on cognitive integrity is a recent discovery. Therefore, it does not yet have a large reference body. Given the replication crisis for psychological studies and the crucial impact of these findings for health and wellbeing it is imperative to provide sound replications of this effect.

The paradigm used in this study was developed by Lenartowicz and colleagues (2014) who demonstrated that it successfully captures task-related changes in occipital alpha and frontal-midline theta activity. We measured electroencephalographic (EEG) neural responses to this task in a sample of older and younger individuals who reported varying degrees of stressful life encounters. We analysed EEG signals using a combination of highly controlled, permutation-based, mass univariate analyses and time-frequency analysis to focus on mid-occipital alpha and frontal-midline theta as established correlates of attention/inhibition and memory maintenance respectively. Based on our foregone work, we predict that members of the older age, high stress group will show significantly reduced alpha and theta event-related activity relative to both younger and older low stress group members. We expect this effect to manifest in encoding and maintenance phases of our task. In the encoding phase, we expect reduced event-related desynchronisation of the alpha frequency range. In the maintenance phase, we predict reduced event-related synchronisation of the alpha and theta frequencies among older adults with high levels of lifetime stress.

2. Materials and Method

2.1 Participants

Thirty young adult participants (14 females; Mean age = 22.5, SD = 3.18; Range = 18 – 30 years) were recruited from the University of Essex student population via institutional e-mail advertising. A second group of 30 older participants (18 females; Mean age = 68.73, SD = 4.65; Range = 61 – 79 years) were recruited from regional clubs and societies and via advertisements placed in local newsletters. Age-ranges (18 – 30 younger; 60 – 80 older adults) were specified in the advertisement. They were chosen based on a reference body of work comparing cognitive effects between younger and older adults (Reuter-Lorenz et al., 2000; Fandakova et al., 2014; Isingrini et al., 2015) as well as our own previous studies observing robust electrophysiological differences between age-groups from similar ranges (Marshall et al., 2015; Marshall et al., 2016a/b). Exclusion criteria specified during recruitment 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 or a history of substance abuse. To ensure against undiagnosed cognitive pathologies, all older participants completed the Mini Mental State Examination for which all scored within the normal range (> 24 marks). All participants provided written informed consent. The study was approved by the University of Essex Ethics Committee.

2.2 Stress and Demographical Measures

Demographics included participants' age, level of education, amount of cigarette and alcohol consumption, levels of physical activity and whether they were currently suffering discomfort from a physical disability which might impact on their task performance. In addition, levels of trait and state anxiety were assessed using the State Trait Anxiety Inventory (Spielberger et al., 1968). We used the STAI to test for individuals with exceptionally high state or trait levels of anxiety as these may confound the effect of lifetime stress on cognitive performance. Scores on both subscales remained low and an established method to define and detect outliers (Tukey, 1977) did not find any individuals who greatly deviated from the sample mean. In line with our previous work (Marshall et al., 2015; Marshall et al., 2016a; Marshall et al., 2016b; Marshall & Cooper, 2017), we assessed the number of participants' stressful experiences using the Social Readjustment Rating Scale (Holmes & Rahe, 1967) for older and the Student Life Events Scale (Clements & Turpin, 1996) for younger adults. Both scales have been validated for respective student and adult population samples and have been shown to provide valid and reliable estimates of cumulative stress (Clements & Turpin, 1996; McGrath et al., 1983; Gerst et al., 1978). The choice for using different stress inventories for each age group has several reasons. Firstly, older adults were on average three times the age of younger participants and thus likely to have experienced more stressful events relative to our young participant sample. Secondly, these stressful experiences had a high likelihood of being qualitatively different between both age groups. Thus, to assess prolonged stress exposure appropriate to each age group different instruments had to be used for each age group. Chosen scales were selected based on an identical format to assess life experiences. Each consists of a brief, self-administered scale (43 and 36 items respectively). Items are weighted according to magnitude so that 'Death of a Spouse/Parent carries a high score of 100 while a mildly stressful incident such as 'Vacation with family or friends' has a low score of 16 (Student Life Events Scale) or 13 (Social Readjustment Rating Scale). Scores range from 0 to 1466 for the Social Readjustment Rating Scale and from 0 to 1849 for the Student Life Events Scale. Higher scores reflect high amounts of experienced stress for both scales. Both scales are commonly used to assess life events occurring in the past year. To assess the cumulative, lifetime impact of stressful events we thus modified the instructions. Participants were asked to indicate which events they remembered occurring in their lifetime. We urged participants to be stringent in their assessment and to name only those events they could explicitly remember. Our previous work demonstrates that this modification does not result in ceiling effects for the number of events reported and produces lifetime stress scores which reliably predict variance in cognitive task performance (Marshall et al., 2015; Marshall et al., 2016a; Marshall et al., 2016b; Marshall & Cooper, 2017). As in previous studies, scores on each scale were used to divide both age groups into high and low stress scorers. The divide was based on the median split of scores from the Social Readjustment Rating Scale for older adults (Value: 628) and the Social Readjustment Rating Scale for younger adults (Value: 574). No significant group differences in Mini Mental State performance, age, gender, educational attainment, cigarette/alcohol consumption or physical activity emerged between stress groups (see Table 1).

2.3 Procedure

To begin, each participant completed an eye-movement calibration session (Croft & Barry, 1998). EEG data gathered from this session was subsequently used to correct for electrical activity reflecting horizontal and radial eye-movements and blinks. For the experimental task, we used a spatial version of the Sternberg working memory paradigm (Sternberg, 1966) developed by Lenartowicz and colleagues (2014). Participants saw a fixation cross for 0.5 s which was followed by an encoding display containing either 1, 3, 5, or 7 yellow circles whose locations participants were instructed to remember. Circles were presented for 2 s after which a further fixation screen was presented for a 3 s maintenance period. Finally, a single green circle (probe) was presented and participants had to decide whether it was located at a position previously occupied by one of the yellow circles (match) or not (non-match). Left and right arrow keys were allocated to match and non-match responses, respectively. The probe was presented for 3 s or until a response was registered from a participant. Trials were separated by a 2 s inter-trial interval. Participants completed a training block of 8 trials (2 trials for each of the four circle displays) until their performance was greater than 50 % accuracy. Subsequently, they completed eight blocks of 48 experimental trials. Trials were equally balanced between load and match/non-match response types. The order of types was randomised within each block.

2.4 Electrophysiological recording and data preparation

Electroencephalography (EEG) was recorded from 64 electrodes placed within a soft-cap according to the 10-10 method of electrode positioning. Recordings were referenced to a point midway between Cz and CPz. Impedances were lowered to below 10 kΩ 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 1000 Hz with a band-pass filter of 0.05 – 200 Hz. Acquired data was visually inspected and noisy data blocks, general artefacts and bad electrodes were rejected. To minimise the impact of eye-movements, principal components analysis was performed on the acquired eye-movement data to obtain components reflecting saccades and blinks. To carry out ocular artefact rejection, these components were subtracted from the experimental data trace (Vigário, 1997; Vigário, Sarela, Jousmiki, Hamalainen & Oja, 2000). Data was re-referenced to a common average reference. Using the Event-related-band-power transformation (SCAN 4.5 editing software) data underwent complex demodulation and concurrent filtering (zero phase-shift, 24 dB roll-off, envelope computed) into the theta (4 – 6 Hz) and alpha (8 – 12 Hz) frequency ranges. Event-related activity was calculated as a percentage change between the active period (time spent either maintaining or encoding the items) and the reference period (500ms period before onset of encoding display) according to the following formula [({reference - test}/reference) * 100]. According to this method (Pfurtscheller & Aranibar, 1977), positive values represent event-related desynchronization (ERD) of frequency bands while negative values indicate event-related synchronization (ERS). Epochs containing remaining artefacts were removed. This resulted in an average of 190 (SD = 14) epochs for younger adults and 188 (SD = 11) epochs for older adults and led to a minimal amount of 23 epochs per condition.

2.5 Statistical analysis

Statistical testing was carried out with ANOVAs and Bonferroni corrected t-tests on behavioral scores and averaged even-related oscillatory values. In addition, we conducted linear regression analysis for all models which produced a significant effect of stress between age groups. For the primary analysis, we treated experienced stress as a categorical variable and formed high and low stress groups based on the median split of individual scores. The regression analysis allowed us to treat stress as a continuous variable to ensure this median split approach did not exaggerate the true impact of stress on behavioural and oscillatory performance. For the behavioral analysis all values were standardized. The formula (Z-scored Hits – Z-scored False Positives) was used to compute d' – a value representing the proportion of correct responses relative to participants' false alarm rate. D' and reaction times acted as dependent variables to assess behavioural performance on the task. For the analyses of our electrophysiological data, we adopted a two-step approach. We began by identifying the topographical distribution and time course in which to analyse task- and group-related changes in the alpha and theta frequency range. Our previous work (Marshall et al., 2015; Marshall et al., 2016a; Marshall et al., 2016b) highlights that high levels of cumulative stress exposure exacerbate electrophysiological effects associated with normal aging. We therefore identified neural phenomena that varied with a main effect of age using the following non-parametric approach: 1) F-values associated with the main effect of age were calculated at every electrode site for the topographical distribution and at every time point for the 2 s encoding and 3 s maintenance phase. 2) Condition-subject assignments were shuffled and statistics computed 1000 times, thereby providing a null distribution associated with each electrode site and time point. 3) the maximal F-value from each time point and electrode comparison was logged for each of the 1000 iterations resulting in a distribution of maximal values under the null hypothesis. 4) original values were compared to this distribution and those falling into the 95th percentile or above (α = .05) were deemed significant. Separate permutations were run for alpha desynchronisation in the encoding period and for theta and alpha synchronisation in the maintenance period. This non-parametric approach is gaining increasing acclaim with the neuroscientific community (Summerfield & Mangels, 2005; Lage-Castellanos et al., 2008; Summerfield et al., 2011; Marshall & Cooper, 2017) and carries a number of advantages specific to dealing with large data sets. The method provides exact statistics corrected for multiple comparisons in a manner equivalent to the 'family wise error' gold standard applied in functional neuroimaging (Nichols & Holmes, 2002). Furthermore, a data-driven approach circumvents the issue of imposing a priori restrictions on the data which are often based on an ill-defined reference literature not specific to the exact effect under investigation. In addition, we adopted this approach as it mirrored the bottom-up, source-localization approach Lenartowicz and colleagues (2014) used to define topographical distributions in their original investigation of this paradigm.

3. Results

3.1 Behavioral analyses

We analysed accuracy (d') and reaction times within a 2 (age: older vs. younger) x 2 (stress: high vs. low) by 4 (load) mixed measures ANOVA in which load acted as the within-subjects factor. Analysis of accuracy revealed a main effect of age ($F_{1,56}$ = 8.7, p = .004) and load ($F_{3,168}$ = 52.7, p < .001). The main effect of age indicated higher performance in younger (Mean = 0.91) relative to older (Mean = 0.86) participants. The main effect of load revealed a linear decrease of performance ($F_{1,56}$ = 195,77, p < .001) which significantly differed between each load level (p < .001). Analysis further revealed a significant load x age interaction ($F_{3,168}$

= 9.16, $p < .001$) which demonstrated that younger participants significantly outperformed older adults at high load levels (5 circles: $p < .001$; 7 circles: $p = .009$; see Figure 1), but not at low load levels.

Crucially, we also observed a significant age x stress interaction ($F_{1,56} = 6.58$, $p = .013$) which highlighted that older adults in the high stress group (Mean = 0.79) performed significantly worse than older adults in the low stress group (Mean = 0.87, $p < .001$) and younger adults in the high stress group (Mean = 0.92, $p < .001$; see Figure 2). No differences were observed between younger low and younger high stress participants ($p = .98$, see Figure 2). To test whether we could reproduce the above interaction with stress score as a continuous variable, we ran a two-step hierarchical regression. In the first step, we regressed age (coded as 1 older and -1 younger) and stress score on the d' score collapsed across load conditions. This produced a significant model ($F_{2,57} = 8.9$, $p = .004$) which accounted for 11% of the variance in performance. Including the interaction term age x stress in the second step accounted for an additional 9% of variance and constituted a significant change to the model ($\Delta F_{1,56} = 11.07$, $p < .001$). We explored this interaction with a simple slopes analysis (Preacher, Curran & Bauer, 2006). This revealed that the addition of a stressful event reduced the performance of older adults to a significant degree ($t_{59} = 7.53$, $p = .001$) while causing no impact on performance among younger adults ($p = 0.41$). Results thus correspond to our primary analysis and highlight that our stress effects were not artefacts of our median split approach.

Analysis of reaction times revealed a main effect of age ($F_{1,56} = 7.3$, $p = .008$) demonstrating that older adults took significantly longer to respond (Mean = 443 ms) than young adults (Mean = 397 ms). No further main effects or interactions reached significance (all $p_s > .05$).

3.2 Electrophysiological analyses

3.2.1 Alpha during encoding.

Within the alpha frequency range, we observed a prominent main effect of age at 300 – 800 ms of the encoding interval. This effect manifested over mid-occipital scalp regions (POz, PO3, PO2, O1, Oz, O2; Cohen's δ > 0.4). In addition to the main effect of age, analysis of the mean oscillatory activity across this electrode pool revealed a significant load x age interaction ($F_{3,168} = 3.12$, $p = .028$). Bonferroni corrected follow-up analysis of this interaction revealed that younger adults (Mean = 16.3 µV) showed significantly higher levels of alpha ERD at the highest load condition relative to older adults (Mean = 5.7 µV; $p = .011$; see Figure 3). To test for an association between alpha activity during encoding and behavioural scores we correlated alpha ERD with d' (both averaged across load conditions). We observed no significant correlation (**ρ** = 0.13, p = 0.43).

3.2.2 Alpha during maintenance.

We observed a strong main effect of age across the same electrode pool reported for the encoding interval (POz, PO3, PO2, O1, Oz, O2; Cohen's δ > 0.4). This effect was most pronounced during 1100 – 2000 ms of the maintenance period. In addition to the main effect of age, analysis of this electrode pool revealed a main effect of load ($F_{3,168} = 88.89$, $p < .001$) which reflected a linear increase of alpha ERS ($F_{1,56} = 33.78$, $p < .001$) which was significant at each load transition ($p < .001$). Importantly, main effects were qualified by an age x stress interaction ($F_{1,56} = 4.53$, $p = .038$). Corrected follow-up comparisons highlighted that older adults in the high stress group (Mean = -9.92 µV) showed significantly reduced alpha ERS compared to older low stress adults (Mean = -21.62 µV, $p = .002$) and younger high stress adults (Mean = -37.55 µV, $p < .001$; see Figure 4). No such differences were found among the younger participant stress groups ($p_s > .05$). To explore whether the reported stress x age interaction remained when treating stress as a continuous variable we conducted a further regression analysis. In the first step, we regressed age and stress on alpha ERS collapsed across load conditions. This produced a significant model ($F_{2,57} = 12.31$, $p < .001$) which accounted for 16% of the variance in alpha activity. In the second step, we added the interaction term. This accounted for an additional 7% of variance which constituted a significant extension to the model ($\Delta F_{1,56} = 7.54$, $p = .003$). Simple slopes analysis of the interaction revealed that the addition of a stressful life experience reduced alpha ERS significantly among older adults ($t_{59} = 8.77$, $p < .001$) while having no impact on younger adults ($p = 0.21$). Results thus equate the primary analysis in which stress is treated as a categorical variable. To test for an association between alpha activity during encoding and maintenance we included a further step in the model. In the third step, we therefore added the percentage of alpha ERD during encoding (collapsed across load conditions) as an additional predictor. Inclusion of this variable accounted for a further 4% of variance which constituted a marginally significant change to the model ($\Delta F_{1,55} = 3.76$, $p = .053$). Importantly, age ($\beta = 0.29$, $p < .001$) as well as the interaction term age x stress ($\beta = 0.27$, $p = .002$) remained significant independent predictors despite controlling for previous encoding activity. This indicates that the stress by age effect relates directly to processes concerning the maintenance of items in working memory and is not a carry-over effect from weakly encoded items in the previous phase. To explore whether alpha activity during the maintenance phase was associated with behavioural scores, we correlated alpha ERS with d' scores (averaged across load conditions). We observed a negative correlation which indicated that increased alpha synchronisation coincided with higher accuracy on the task. However, this association fell outside of conventional significance levels ($\boldsymbol{\rho} = -0.23$, $p = .058$).

3.2.3 Theta during maintenance.

Within the theta range, we observed a significant main effect of age across the frontal-midline (FP1, FPz, FP2, AF3, AF4, F1, Fz, F2; Cohen's δ > 0.45). This effect was most pronounced at 900 – 1800 ms of the maintenance phase. Subsequent analysis revealed an additional main effect of load ($F_{3,168}$ = 18.03, p < .001), which revealed a linear increase of theta ERS ($F_{1,56}$ = 27.81, p < .001) at all load transitions (p < .01). Most importantly, we once more observed an age x stress interaction F($_{1,56}$ = 6.83, p = .012). Corrected follow-up comparisons revealed that high stress older adults (Mean = -7.96 µV) showed significantly reduced theta ERS compared to both older low stress adults (Mean = -12.03 µV, p < .001) and younger high stress adults (Mean = -19.87 µV, p < .001; see Figure 5) while no differences were observed between younger high and low stress participant groups (p = 1.73) and between younger and older low stress samples (p = .87). We conducted a further regression analysis to test whether our age x stress effect was manifest when treating stress as a continuous variable. Regressing age and stress score on theta ERS in the first step produced a significant model ($F_{2,57}$ = 13.27, p < .001) which accounted for 14% of variance in theta activity. Adding the interaction term age x stress in the second step accounted for an additional 10% of variance which constituted a significant extension to the model (($\Delta F_{1,56}$ = 8.73, p = .001). Simple slopes analysis revealed that the addition of a stressful event significantly reduced theta ERS among older adults (t_{59} = 9.83, p < .001) while causing no significant change among younger adults (p = 0.17). Exploring the association between theta activity and behavioural scores (d') found a significant correlation (**ρ** = -0.38, p = .019). This highlighted that increased theta synchronisation during the maintenance period coincided with increased performance on the memory task.

4. Discussion

We explored the effects of cumulative life stress on oscillatory processes known to contribute to the successful encoding and maintenance of stimuli. This allowed us to extend existing knowledge of the way in which stress impacts cognitive health in older age. Our results show reduced memory performance among older members of the high stress group. Their performance lies significantly below the scores of older low stress participants and both groups of young participants. Behavioral impairments of high stress older participants coincided with reductions of alpha and theta event-related synchronisation during the memory maintenance period. Combined, results suggest that the behavioral deficits manifesting after prolonged cumulative stress exposure are the result of a detriment to several sub-processes contributing to the successful retention of encoded items.

4.1 Behavioral performance.

Performance scores revealed a significant main effect of age and load. This indicated that young participants obtained higher scores than older adults and that performance was generally higher for lower than for higher load levels. Crucially, older adults reporting high levels of cumulative stress performed significantly below older adults with low levels of stress and younger high stress adults. Finding a stress-related performance detriment among older adults which does not manifest among younger high stress participants suggests that the adverse effects of stress are not immediate but manifest over a long period of time. This corresponds to previous reports (Dickinson et al., 2011; Pesonen et al., 2013) as well as our own work (Marshall et al., 2015; Marshall et al., 2016a; Marshall et al., 2016b) for which we report the same pattern of behavioral findings. For example, studying the behavioral performance of age and stress groups in an object location task revealed that older members of the high stress group recalled significantly less original object locations than younger and low stress older counterparts. Combined, this re-occurring data pattern constitutes evidence that the effect of stress exposure acts in a cumulative manner and only manifests during later periods of life.

4.2 Alpha during encoding.

Compared to older, younger adults showed significantly higher levels of alpha desynchronization during periods of stimulus encoding. This difference was most pronounced for the highest stimulus load. Our statistical approach discovered alpha activity to be highest across mid-occipital regions. Desynchronisation of the mid-occipital alpha rhythm in response to the visual encoding of stimuli is a well-documented occurrence (Vanni, Revonsuo & Hari, 1997). As such, it has been suggested to reflect a visual gating mechanism in which attended information is passed to downstream areas while unattended information is blocked. Zumer and colleagues (2014) reported that decreased occipital alpha power contralateral to an attended object predicted the fMRI BOLD response representing the attended object in ventral regions for object selection. Conversely, increased alpha power ipsilateral to attended objects predicted a decrease in the corresponding BOLD signal. The authors thereby highlight the role of alpha in enhancing attended information while simultaneously suppressing distracting stimulus material during the encoding process. Results thus suggest that young participants are superior at selectively encoding relevant stimulus material. Furthermore, higher, more demanding load conditions elicit greater expenditure of this mechanism.

4.3 Alpha during maintenance.

Oscillatory alpha patterns during stimulus maintenance revealed increased event-related synchronisation in younger compared to older participants and for high compared to low load conditions. Crucially, we also observed significantly reduced alpha ERS among high stress older participants relative to older adults with low levels of cumulative stress and younger adults with high stress levels. Despite falling outside of conventional significance levels, a correlational analysis indicated that increased alpha synchronisation coincided with enhanced memory performance. Akin to its role during encoding, alpha activity during stimulus maintenance has been implicated in attentional regulation and inhibitory mechanisms which facilitate successful memory retention (Klimesch, 2012). As such, higher levels of alpha synchronisation during Sternberg maintenance periods have been attributed to the successful inhibition of brain regions unnecessary for ongoing stimulus maintenance (Klimesch, 2012), thereby reducing the intake of potentially distracting information (Sauseng et al., 2009). In line with this account, past work has linked increases of alpha power with successful Sternberg task performance (Jensen et al., 2002). The reduced alpha synchronisation displayed by older high stress adults may therefore signify reduced capability to inhibit mid-occipital brain regions during the maintenance process. These regions are involved in the visual uptake and encoding of new information. Therefore, impaired capacity to regulate them may result in conflicting information detracting from ongoing memory retention. Our alpha findings could also be interpreted in terms of the active processing hypothesis. This theory suggests that age-related cognitive deficits arise from an inability of cortical neuronal assemblies to maintain an active state (Dringenberg, 2000). It is often used to account for the general slowing of the EEG, a phenomenon we have also observed among older adults with high levels of cumulative stress (Marshall & Cooper, 2017). Dringenberg suggested that a breakdown of active cortical circuits may arise from a cholinergic deficit coupled with lowered serotonergic and noradrenergic activity. Previous work has reported that a cholinergic agonist enhances cortical alpha activity and elevates performance on a visuospatial task (Bauer et al., 2012). Thus, our findings in the alpha range may also signal an impact of stress on cholinergic neurons in the basal forebrain which are responsible for innervating cortical and subcortical brain regions integral for successful cognitive operations.

Importantly, we observed an effect of alpha ERS in the maintenance period after controlling for alpha ERD during encoding. Stimulus encoding and maintenance are highly related processes. As ageing exerts an established effect on encoding speed (Jost, Bryck, Vogel & Mayr, 2010) it was thus necessary to control for a potential influence on alpha ERS during the maintenance period. Including alpha ERD during encoding significantly enhanced the model, corresponding to previous reports emphasising the relation between both processes (Woodward et al., 2006). However, our stress by age effect during encoding remained a significant predictor which highlights that our reported stress effect concerns cognitive processes relating to the maintenance of items in spatial working memory. This pattern of results mirrors an effect we discovered when comparing age and stress group performance on a standard Sternberg paradigm in which participants memorised strings of letters (Marshall et al., 2015). Here, we likewise reported reduced alpha ERS among members of the high stress older age group during maintenance. The replication of this effect in a memory task for object locations highlights that cumulative life stress affects spatial working memory as well as general forms of working memory. Thus, the damaging effects of cumulative stress extend to multiple domains of working memory.

4.4 Theta during maintenance

Frontal-midline theta activity during the maintenance interval revealed a similar pattern as the alpha frequency range. High stress older adults showed significantly reduced levels of theta ERS compared to younger high stress and older low stress counterparts. Crucially, this difference did not manifest when comparing older and younger low stress groups. Additionally, higher levels of theta ERS significantly correlated with enhanced memory performance providing a direct implication of this oscillatory process for the successful upkeep of item locations in working memory. Increases of frontal midline theta (FMθ) during the performance of working memory tasks have been reported extensively (Raghavachari et al., 2001; Meltzer et al., 2007; Scheeringa et al., 2009; Hsieh et al., 2011). For example, Jensen and Tesche (2002) observed increases of FMθ during the maintenance period of a digit Sternberg task which increased with the number of digits participants were required to retain. A parametric modulation of FMθ by memory load has been reported by a series of studies (Meltzer et al., 2007; Scheeringa et al., 2009; Hsieh et al., 2011; Roberts et al., 2013) and has led to the suggestion that FMθ may reflect medial pre-frontal working memory networks operating in conjunction with the anterior cingulate cortex and hippocampus (Burgess & Gruzelier, 2000; Kubota et al., 2001; Rippon et al., 2002). However, despite its apparent link to WM, the functional significance of FMθ is still unclear. An idea in line with the way FMθ manifests in the Sternberg task claims that FMθ is recruited to maintain temporal order information. Past work suggests that for highly demanding memory tasks, such as the Sternberg, participants may automatically maintain the temporal order of items to aid retention (Mangels, 1997; Hsieh et al., 2011; Hsieh & Ranganath, 2014). According to this account, cumulative stress may impact on older adults' recruitment of this strategy, thereby impacting on the effectiveness of their maintenance process. However, alternate accounts postulate that FMθ reflects the activation of neuronal assemblies corresponding to individual WM items (Lisman & Idart, 1995; Lisman & Jensen, 2013)θ. Interpreting reduced FMθ in line with this idea would speak to a reduced, possibly more diffuse, representation of encoded items among high stress older adults which may be harder to maintain. A final account, implicates FMθ in the co-ordination of reactivating visual stimulus information represented in WM (Lee et al., 2005). We explored this possibility by correlating FMθ during the maintenance period with alpha ERD during encoding. Our results show no relationship between activity representing the visual intake and encoding of stimuli and their subsequent maintenance reflected in FMθ activity and thus speak against this interpretation.

4.5 Further directions, limitations and conclusion

Our data highlights the wide-ranging impact cumulative stress exerts on older adults' cognitive health. It complements a body of work indicating that lifetime stress exposure produces performance deficits in the domains of memory, inhibition, executive control and pattern separation by demonstrating that performance decrements among older adults also manifest in spatial working memory. Importantly, analysis of oscillatory patterns provide insight on the functional mechanisms disrupted by prolonged exposure to stressful encounters. Thus, findings in the alpha and theta frequency highlight that stress impacts on older adults' attentional/inhibitory capacity as well as specific maintenance processes relating either to the retention strategy or the representational strength of maintained items. Promising follow-ups to our study include exploring the effects of cumulative stress in a paradigm that contrasts the two accounts of FMθ. Exploring the impact of stress across conditions in which either item information or their temporal order needs to be maintained would shed light on the functional significance of FMθ and provide insight on the way stress affects WM maintenance. A further extension lies in applying this work to less able bodied and active older populations. For this study, we recruited older participants from regional clubs and societies which resulted in a sample of socially and cognitively active individuals. To increase the findings' generalisability and external validity an important further step would therefore lie in exploring the impact of stress on less active and socially engaged older individuals who for example live in residential housing and or care homes.

We would also like to note that we used a modified version of the stress item scales.

Rather than indicating events of the past year, we requested that participants highlight stressful experiences across a much longer (life-) time period. We asked participants to be stringent concerning their recollections. However, it is plausible that despite the item list to trigger their memory certain events may have been forgotten or misremembered. Furthermore, our measure of stress differed between age groups. To assess the severity of stress relative to longer and shorter lifespans we adopted scales tailored to younger and older adults. However, this means we are unable to fully rule out that the effects of stress between age groups are not in part driven by a difference in commensurability. Thus, direct comparisons between older and younger adults for the different levels of stress should be interpreted with caution. However, we also find a difference in performance and oscillatory activity between older adults with high and low levels of stress. This difference manifests between groups assessed with the same scale and indicates that stress has a tangible impact on older adults' cognitive performance which cannot be captured to the same extent among younger individuals.

Present findings demonstrate that higher numbers of stressful life events coincide with reduced spatial working memory and alter oscillatory activity in frequencies tied to successful memory operations. Furthermore, we established a direct link between performance and theta activity in the maintenance phase of the task. This suggests that stress-incurred reduction of theta oscillations may act as one of the underlying cortical mechanisms by which stress hampers spatial memory. Findings extend a newly-developing field which suggests that the accrual of stressful experiences across the lifespan exerts an adverse effect on the cognitive operations of older adults. This highlights the importance of recognising and minimising exposure to stressful situations and environments from an early age onwards to facilitate cognitive health in old age.

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Table 1. Demographics of old and young participants split by experienced stress group

	Older Adults		Younger Adults	
	High Stress	Low Stress	High Stress	Low Stress
Group Size	15	15	15	15
Age	68.9 (3.8)	68.6 (5.4)	24.0 (3.7)	23.8 (1.8)
Gender	10 females	8 females	6 females	8 females
Education	4.07 (1.1)	3.98 (1.1)	4.69 (0.5)	4.71 (0.9)
Cigarette Consumption	0	0	0.54 (0.8)	0.29 (0.9)
Alcohol Consumption	1.5 (1.2)	2.69 (1.9)	1.46 (1.1)	1.65 (1.2)
Presence of Physical Disability	3	4	0	2
Exercise	2.36 (1.1)	2.06 (0.9)	1.62 (0.7)	2.06 (0.9)
Mini Mental State Score	28.4 (2.1)	29.3 (1.4)	n/a	n/a
Trait Anxiety Score	32.76	33.04	35.94	34.22
State Anxiety Score	36.88	35.38	34.87	33.93
Experienced Stress Score	899.1* (103.4)	473.6* (97.7)	730.4* (93.7)	351.7* (89.2)

Figure captions

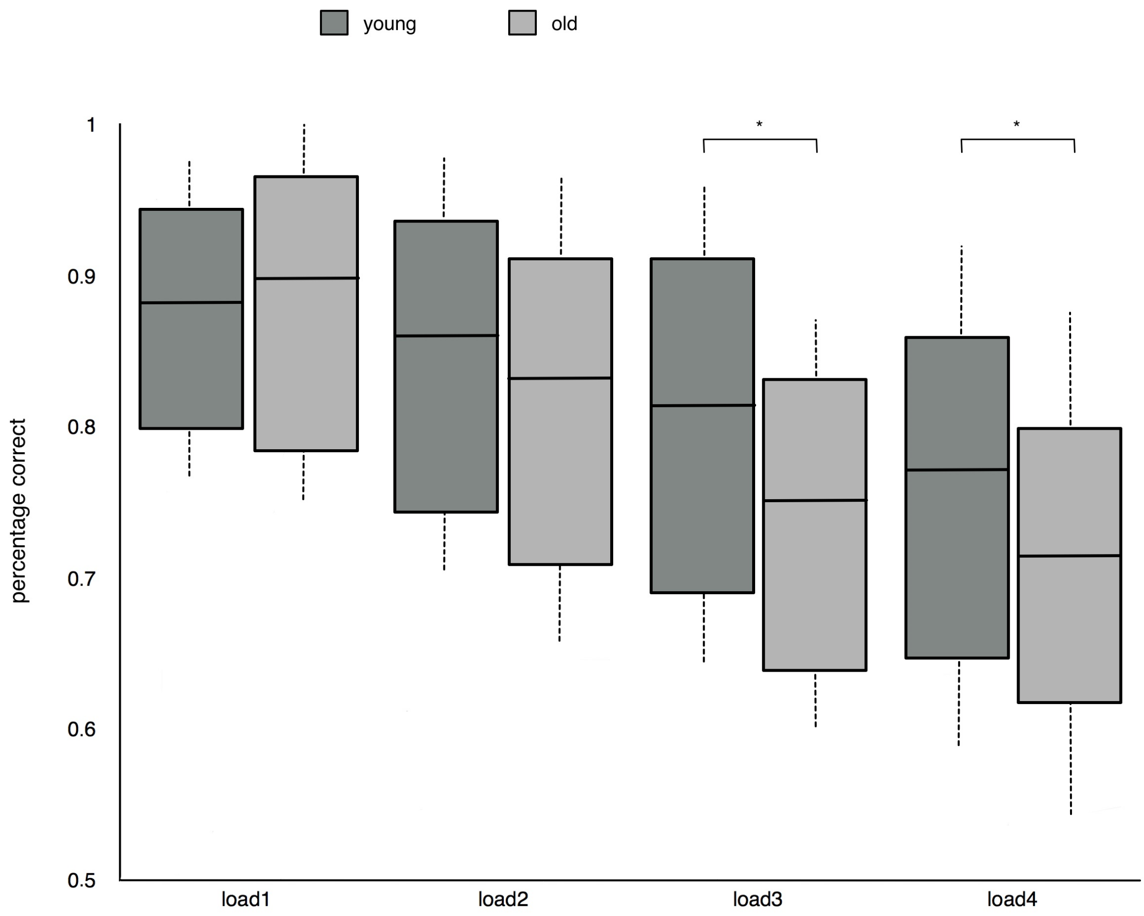
Figure 1. Box and plots displaying the performance of old and young participant groups across all four load conditions (whiskers represent standard deviations). Young adults outperformed old adults for the high memory load conditions.

Figure 2. Box plots of accuracy scores displayed across age and stress groups (whiskers represent standard deviations). Old adults reporting high levels of cumulative stress performed significantly below old low stress and young high stress group members.

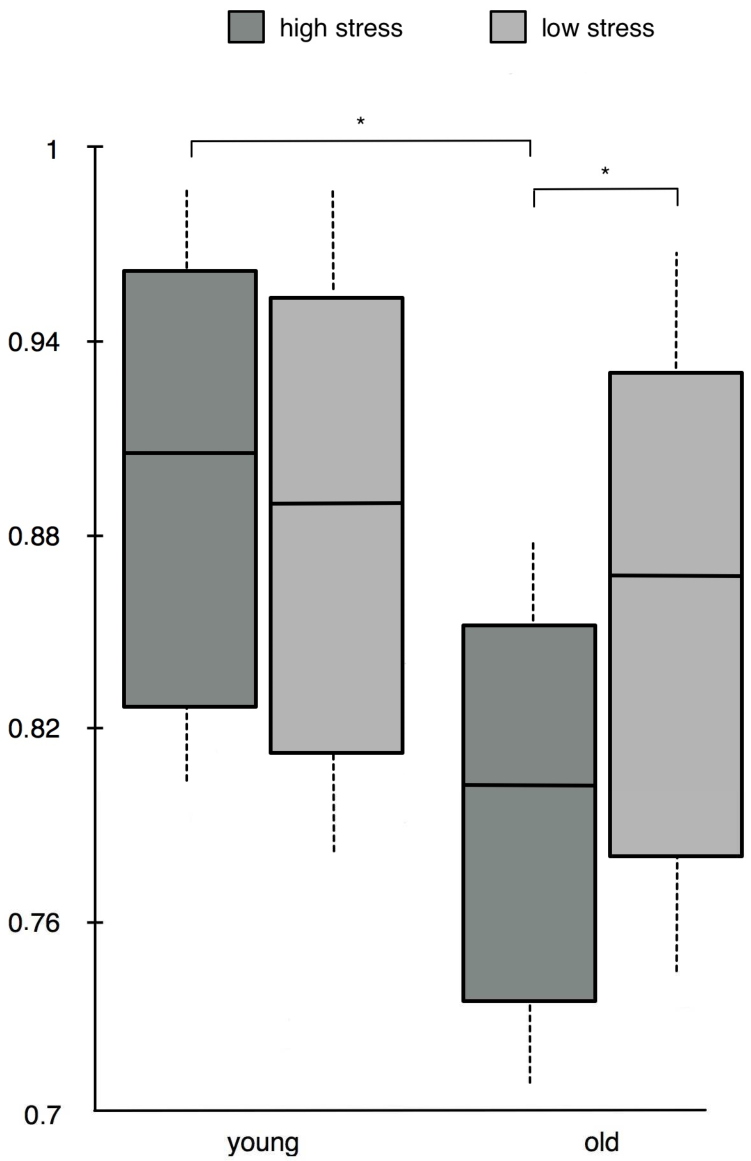
Figure 3. Grand average wave-forms displaying the percentage change of event-related alpha desynchronization during stimulus encoding. While no age difference manifested for low (load 1) demands on working memory, young participants showed higher levels of alpha ERD than old adults for high (load 4) demands on working memory.

Figure 4. Grand average wave-forms of the percentage change in alpha event-related synchronisation during stimulus maintenance. Old adults with high levels of stress displayed significantly reduced mid-occipital alpha activity compared to young high stress and old low stress counterparts.

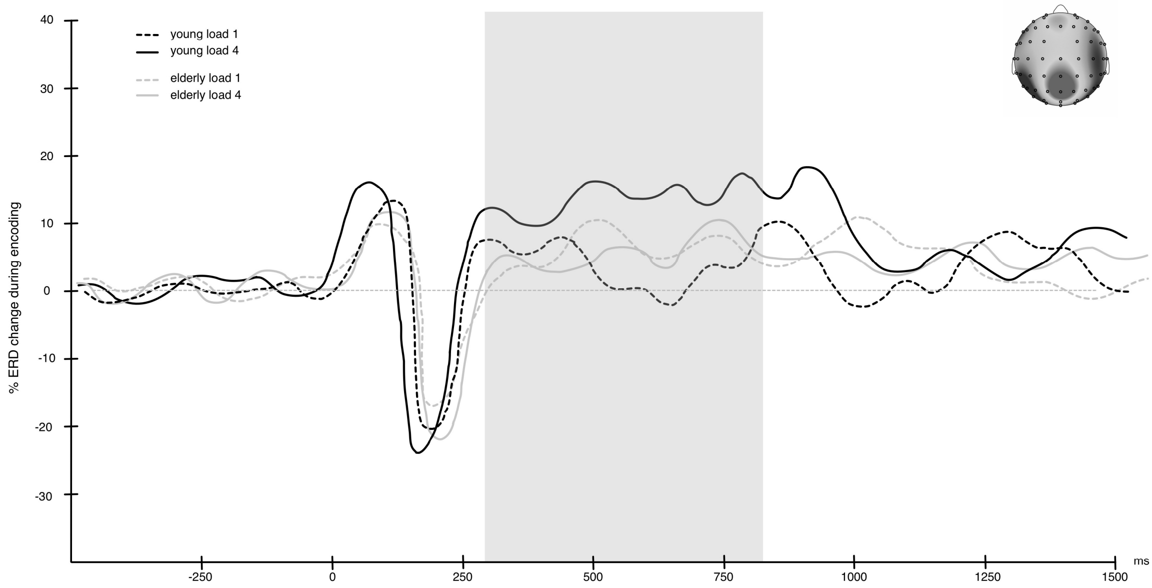
Figure 5. Grand average wave-forms of the percentage change in theta event-related synchronisation during stimulus maintenance. Old adults with high levels of cumulative stress displayed significantly reduced levels of frontal-midline theta synchronisation compared to young high stress and old low stress individuals.



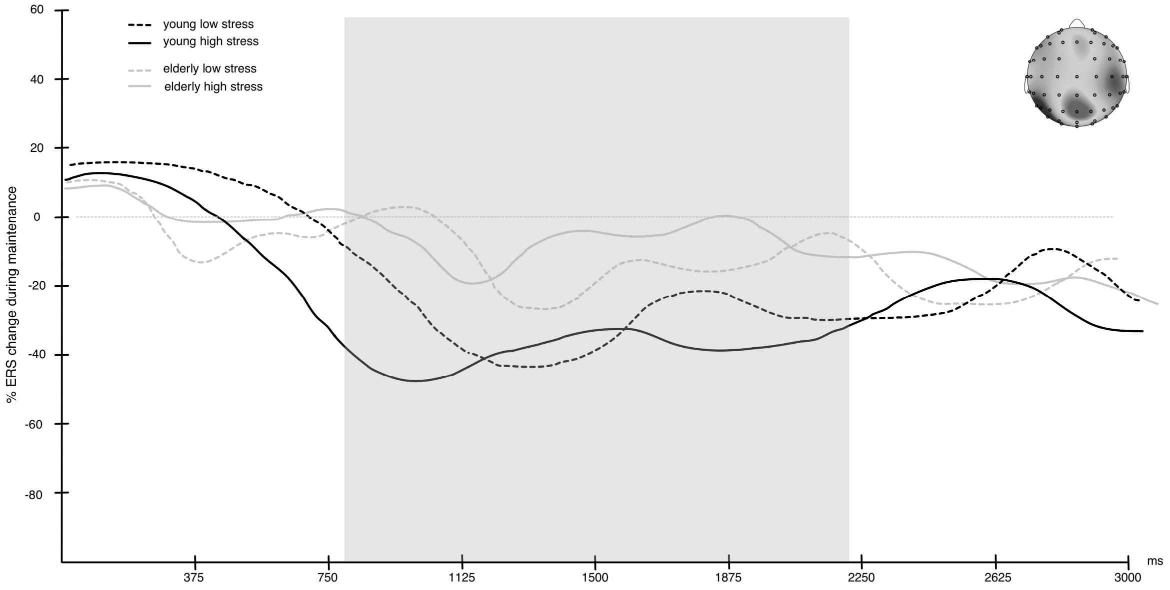
young
old
1
0.9
0.8
0.7
0.6
0.5
percentage correct
*
*
load1
load2
load3
load4



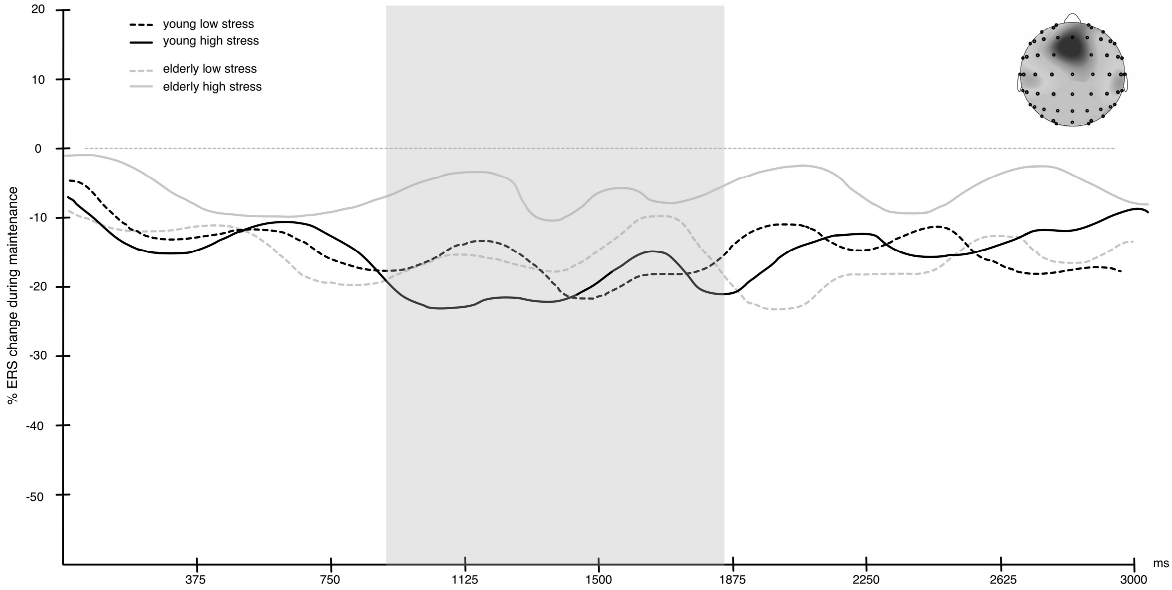
high stress
low stress
*
*
1
0.94
0.88
0.82
0.76
0.7
young
old



young load 1
young load 4
elderly load 1
elderly load 4
% ERD change during encoding
40
30
20
10
0
-10
-20
-30
-250
0
250
500
750
1000
1250
1500
ms



young low stress
young high stress
elderly low stress
elderly high stress
60
40
20
0
-20
-40
-60
-80
% ERS change during maintenance
375
750
1125
1500
1875
2250
2625
3000
ms



20
10
0
-10
-20
-30
-40
-50
% ERS change during maintenance
young low stress
young high stress
elderly low stress
elderly high stress
375
750
1125
1500
1875
2250
2625
3000
ms

- Life-time stress causes cognitive impairments among old adults
- These can be measured at the behavioral and electrophysiological level
- This study assessed stress-induced working memory impairments in old age
- Old high stress adults retained fewer memory items
- Behavioral impairments coincided with changes in the alpha and theta frequency