The Effects of Long-Term Stress Exposure on Aging Cognition: A Behavioral & EEG Investigation

Running Title:
The Effects of Long-Term Stress Exposure on Aging Cognition

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Abstract

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

Keywords

Alpha rhythm; Cognitive aging; EEG; Gamma rhythm; Stress

1. Introduction

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

In a rare longitudinal study, Peavy and colleagues (2009) reported that higher incidences of cumulative stressful experiences over the course of three years resulted in decreased memory performance among both normally ageing individuals and elderly participants suffering from Mild Cognitive Impairment. Additionally, cross sectional studies have established a link between heightened exposure to cumulative life stress and reduced memory performance in old age regardless of age or level of education (Dickinson et al., 2011; Tschanz et al. 2013). While presenting robust behavioral findings, the above cross sectional studies fail to control for health behaviors which have been found to affect cognitive aging such as the amount of cigarette and alcohol consumption (Kalminjn et al., 2002), the amount of physical exercise (Kimura et al., 2013) or the presence of a physical disability. More importantly, these studies do not recognize the actual importance of the subjective appraisal of the stress experience (Sands, 1981; Aggarwal et al., 2014).

The present study aimed to explore the relationship between cumulative life stress and cognitive aging while accounting for a range of mediating factors (see Table 1), including a measure of stress tolerance to address previous shortcomings highlighted by Sands (1981). A further objective of this study was to investigate the way in which cumulative stress affects maturation of the human brain. A good method to achieve this is the study of oscillatory dynamics (in the form of rhythmic fluctuation in the electrical activity across the cortex). These are increasingly seen as reflecting the brain's storage and manipulation of information necessary for successful behavioral performance (Buzsaki & Draghun, 2004; Engels, Fries & Singer, 2001; Varela et al., 2001). Oscillatory dynamics can be split into a number of different bands, which oscillate at different frequencies ranging from 0.5Hz to >60Hz. Specifically, increased synchronous activity in the theta (4-6Hz), alpha (8-12Hz) and gamma (30-60Hz) bands has been observed to predict enhanced cognitive performance. For instance, synchronous activity in the alpha band has been linked to the efficient suppression of task irrelevant information during memory maintenance periods (Klimesch et al., 2007; Sauseng et al. 2009) whereas theta and gamma activity have been linked to the successful maintenance and binding of a retained memory set (Perez et al., 2013; Roux & Uhlhaas, 2014).

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

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

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

In general, modulation of cortical oscillations during performance of both tasks has been reported to take place in the alpha, theta and gamma bands. Prominent findings report an increase in alpha event-related synchronization (ERS) during mid to late maintenance periods of the Sternberg task (Jensen, Gelfand, Konunios & Lisman, 2002). Similarly, both alpha and theta ERS have been reported to increase with N-back task demands (Brouwer et al., 2012), whereas excessive gamma ERS has been linked to reduced N-back task performance particularly among patients suffering from schizophrenia (Díez et al., 2014). Pronounced age differences have been reported in both the alpha and theta frequency range for the Sternberg paradigm (Karrasch, Laine, Pekka & Krause, 2004; Karrasch et al. 2006) and in the theta, alpha and gamma frequency range for the N-back task (Barr et al., 2014; Missonnier et al., 2011).

At the time of writing, investigations into the way cumulative experienced stress may affect cognitive aging have been undertaken on a behavioral level. A useful addition to the literature would therefore lie in pairing behavioral measures with an insight into the way stress affects the neural mechanisms underlying task performance. Accordingly, the present research aims to employ EEG to examine whether the impact of stressful life experience on cognitive performance is accompanied by corresponding changes in brain activation. Based on the hypothesis that long-term stress exposure may adversely affect brain structures necessary for cognitive functioning, highly stressed elderly participants were predicted to display reduced levels of behavioral performance, coupled with oscillatory changes, compared to young and low stress group elderly participants. Reduced event-related synchronization among elderly high stress group participants was predicted to occur in the theta, alpha and gamma frequency bands for the N-back and (based on the pronounced age differences discovered in these frequency bands when using this paradigm) in the theta and alpha bands for the Sternberg task.

2. Materials and Method

2.1 Participants

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

2.2 Stress and Demographical Measures

The present study focussed on the detrimental effect of experienced stress, accumulated over the course of a lifetime, on cognitive performance. However, given that our elderly participants have on average three times the age of the younger participants, they are likely to have experienced more stressful events. In addition, the types of stressful events are likely to be different for both our populations. Thus, in order to assess prolonged stress exposure appropriate to each age group and make the argument that the long-term effects of cumulative stress exposure are responsible for behavioral shortcomings and not purely high amounts of immediate stress, different instruments had to be used for elderly and young participants. Both the Social Readjustment Rating Scale (Holmes & Rahe, 1967; for elderly participants) and the Student Life Events Scale (Clements & Turpin 1996; for young participants) have a similar format, consisting of a brief, self-report scale (43 and 36 items respectively) containing incidents ranging from extremely stressful (i.e. 'Death of Spouse/Parent') to mildly stressful ('Finding a part-time job'). Participants' scores range from 0-1466 for the Social Readjustment Rating Scale and 0-1849 for the Student Life Events Scale with higher scores reflecting high amounts of experienced stress. To ensure values measured from different scales contributed equally to the analysis, the scores for each participant were standardised within age groups.

Stress tolerance was assessed via the Perceived Stress Scale (Cohen, 1983), a 10-item self-report scale assessing how unpredictable and stressful respondents have experienced their lives over the past month. Items include questions such as 'In the last month, how often have you felt nervous and stressed?' Further background demographics included participants' age, gender, level of education, cigarette and alcohol intake, amount of physical exercise and whether respondents suffered from a disability, which might compromise performance. Units and time frames of demographics assessment can be viewed in Table 1.

2.3 Procedure

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

For the N-back task (see Figure 1), participants viewed white numbers 1 to 4 (Helvetica) embedded within a 50% random noise grey patch with an additional blank 50% noise square for the control task. For the 2-back task, participants were asked to memorize the last two presented numbers and respond each time the number matched the one seen two positions previously. The control task consisted of responding each time the blank square appeared within the sequence. Participants responded to targets by pressing a response pad button with their right index finger. Each condition began with a blank screen presented for 200ms, after which the numbers were presented for 500ms with an inter-trial interval of 2500ms. Each condition of the N-back protocol comprised 120 trials. In the 2-back condition, 39 numbers acted as targets and 81 numbers as non-targets. In the zero-back condition, 39 blank grey squares acted as targets and 81 numbers as non-targets. No response was required for non-targets. Each condition was split into three blocks of 40 trials by two breaks lasting for 10 seconds in the control and 40 seconds in the experimental condition. Control and 2-back conditions were presented to participants in counter-balanced order. Consequently, half the participants completed the control trials first, then moved on to the 2-back condition. The other half of participants experienced the reverse order.

For the Sternberg protocol (see Figure 1), participants viewed a sequence consisting of a blank screen presented for 1000ms, followed by a letter-set displayed for 4000ms. Letter-sets and single probe letters consisted of 15 pseudo-randomly combined consonants (Helvetica) enclosed within a 5% noise grey patch. After a further blank screen presented for 3000ms, a single probe letter appeared for 2000ms during which participants were asked to indicate whether the letter had been part of the original letter-set or not. Participants responded by pressing a button on the response pad with their right index finger each time they believed the probe had been part of the original letter set. The sequence ended with a brief 115 ms masking stimulus. The Sternberg task was comprised of 100 trials of which 60 included a target probe letter and 40 a non-target probe. No response was required for non-targets. Participants were given the opportunity to take a break after 50 trials.

2.4 Psychophysiological recording and analysis

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

Acquired data was visually inspected and noisy data blocks, general artifacts and bad electrodes subsequently rejected. Ocular artifact rejection was carried out by performing principal component analysis on the acquired eye movement data to obtain the components reflecting saccades and blinks (Vigario et al. 2000). These were subsequently subtracted from the task data traces. All data was re-referenced to a common average reference. In order to investigate age and stress related group differences in response to completing both tasks the 64 electrodes were averaged into nine brain regions: left (FP1,AF3, F7, F5, F3, F1, FT7, FC5, FC3, FC1), mid (FPz, Fz, FCz) and right (FP2, AF4, F8, F6, F4, F2, FT8, FC6, FC4, FC2) frontal; left (T7, C5, C3, C1, TP7, CP5, CP3, CP1), mid (Cz, CPz) and right (T8, C6, C4, C2, TP8, CP6, CP4, CP2) central; left (P7, P5, P3, P1, PO7, PO5, PO3, CB1, O1), mid (Pz, POz, Oz) and right (P8, P6, P4, P2, PO8, PO6, PO4, CB2, O2) posterior.

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

To investigate ERD/S activity during the maintenance period of the Sternberg task, data segments were cut into a 3000ms retention test period used for subsequent analysis. This was based on findings by Jensen and colleagues (2002) who reported oscillatory differences, as a function of memory load, manifested in the last 2 seconds of the retention interval. The reference period consisted of 1000ms at the beginning of each sequence during which participants viewed a blank screen. Calculation of the ERD/S activity for the Sternberg maintenance period included epochs from correct (target and non-target) trials as no motor response was required during this period.

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

2.5 Data Preparation

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

To investigate the impact of experienced stress on cortical oscillations, experienced stress scores of young and elderly participants were grouped into high and low stress groups employing the median split of scores from the Social Readjustment Rating Scale for elderly (Median Split value 671) and the Student Life Events Scale for young participants (Median Split value 568). No significant group differences in Mini Mental State performance, age, gender, level of education, cigarette or alcohol consumption or amounts of exercise were observed between stress groups (see Table 1).

3. Results

3.1 Behavioral Analysis

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

3.1.1 Sternberg Results

For the accuracy data (see Table 2), the first model was significant, accounting for 18% of the variance in performance, ($F(2,57) = 6.31$, $p = .003$). Both age and experienced stress scores were independently associated with a decrease in accuracy. The inclusion of the interaction of age by experienced stress accounted for an additional 11% of the variance, ($F(1,56) = 8.72$, $p = .003$). Simple slopes analysis was conducted (see Figure 2). An age-group difference emerged when experienced stress was high ($t(59) = 9.12$, $p < .001$). No other comparison was significant. This suggests that being a member of the older age group coupled with high experienced stress scores was associated with decreased cognitive performance on the Sternberg task. Crucially, the nature of this interaction was identical when controlling for other variables in step 3.

For the rt data, the association between age, experienced stress and reaction times produced an overall significant model ($F(2,57)= 4.17$, $p=.036$) which accounted for 11% of variance in reaction times. Age was the sole predictor showing that elderly participants were generally slower. Neither the addition of the interaction (step 2), nor the addition of the control variables improved the model ($p > .05$).

3.1.2 N-back Results

Looking at the N-back accuracy data next (see Table 2), the first model accounted for a significant 17% of the variance ($F(2,57) = 5.90$, $p = .005$). In terms of individual predictors, only participants' age was positively associated with decreased performance. The inclusion of the age by experienced stress interaction accounted for an additional 15% of variance ($F(1,56) = 12.23$, $p = .001$). Simple slopes analysis (see Figure 2) found a significant age-difference when experienced stress was high ($t(59) = 6.74$, $p < .001$). No other comparisons reached significance. Importantly, the interaction remained significant after control variables were included (step 3).

Similar to analysis of the Sternberg task, investigating the relationship between age, experienced stress and reaction times produced a significant model in the first step ($F(2,57)= 4.2$, $p=.43$). Age as the only independent predictor accounted for 9% of the variance in reaction times. Adding the interaction term and demographical factors in the following stages produced non-significant models ($p>.05$) in which only age acted as a significant predictor of reaction times.

3.2 Electrophysiological Analysis Sternberg

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

3.2.1 Sternberg Mid (1000 to 2000ms) Maintenance Period

Analysis of the mid period indicated a significant Laterality x Sagittality x Age x Experienced Stress interaction for the upper alpha frequency range ($F(4,224)= 2.69$, $p= .032$). To further decompose this interaction, a Laterality x Sagittality x Age ANOVA was conducted separately for both stress groups. The three-way interaction for the low stress group was not significant ($p> .20$). The three-way interaction for the high stress group approached near significance ($F(4,112)= 2.84$, $p= .058$). Due to the exploratory nature of the present study and given that hypotheses related to simple main effects, follow-up comparisons were conducted for this interaction. These revealed that among individuals with high experienced stress scores, young participants, compared to elderly counterparts, showed substantially increased upper alpha synchronization over left central ($F(1,56)= 4.28$,$p= .043$) and right posterior ($F(1,56)= 5.63$, $p= .021$) regions (see Figure 3). No significant main effect or interactions were discovered in the lower alpha or theta frequency range ($p>.05$).

3.2.2 Sternberg Late (2000 to 3000ms) Maintenance Period

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

3.2.3 Sternberg Behavioral Correlations

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

3.3 Electrophysiological Analysis N-back

Based on previous findings in the theta, alpha and gamma frequencies, upper/lower alpha, upper/lower gamma and theta frequencies were analysed using a 3 (Laterality: left, mid, right cortical regions) x 3 (Sagitality: frontal, central, posterior cortical regions) x 2 (Condition: control/2-back) x 2 (Age: old/young) x 2 (Experienced Stress: high/low) mixed measures ANOVA. The former three factors comprise within-subjects variables.

A main effect for age was found for the upper gamma frequency band in which young participants showed more synchronization compared to elderly counterparts ($F(1,44)= 7.5$, $p= .009$). Results further revealed a significant Condition x Age x Experienced Stress interaction ($F(1,44)= 5.56$, $p= .023$). To decompose this, the analysis was run with two separate ANOVAS for both Stress groups. For the low experienced Stress group, the Condition x Age interaction was not significant ($p>.05$). The model for the high experienced Stress group showed a significant Condition x Age interaction ($F(1,20)= 5.2$, $p= .034$). Follow-up comparisons indicated a significant age difference for the 2-back condition ($F(1,20)= 6.4$, $p= .02$) in which elderly participants showed lower levels of upper gamma synchronization compared to young (see Figure 4). Furthermore, a significant difference was observed between the control and 2-back condition for highly stress group elderly $F(1,20)= 5.4$, $p= .031$) in which higher levels of upper gamma synchronization were shown in the control detection condition compared to the 2-back condition (see Figure 4). Both differences were observed over the entire cortex. No significant main effect or interactions were discovered for the theta or upper/lower alpha frequency range ($p>.05$).

3.3.1 N-back Behavioral Correlations

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

4. Discussion

The present study explored the possible impact of cumulative experienced stress on cognitive aging. Results indicated that experienced stress negatively impacted on elderly participants' performance as elderly participants with high levels of cumulative experienced stress displayed lower overall performance scores (d') on both Sternberg and N-back tasks. Furthermore, reduced behavioral performance among the elderly participant sample was found to coincide with differences in oscillatory dynamics linked to successful cognitive task performance.

4.1 Behavioral Results

Performance scores on both tasks found a significant age difference between young and elderly participants, which only occurred among individuals with high cumulative experienced stress scores. Behavioral results therefore indicate that experienced stress has selectively compromised elderly participants' ability to perform successfully on either cognitive WM task. Behavioral results remain stable after controlling for a number of mediating factors including perceived stress. This supports both previous longitudinal and cross-sectional work (Peavy et al., 2009; Dickinson et al. 2011) reporting that larger amounts of cumulative experienced stress coincided with decreased WM performance among elderly individuals. Finding no cognitive impairments among young individuals reporting high amounts of experienced stress indicates that it is not a large amount of experienced stress per se which causes cognitive impairment. Thus, results support the study's argument that only long-term exposure to high amounts of cumulative stress experienced over the lifespan results in cognitive impairment. Furthermore, failure to find an impact of perceived stress indicates that it is not the subjective feeling generated by the stressful life event but the experience of the event that has an adverse effect on elderly cognitive performance. The study's behavioral findings therefore indicate that the total amount of experienced stress sustained throughout the lifespan may impact on cognitive performance and the rate of cognitive aging.

4.2 Electrophysiological Results Sternberg

Stress-related differences in oscillatory activity for both tasks were found in alpha and gamma frequency ranges. For the Sternberg paradigm, findings in the mid epoch of the retention period revealed a difference in high alpha ERS among young and elderly participants in the high experienced stress group: young participants were found to display increased alpha ERS compared to elderly over left central and right posterior cortical regions. Correlating high alpha activity with behavioral scores showed that the reduced alpha synchronization displayed by elderly participants in the high stress group related to reduced performance on the Sternberg task.

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

The reduction of upper alpha ERS among high stress elderly participants may also indicate an adverse effect of cumulative stress on areas of the hippocampus proposed by Sapolsky and Meaney (1986). The work of Babiloni and colleagues (2009) reported that reduced hippocampal volume among elderly individuals coincided with a reduction in alpha power, therefore these results may indicate increased damage to the hippocampus sustained by elderly participants in the high stress group.

4.3 Electrophysiological Results N-back

Results for the N-back paradigm showed that in the high experienced stress group, young participants displayed higher levels of upper gamma synchronization compared to elderly participants. Furthermore, elderly participants in the high experienced stress group showed a significant reduction of upper gamma ERS from the control to the demanding memory task. Both differences were observed over the entire cortex. Furthermore, correlational analysis revealed that increased levels of upper gamma ERS over the entire cortical region were related to increased overall performance.

Gamma ERS during memory maintenance periods is commonly interpreted as the active binding and maintenance of a memory set (Roux & Uhlhaas, 2014). Contrary to the maintenance period of the Sternberg task, successful monitoring of an N-back sequence requires the engagement of numerous aspects of WM and entails ongoing fast paced binding and updating of information. A significant age difference among individuals in the high stress group, therefore indicates that experienced stress may have impacted on elderly participants' ability to maintain the continual active binding required for successful N-back task performance and could account for the observed reduction in performance displayed by elderly individuals with higher levels of experienced stress. The significant reduction of gamma ERS from the control to the memory demanding 2-back task among elderly participants in the high experienced stress group forms a further indication of impaired functioning. Inspection of group averages revealed that both young and elderly participants in the low stress group increased levels of gamma ERS from the control to the 2-back task, which reflects heightened task demands. The reduction of gamma synchronization among elderly participants in the high stress group may therefore suggest a breakdown of cortical activity once a task becomes too demanding and exceeds coping abilities. In keeping with this, a number of studies investigating age-related performance differences on the N-back task have reported that age differences only appear once demands require matching the current stimulus to the stimulus two positions back (Verhaeghen & Basak, 2005). Similar to the claim made by Babiloni and colleagues (2009), synchronous oscillatory activity in the gamma frequency range has been argued to reflect hippocampal activation, indicating a dynamic interaction between the cortex and hippocampus (Wang & Buzsaki, 1996). The reduction of upper gamma ERS among high stress elderly participants may therefore form a further indication of damage sustained to the hippocampus through heightened levels of experienced stress.

4.4 Further directions and conclusion

This study sheds an interesting light on the way cumulative experienced stress may impact on cognitive aging. However, capturing the impact of mediating factors when aiming to assess a long-term impact using cross-sectional data is a great concern. Further contributions to this area of research could therefore lie in accounting for further potential mediators such as measurement of participants' cortisol levels or life-style factors not assessed by the current study such as diet or living environment. Also, the current study used two different measures to assess cumulative experienced stress among elderly and young individuals, which may have affected stress-related differences. However, employing two different measures was necessary to test the study's argument that experienced stress acts detrimentally to cognitive performance only in its cumulative form (as sustained over the life span). Moreover, by standardising cumulative stress scores within age groups, measures were taken to ensure differences resulting from the use of two different scales were kept to a minimum. Furthermore, we argue that if the same scale had been used to ascertain experienced stress for both age groups, it would not be pertinent to compare this main effect. Compared to young individuals, elderly participants would necessarily obtain a higher stress score due to having lived longer. Furthermore they might construe the scale differently or have a different outlook on their lives based on their viewpoint (looking back after having lived most of their lives whereas young individuals have most of their time still ahead). Therefore different stress scores could manifest for a variety of different reasons and would not reliably reflect how stressful a live a young individual has led relative to an elderly counterpart. In order to circumvent this issue, the current study employed two different scales tailored to the different stressful experiences individuals of different age groups may experience. Also we refrained from comparing main effects of experienced stress scores and focus instead on the interactive relationship between age and cumulative experienced stress, which we argue, provides more meaningful insight into the way cumulative stress impacts on cognitive performance. Finally, despite past studies successfully establishing links between oscillatory activity and the integrity of subcortical brain structures this remains an indirect measure. Therefore, the current results provide an insight into the way stress affects the brain on a cortical level but cannot directly indicate how it may have affected the hippocampus. To study the effect of stress on subcortical areas of the brain, further research will need to utilize neuroimaging techniques able to investigate subcortical structural changes.

Findings of this study highlight the potentially adverse effect of cumulative experienced stress on age-related cognitive WM performance and provide insight into the way experienced stress may affect cortical oscillatory dynamics. Behavioral findings on both the Sternberg and N-back task demonstrate a clear association between higher experienced stress scores and reduced performance, which was specific to elderly participants. In terms of electrophysiological data, cumulative experienced stress impacted on the upper alpha and gamma frequency ranges resulting in a possible impairment of inhibitory upper alpha activity in the Sternberg task and a reduced capability in the upper gamma range in maintaining a sequential memory set in the N-back task. Sternberg demands requiring the sustained 'static' maintenance of stimuli produced differences in the upper alpha frequency range. Conversely, the continuous updating of the WM store required by the N-back task produced differences in the upper gamma band. This suggests cumulative stress may have a broad effect on WM and affect multiple aspects conducive to successful performance. Furthermore, both alpha and gamma ERS have been argued to index intact hippocampal functioning. Therefore, the reduction of event-related-synchronisation in both frequency bands forms a further indication of the adverse effect of cumulative experienced stress on the hippocampus and indicates how it may affect the brain on both cortical and subcortical levels. The present paper therefore constitutes further evidence that cumulative experienced stress should be considered as a possible risk factor for accelerated cognitive decline.

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Tables:

Table 1: Demographical variables of the participant sample split by age and experienced stress group.

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

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

Table 2 Linear regression models of Demographics and Experienced Stress by Age interactions predicting scores on the Behavioral paradigms

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

Note: *p<.05, **p<.01; gender coded as 1=male, 2=female

Captions to figures:

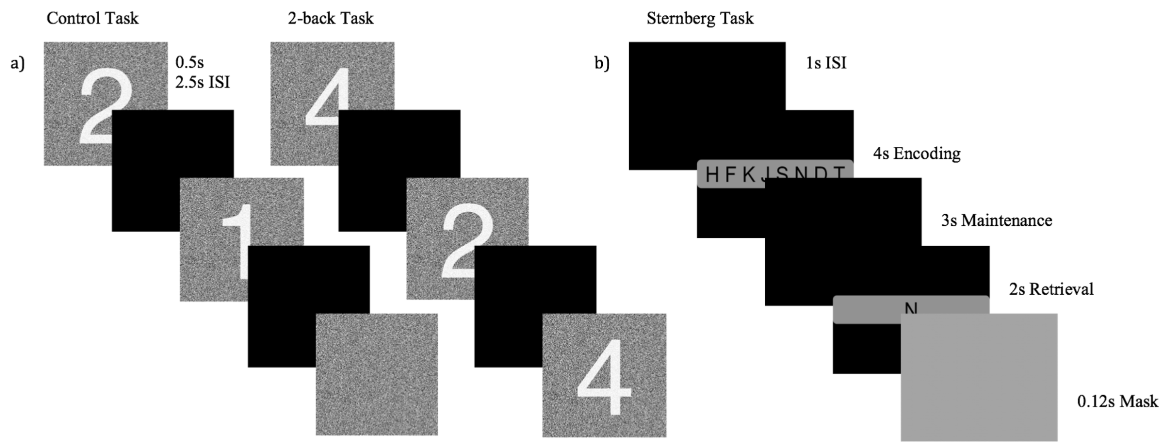

Figure 1

Figure 1: a) Control and 2-back versions of the N-back task. The control task required participants to respond each time they saw an empty grey square, whereas the 2-back version required a response each time the currently presented number matched the one seen two positions back. For both versions presented in figure 1a) the correct response would be to the third stimulus. b) Schematic representation of the Sternberg task indicating the duration each image was presented. Participants were asked to memorize the 8-letter sequence and respond each time the single probe letter was included in the foregone array.

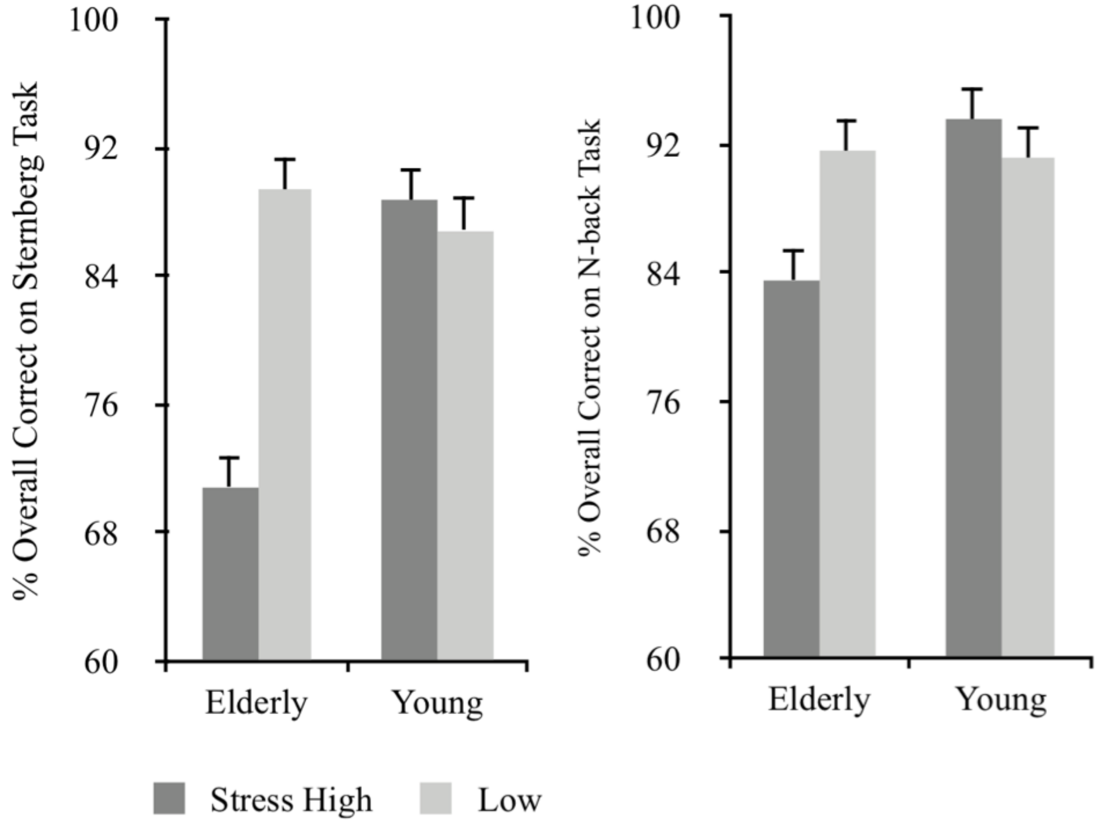

Figure 2

Figure 2: Performance scores of young and elderly participants split into high and low experienced stress groups. For both the Sternberg and N-back task, the difference between high and low stress group elderly participants reached significance. Error bars represent SEM.

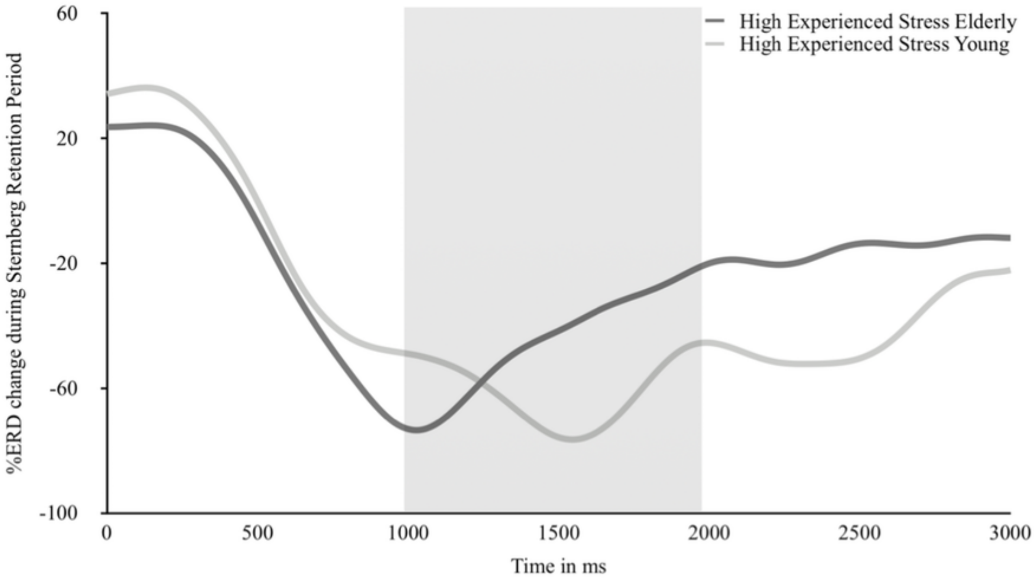

Figure 3

Figure 3: High Alpha grand average waveforms computed over the right posterior cortex for both high stress age groups. The percentage of ERD change indicates high stress group elderly participants display reduced high alpha synchronization during the Sternberg maintenance period when compared to high stress group young counterparts.

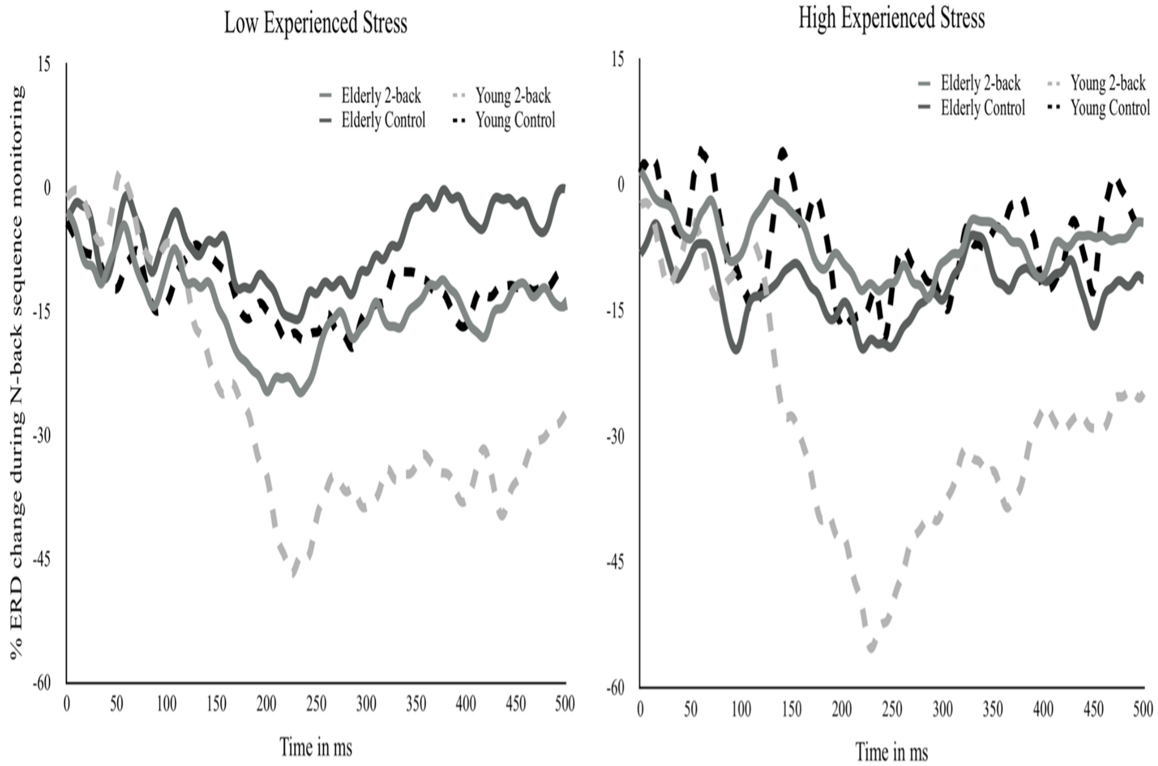

Figure 4

Figure 4: Grand average waveforms for high gamma range computed over the entire cortex during N-back sequence monitoring. Among the high experienced stress groups the difference between elderly and young participants on the 2-back task reached significance, as well as the difference between the control and the 2-back task for elderly participants. Low experienced stress group averages show the increase in high gamma ERS among elderly individuals when moving from the control to the 2-back task which is reversed for high stress group elderly participants.