The Association between High Levels of Cumulative Life Stress and Aberrant Resting-state EEG Dynamics in Old Age

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Abstract

Cumulative experienced stress produces shortcomings in old adults' cognitive performance. These are reflected in electrophysiological changes tied to task execution. This study explored whether stress-related aberrations in older adults' electroencephalographic (EEG) activity were also apparent in the system at rest. To this effect, the amount of stressful life events experienced by 60 young and 60 elderly participants were assessed in conjunction with resting state power changes in the delta, theta, alpha, and beta frequencies during a resting EEG recording. Findings revealed elevated levels of delta power among elderly individuals reporting high levels of cumulative life stress. These differed significantly from young high and low stress individuals and old adults with low levels of stress. Increases of delta activity have been linked to the emergence of conditions such as Alzheimer's Disease and Mild Cognitive Impairment. Thus, a potential interpretation of our findings associates large amounts of cumulative stress with an increased risk of developing age-related cognitive pathologies in later life.

Keywords: Cognitive aging; Experienced stress; Electroencephalography (EEG); Delta power; Cognitive pathology

Introduction

Aging research faces a prime challenge: to develop a better understanding of the neurobiological mechanisms that mediate cognitive decline and its associated cognitive pathologies (Albert et al., 2011; Braak & Braak, 1991; Dubois et al., 2007; Nestor et al., 2004). A widely available, low-cost way to discover neurocognitive markers of age-related decrements is the recording of resting-state electroencephalographic (EEG) rhythms (Rossini et al., 2007; Babiloni et al., 2015). Abnormalities in the power spectra of different frequency ranges have been linked to altered cerebral blood flow, impaired cognitive functioning as well as reduced structural integrity of associated brain regions (Rodriguez et al., 1999a, 1999b; Sloan et al., 1995; Babiloni et al., 2012). In recent years, they have gained widespread credibility as an indicator of age-related cognitive change and have been used extensively to study both healthy and pathological aging (Bruce et al., 2009; Knyazeva et al., 2010; Dauwels et al., 2011; Scheltens et al., 2012; Morabito et al., 2012; Babiloni et al., 2016; Cozac et al., 2016; Neto et al., 2016).

Pathological Aging

A consistent finding when comparing old adults suffering from Alzheimer's Disease (AD), Amnesic Mild Cognitive Impairment (MCI) or vascular dementia (VaD) to healthy aging individuals is an increase of resting power in low frequency bands delta (0.5 – 4 Hz) and theta (4 – 6 Hz) (Signorino et al., 1995; Moretti et al., 2012; Babiloni et al., 2013; Chen et al., 2015) coupled with a reduction of power in higher frequencies such as posterior alpha (8 – 12 Hz) (Jeong, 2004; Koenig et al., 2005; Babiloni et al., 2015) and beta (12 – 20 Hz) (Brenner et al., 1986; Wu et al., 2013). This power shift from high to low frequencies has been found to correlate with the severity of the condition (Kowalski et al., 2002). It has also been documented in longitudinal studies (Rae-Grant et al., 1987; Soininen et al., 1989; Morabito et al., 2015). For example, Coben and colleagues (1985) observed that over a follow-up period ranging from 2.5 – 5 years, the resting power spectra of elderly AD patients exhibit significantly increased delta and theta power, in conjunction

with severely reduced alpha and beta power. Similarly, Luckhaus and colleagues (2008) reported that compared to healthy controls, individuals suffering from Mild Cognitive Impairment displayed a significant decrease of posterior alpha power over a 1-year follow-up period, which correlated with reduced cognitive performance.

Healthy Aging

Reports on the resting power spectra of healthy aging individuals highlight a reduction of alpha power, particularly over temporal regions of the cortex (Busse et al., 1956; Cheng et al., 2015). Contrary to findings of elevated theta power among old adults suffering from AD, MCI or VaD, Finnigan and Robertson (2011) reported that resting theta power (4 - 6.5 Hz) significantly correlated with measures of memory, attention and executive functioning in a sample of 73 healthy older adults. To dissociate their findings from reports on aging decline, the authors suggested the possibility of two forms of theta power: one reflecting 'true' theta network activity which indicates healthy cognitive aging; the other comprised of slowed alpha activity which has dropped into the theta frequency range and indicates cognitive impairment. Further power changes among healthy elderly participants were reported by Babiloni and colleagues (2006) whose investigation of the resting power spectra of 108 young and 107 elderly individuals highlighted a decrease of occipital delta power with advancing age as well as a global reduction of alpha power which manifested independently of the known slowing of the alpha rhythm.

Cumulative Life Stress and Cognitive Aging

An emerging field in the aging literature concerns the link between cumulative life stress and cognitive decline in old age. Cumulative stress refers to the sum total of stressful life experiences individuals accumulate during their lifespan and has been shown to impair cognition in both its chronic (Juster et al., 2010) and acute form (Dominique et al., 2000). Long-term exposure to the stress hormone cortisol (glucocorticoids) has been linked to memory impairment and smaller hippocampal volume (Wignall et al., 2004; Gerritsen et al., 2011; Teicher et al., 2012; Pinheiro et al., 2015). Similarly, memory performance of

older adults can be acutely modulated by pharmacological manipulation of glucocorticoids, while in young adults, cognitive performance sustained by the frontal lobes is likewise sensitive to increased levels of glucocorticoids (Lupien et al., 2005; Cao et al., 2010). Acute stress has been found to impact cognition by promoting engagement in repetitive thinking, negative emotions and social isolation, each of which have also been shown to result in decreased memory performance (Scott et al., 2015; Richard & Gross, 2000; Kremen et al., 2012). In addition, cumulative stress has been shown to produce lifestyle changes such as a poor diet, increased consumption of alcohol/tobacco and reduced physical activity (Steptoe et al., 1996). In turn, these changes can result in chronically reduced perfusion and oxygenation of the brain and may ultimately lead to vascular cognitive impairment or vascular dementia (Román, 2004). Old age has been theorised to coincide with an increased vulnerability to the adverse effects of stress, resulting from decreased cognitive/coping resources (Lupien et al., 2009) as well as from neurobiological changes that may enhance the damaging effect of stress on the brain. The aging brain shifts from a homeostatic balance of inflammatory mediators to increased concentrations of active microglia, increased levels of inflammatory cytokines and decreases of anti-inflammatory molecules (Sparkman & Johnson, 2008); a pro-inflammatory state that may constitute increased susceptibility to the adverse effects of stress.

In keeping with this literature, cross-sectional and longitudinal work has demonstrated that large amounts of cumulative stress reduce the performance of elderly participants completing working memory and executive control tasks (Dickinson et al., 2011; Peavy et al., 2009; Pesonen et al., 2013). Controlling for age, education and sex, Dickinson and colleagues (2011) reported that the total number of stressors experienced by old adults acted as a significant predictor of cognitive performance on tasks of working memory, category fluency and verbal learning. Similarly, a longitudinal design by Pesonen and colleagues (2013) reported that individuals separated from their parents during the Second World War showed accelerated cognitive decline at age 70 when compared to age-

matched controls, while no such difference emerged between both groups at age 20. These findings highlight the damaging effect of cumulative lifetime stress, which emerges in later life and accelerates senescence in old adults. Our own work extended these behavioral findings by demonstrating that they coincide with task dependent alterations in the theta, alpha and upper gamma frequencies (Marshall et al., 2015; Marshall et al., 2016a, 2016b). For example, we recently demonstrated that among old adults, stress-related reductions of memory performance coincided with reduced upper gamma activity (Marshall et al., 2015) while executive impairments correlated with reduced synchronisation of the alpha rhythm (Marshall et al., 2016a). Our findings thus highlight that cumulative stress impacts on cortical neurocognitive processes necessary for intact cognitive performance.

Overview of experiment

This study aims to investigate whether electrophysiological changes during task execution are associated with altered power differences at rest. To this effect, resting state recordings were obtained from a sample of 120 individuals (60 old, 60 young). These were analysed with regard to power spectrum differences in the delta, theta, alpha and beta frequency ranges. Should the detrimental effects of cumulative stress be associated with changes in the system at rest, significant power spectrum differences were expected to manifest for old adults with high levels of stress compared to young (low and high stress) individuals and low stress old counterparts. Based on reported changes related to healthy aging, reductions of alpha, beta and theta power among high stress old adults were expected. Should stress exposure have resulted in increased vulnerability towards contracting age-related pathologies, an increase in low frequency delta and theta power among high stress older adults was hypothesised.

Materials and Method

Participant selection

Sixty young adult participants (41 females; Mean age = 22.3, SD = 1.4; Range = 18-30 years) were recruited from the University of Essex student population via

institutional e-mail advertising. Sixty elderly participants (39 females; Mean age = 68.1, SD = 2.3; Range = 60-85 years) were recruited from advertisements to local clubs and societies. Exclusion criteria specified in the advertisement included major medical conditions (i.e. diabetes, heart disease), major neurological damage (i.e. stroke) and a current diagnosis of a mental or psychiatric disorder (dementia, depression or anxiety disorder). As this study focussed on stressful events commonly encountered throughout the lifespan, adverts specified that participation was only possible without the experience of traumatic life events. In addition, participants were asked prior to study commencement whether they had experienced a traumatic stressful incident, such as emotional, physical or sexual abuse at any point in their lives. None of the participants reported the occurrence of past trauma[1]. Potential group differences concerning anxiety levels were further assessed by the State-Trait Anxiety Inventory (Spielberger et al., 1968). However, no stress or age group differences emerged for scores on either the state or trait anxiety subscale (see Table 1). Elderly participants were further screened for the use of psychoactive medication, a history of substance abuse and consumption of anti-depressant/anxiolytic drugs in the recent past (< 4 months). To ensure against undiagnosed cognitive pathologies, elderly participants completed the Mini Mental State Examination (Folstein, Folstein & McHugh, 1975) in which all scored within the range of normal cognitive functioning (>26).

Procedure

For the purpose of this study, the resting-state condition is defined as a mode of brain activity unrelated to visual processing, task demands or goal-oriented cognitive operations (planning, problem solving or expectations about personal matters or tasks). As such, participants were instructed to close their eyes, remain awake and refrain from any

[1] We must note that we relied on a simple exclusion criterion in this regard. Given that prevalence rates for different forms of abuse and neglect in childhood and later life lie between 12 % – 32.1% (Häuser et al., 2011; König et al., 2015) we are not able to fully rule out that a more advanced interview technique may have uncovered certain forms of trauma in a subset of our participants. This limitation should be noted when considering present findings.

specific goal-oriented activity for the duration of the 2-minute recording. Each resting state recording was preceded by an eye-movement calibration session (Croft & Barry, 1998).

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 references to a point midway between Cz and CPz. Impedances were lowered to below 10kΩ in all electrodes before acquisition. EEG signals were recorded and analysed using a Neuroscan Synamps2 system in conjunction with SCAN 4.5 software (Compumedics, Melbourne, Australia). Data was recorded at a sampling rate of 1000Hz with a band-pass filter of 0.05-200Hz.

Acquired data was visually inspected and noisy data blocks, general artefacts and bad electrodes were 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, the acquired components were rejected from the resting state data trace (Vigario, 199; Vigario et al., 2000). The minimal total amount of available artefact free data was 40 s for each participant. Past work has demonstrated that 20 s of EEG are sufficient to adequately reduce the EEG's variability (Gasser et al., 1985; Koenig et al., 2005). We therefore deemed this time period as sufficient for analysis. All data was re-referenced to a common average reference and was subsequently divided into the delta (0.5-4Hz), theta (4-6Hz), alpha (8-12Hz) and beta (12-20Hz) frequency range by means of a digital Fast Fourier Transform-based spectrum analysis (frequency domain, cosine windowing function). We converted the obtained absolute power values into z-scores normalised by the mean and SD of the recording interval. Following the procedure described by Lage-Castellanos and colleagues (2008), we proceeded to compare each age and stress groups' z-transformed oscillatory power for each channel and frequency, computing the independent t-statistic and p-value for each comparison. Based on our past work (Marshall et al., 2015; Marshall

et al., 2016a; Marshall et al., 2016b), we undertook four relevant comparisons. To explore the experimental hypothesis, we compared (1) old high stress to old low stress participants and (2) old high stress to young high stress participants. In addition, we compared (3) young low stress to young high stress participants and (4) old low stress to young low stress participants. These additional comparisons enabled us to investigate whether the effect selectively manifested only for comparisons that included the target experimental group (old adults with high levels of stress). For each comparison, a corresponding permutation distribution with 1000 iterations was computed by randomly reassigning each oscillatory power value (dependent variable) to each of the four age/stress groups (independent variable). For each of the permutations per comparison, we selected the maximal t-value, thus obtaining a distribution of maxima corresponding to the null hypothesis that there is no difference between oscillatory power and each age/stress group. Setting α at the conventional level of 0.05, we determined the 1- α percentile of this distribution to define the significance threshold obtained by the permutation distribution. Finally, we compared the empirical to the permutation distributions of t-values to determine which channels exceeded the permuted significance threshold (Lage-Castellanos et al., 2008). This method of controlling for multiple comparisons has gained increased scientific acclaim within neuroscience in recent years. It provides exact statistics corrected for multiple comparisons in a manner equivalent to the 'family wise error' gold standard applied in functional neuroimaging where large data sets are often dealt with (Nichols & Holmes, 2002; Summerfield et al., 2011).

Results

1. **Stress and Demographical Variables**

Demographics were obtained on participants' age, level of education, their amount of cigarette and alcohol consumption, their levels of exercise and whether they were suffering from a physical disability whose discomfort may impact on their sense of well-

being at the present moment. Demographics and units of measurement can be viewed in Table 1.

Table 1: Demographics of old and young participants split by experienced stress score

	Elderly			Young		
	High Stress	Low Stress	Test-statistic	High Stress	Low Stress	Test-statistic
Group Size	30	30	n/a	29	31	n/a
Age (years)	68.3 (3.1)	67.9 (2.2)	t(58) = 0.86, p = 0.48	21.9 (1.3)	22.6 (1.7)	t(58) = 0.91, p = 0.48
Gender	9 males	12 males	$\chi^2(1, N = 58) = 2.07, p = 0.57$	11 males	8 males	$\chi^2(1, N = 58) = 2.07, p = 0.57$
Education (1 < High School – 6 PhD)	3.25 (0.8)	3.57 (1.1)	t(58) = 0.87, p = 0.48	4.07 (0.6)	4.25 (0.4)	t(58) = 0.65, p = 0.53
Cigarettes (per day)	0	0.7 (0.2)	t(58) = 1.06, p = 0.37	0.32 (0.4)	0.06 (0.01)	t(58) = 0.83, p = 0.41
Units Alcohol (per week)	2.88 (1.2)	2.36 (1.8)	t(58) = 1.51, p = 0.19	2.21 (1.9)	2.97 (2.1)	t(58) = 1.71, p = 0.11
Presence of Physical Disability	6	4	$\chi^2(1, N = 58) = 1.37, p = 0.87$	0	0	n/a
Exercise (hours per week)	2.44 (0.7)	2.54 (1.1)	t(58) = 0.69, p = 0.52	2.52 (1.9)	2.17 (0.6)	t(58) = 0.79, p = 0.46
Mini Mental State Score	28.4 (2.1)	29.3 (1.4)	t(58) = 0.71, p = 0.57	n/a	n/a	n/a
Trait Anxiety Score	32.76	33.04	t(58) = 0.87, p = 0.42	35.94	34.22	t(58) = 0.86, p = 0.48
State Anxiety Score	36.88	35.38	t(58) = 0.73, p = 0.42	34.87	33.93	t(58) = 0.68, p = 0.52
Social Readjustment Rating Scale Score	899.1 (103.4)	473.6 (97.7)	*t(58) = 2.32, p = 0.027	n/a	n/a	n/a
Student Life Events Scale Score	n/a	n/a	n/a	730.4 (93.7)	351.7 (89.2)	*t(58) = 2.34, p = 0.029

Note. High and low stress scorers were compared within respective age groups. The column 'test statistic' thus refers to the comparison between elderly high vs. low stress scorers (left) and young high vs. low stress scorers (right). * denotes a significant difference between stress groups.

The amount of cumulative life stress was assessed by the Social Readjustment Rating Scale (Holmes & Rahe, 1967) for elderly and the Student Life Events Scale (Clements & Turpin, 1996) for young participants. Different scales for each age group

were deemed appropriate as our elderly participants were on average three times the age of younger participants and will therefore have experienced more and potentially different stressful events. As in previous studies, appropriate scales were therefore chosen in order to assess experienced stress exposure relevant to each age group and to test the argument that the long-term effects of cumulative stress exposure result in detriments to cognition rather than purely large amounts of immediate stress (Marshall et al., 2015, Marshall et al., 2016a, 2016b). Both scales comprise a similar format, consisting of a brief, self-administered scale (Social Readjustment Rating Scale: 43 items; Student Life Events Scale 36 items). Both instruments enumerate life events ranging from severely to mildly stressful. Each event is weighted to indicate the severity of the incident. For example, the event 'Death of a spouse' (Social Readjustment Rating Scale) or 'Death of a parent' (Student Life Events Scale) carries a score of 100, whereas a comparatively minor event such as 'Vacation with family or friends' carries a score of 16 (Student Life Events Scale) or 13 (Social Readjustment Rating Scale). The weights of each experienced incident are subsequently added to determine the individual stress score. Participants indicated which events had/had not taken place in their lives. Multiple occurrences of events are not accounted for by the scale. Past work in this respect has indicated that including event frequency in addition to the simple occurrence of the event has only a slight impact on increasing predictability regarding the effects of stress on lifetime psychopathology (Wilker et al., 2015). Scores can range from 0-1466 for the Social Readjustment Rating Scale and 0-1849 for the Student Life Events Scale (higher scores reflect higher amounts of stressful experiences for both scales).

In line with our previous work (Marshall et al., 2015, 2016a, 2016b), scores on each scale were used to divide both age groups into high and low stress groups. The split was based on the median split of scores from the Social Readjustment Rating Scale for old (Value: 659) and the Student Life Events Scale for young participants (Value: 598). No significant group differences in Mini Mental State performance, age, gender, educational attainment,

cigarette/alcohol consumption or amounts of exercise were observed between stress groups (see Table 1).

2.1 Resting power in the delta frequency range

Within the delta frequency, the first comparison between old high stress and old low stress participants revealed a significant difference for mid frontal electrodes (FP1, FPz, FP2, AF3, AF4, F3, F1, Fz, F2, F4; $p < .001$), left parietal electrodes (T7, TP7, P7, P5, PO7, PO5; $p < .001$) and right parietal electrodes (T8, TP8, P8, PO8; $p < .001$) as well as for midline electrode Pz ($p < .01$; see Figure 1).

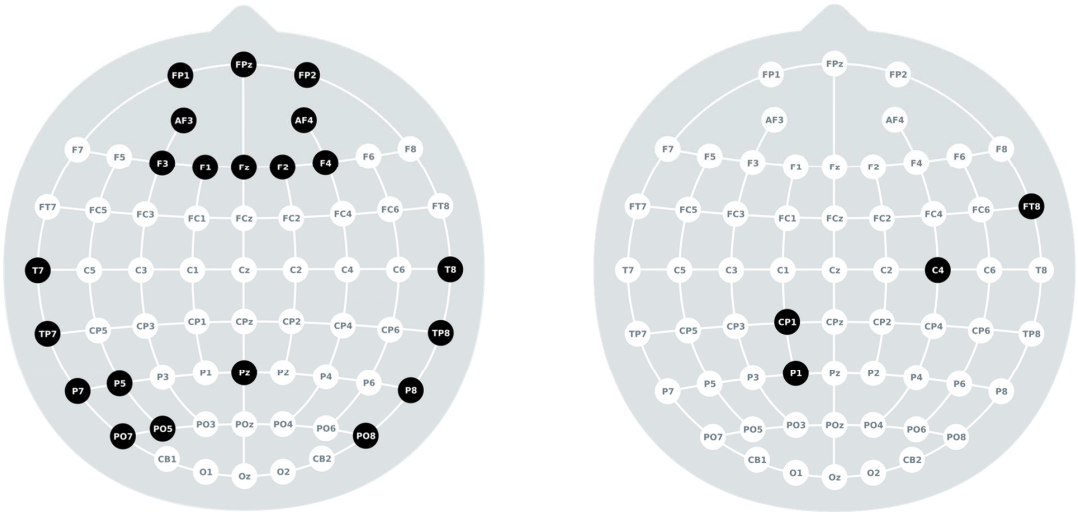

Figure 1. Electrodes showing significant differences in absolute delta power for the comparisons of stress within age groups. For the comparison within the old age group (left panel), high stress individuals showed higher levels of delta power compared to low stress counterparts.

For all electrodes, old adults with high levels of stress showed significantly higher resting state delta power than old adults with low levels of stress (see Figure 2).

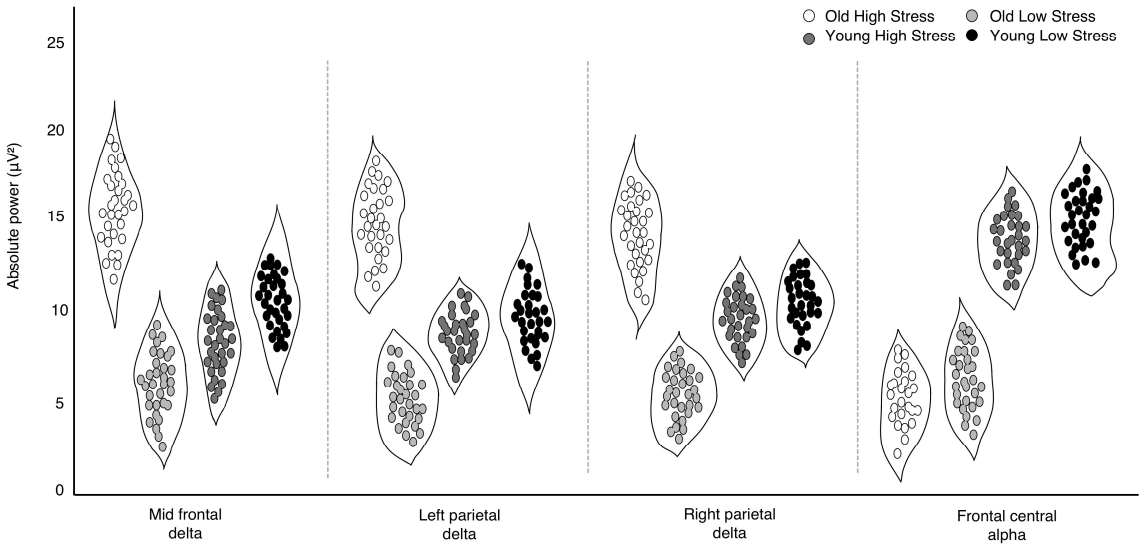

Figure 2. Violin plot, depicting individual power scores for findings in the alpha and delta frequency range. For the delta frequency, means were computed by averaging electrodes which were significant for both experimental comparisons (old high stress vs. old low stress; old high stress vs. young high stress). Thus, mid frontal = FP1, FPz, FP2, AF3, AF4, F3, F1, Fz, F2, F4; left parietal = T7, TP7, P7, P5, PO7, PO5; right parietal = T8, TP8, P8, PO8. For the alpha frequency, the mean was computed from electrodes significant for both age-group comparisons (frontal central = FP1, FPz, FP2, AF3, AF4, F7, F5, F3, F1, Fz, F2, F4, FT7, FC3, FCz, FC2, FC6, FT8).

For the relevant control analyses, we compared young high stress to young low stress participants. Only four electrodes reached significance. For electrodes CP1 and C4 young adults with low levels of stress showed higher levels of delta power ($p < .01$) than young adults with high stress, while for electrodes P1 and FT8 young adults with high levels of stress showed elevated levels of resting state delta compared to low stress counterparts ($p < .05$).

The comparison between old adults with high levels of stress and young adults with high levels of stress once again found a significant difference for mid frontal (FP1, FPz, FP2, AF3, AF4, F3, F1, Fz, F2, F4; $p < .001$), left parietal (T7, TP7, P7, P5, PO7, PO5; $p < .001$) and right parietal (T8, TP8, P8, P6, PO8, PO6, PO4; $p < .001$) electrodes as well as for midline electrode Pz ($p < .001$, see Figure 3).

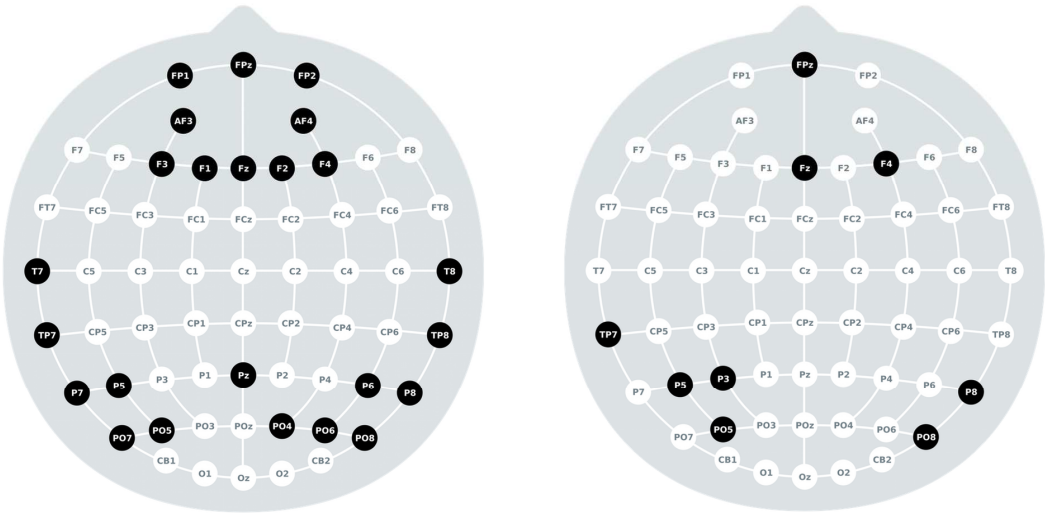

Figure 3. Electrodes showing significant differences in absolute delta power for the comparisons of age within stress groups. For the high stress comparison (left panel), old adults showed elevated levels of resting delta power compared to young participants. Conversely, for the low stress comparison (right panel), old adults showed lower delta power compared to young participants.

Once again old adults with high stress levels showed significantly enhanced delta power compared to young high stress counterparts over all electrode sites (see Table 2). The control comparison for old adults with low levels of stress and young adults with low levels of stress revealed a significant difference for mid frontal (FPz, Fz, F4; $p < .01$), left parietal (TP7, P5, P3, PO5; $p < .01$) and right parietal (P8, PO8; $p < .01$) electrodes. However, contrary to the comparison between high stress age groups, old adults with low levels of stress displayed significantly lower levels of delta power compared to young low stress counterparts.

2.2 Additional regression analyses

For the above analyses, we formed high and low stress groups based on the median split obtained on each respective stress scale for young and old participants. To ascertain whether our effects remain when adopting a continuous variable approach, we conduced additional regression analyses in which we treated the stress score as a continuous variable. Initially, we standardised experienced stress scores within age groups by subtracting the mean from each participant's stress score and then dividing it by the standard deviation. This ensured that values measured from different scales contributed equally to the

analyses. Based on the results of our permutation test, we proceeded to form three regions of interest (ROI) (mid frontal = FP1, FPz, FP2, AF3, AF4, F3, F1, Fz, F2, F4; left parietal = T7, TP7, P7, P5, PO7, PO5; right parietal = T8, TP8, P8, PO8). In separate models, delta power in each ROI was regressed on participants' experienced stress score and age group (coded -1 for young and 1 for older adults; see Table 2). In the second step, the interaction term of experienced stress by age was added. For the mid frontal region, the first model was significant accounting for 13% of the variance in delta power ($F[2,109] = 3.71$, $p = 0.031$). Inclusion of the interaction term in the second step accounted for an additional 9 % of variance ($\Delta F[1,109] = 4.2$, $p = 0.011$). We conducted a simple slopes analysis, an established means to explore significant interaction terms in multiple-linear regression (Preacher, Curran & Bauer, 2006). The method involves forming a regression equation for each of the criterion variables and conducting a t-test to explore whether the slope of this equation differs significantly from zero. Among old adults, the addition of a stressful experience was found to produce a significant increase of 1.75 μV^2 delta power ($t[109] = 1.93$, $p = 0.032$), while the change in delta power due to a stressful experience in young adults (-0.21 μV^2) remained non-significant ($p = 0.13$).

For the left parietal region, the first step of the model accounted for 8 % of variance in delta power ($F[2,109] = 3.11$, $p = 0.039$). Inclusion of the interaction term accounted for an additional 11 % of variance ($\Delta F[1,109] = 4.8$, $p = 0.028$). Simple slopes analysis found a significant increase of 1.64 μV^2 delta power per stressful life experience among older adults ($t[109] = 2.07$, $p = 0.026$). Once again, the difference among young participants (-0.28 $\mu V^{2)}$ did not reach significance ($p = 0.32$).

For the right parietal region, the first step of the model accounted for 12 % of variance in delta power ($F[2,109] = 4.05$, $p = 0.027$). Including the interaction term accounted for an additional 10% of variance ($\Delta F[1,109] = 4.1$, $p = 0.037$). Simple slopes analysis revealed a significant increase of 1.76 μV^2 delta power per stressful experience among older adults

(t[109] = 2.01, p = 0.027). Once again, the difference among young adults failed to reach significance (-0.28 $\mu V^{2,}$ p = 0.33).

Our additional analyses hereby confirm the results of the permutation test and indicate that the stress by age effect observed in the initial analysis remains after treating stress as a continuous rather than a dichotomous variable.

Table 2: Linear regression models predicting power changes in the delta and alpha frequency range

	Delta									Alpha		
	mid frontal			left parietal			right parietal			frontal central		
	Step 1	Step 2	Step 3	Step 1	Step 2	Step 3	Step 1	Step 2	Step 3	Step 1	Step 2	Step 3
Age Group	2.47**	2.32**	2.11**	1.74*	1.77*	1.68*	2.19**	2.13*	2.11**	2.88*	2.64*	2.43*
Stress Score	0.78*	0.77*	0.68*	0.72*	0.74*	0.76*	0.85*	0.82*	0.79*	0.11	0.24	0.19
Age*Stress		0.98*	0.96*		1.02**	1.08**		0.98*	1.03*		0.79	0.86
Gender			-0.17			0.23			-0.07			-0.08
State Anxiety Score			0.042			0.17			0.57			0.21
Trait Anxiety Score			1.01			0.06			0.44			0.11
F	3.71*	5.01**	4.13*	3.11*	4.76**	4.22**	4.05*	5.13**	4.73*	3.5*	2.6	1.71
df	2/109	3/108	6/103	2/109	3/108	6/103	2/109	3/108	6/103	2/109	3/108	6/103
R^2	0.13	0.22	0.24	0.08	0.19	0.22	0.12	0.22	0.26	0.14	0.17	0.21
ΔF		4.2*	0.76		4.8*	1.03		4.1*	1.27		0.69	0.83
Δdf		1/108	3/103		1/108	3/103		1/108	3/108		1/108	3/103
ΔR^2		0.09	0.02		0.11	0.03		0.10	0.04		0.03	0.04

Gender coded as -1 = female, 1 = male.
*p < 0.05, **p < 0.01.

3.1 Resting power in the alpha frequency range

For the alpha frequency, the comparison between old high and old low stress participants as well as for young low and young high stress individuals found no significant differences for any of the electrode sites. However, the comparison between old high stress and young high stress participants resulted in significant differences between electrodes in the frontal-central region (FP1, FPz, FP2, AF3, AF4, F7, F5, F3, F1, Fz, F2, F4, F6, FT7, FC5, FC3, FC1, FCz, FC2, FC4, FC6, FT8; p < .001), as well as for electrodes PO4 and

PO8 ($p < .001$). A similar frontal pattern of significance emerged by comparing old low stress with young low stress adults (FP1, FPz, FP2, AF3, AF4, F7, F5, F3, F1, Fz, F2, F4, FT7, FC3, FCz, FC2, FC6, FT8; $p < .001$) with additional significance for electrodes C2, CP3, TP8, P1, P4, P6, CB1, O1 ($p < .001$; see Figure 4)[2].

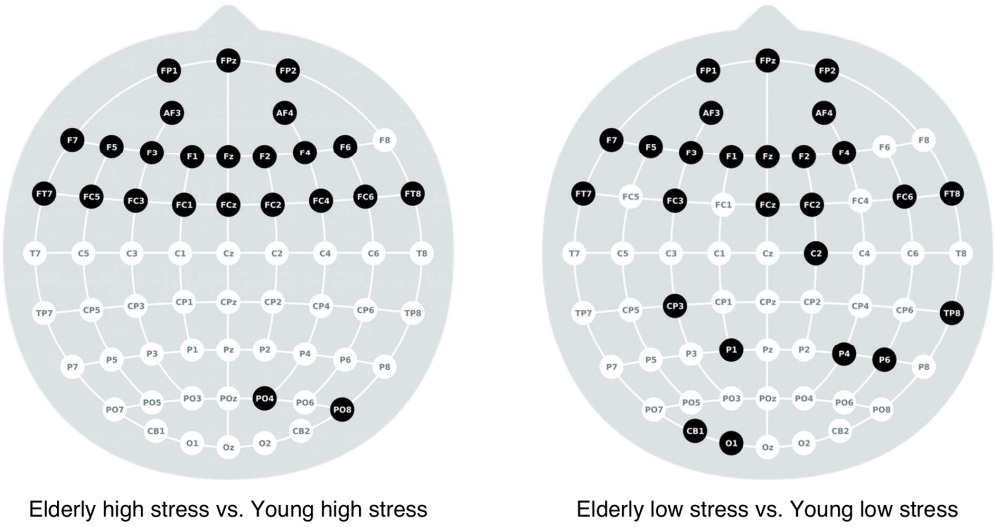

Figure 4. Electrodes showing significant differences in absolute alpha power for the comparisons of age within stress groups. For both high and low stress comparisons, old adults showed reduced alpha power compared to young adults.

For both comparisons, old (low/high stress) adults manifested reduced levels of alpha power when compared to young (low/high stress) adults over all significant electrode sites.

No further significance between electrodes emerged for either age and stress groups for any of the other frequency bands under investigation[3].

3.2 Additional regression analyses

[2] In order to test whether findings of reduced alpha power among old (high and low stress) adults compared to young (high and low stress) counterparts manifested independently of the known slowing of the alpha frequency peak in old age, we compared the peak frequencies of both participant groups using an independent samples t-test. We discovered a slightly reduced frequency among old (9.45) compared to young (10.12) adults. However, this did not reach statistical significance ($t_{118} = 1.42$, $p = .077$), indicating that slowed alpha frequency among older adults did not significantly contribute to the present findings.

[3] With respect to calculating analysis of covariance, we must note that limitations apply to both our variables of age and experienced stress. Age is known to exert a significant impact on resting state power. In addition, there is a significant difference in the amount of stress experienced by young and old adults. Our research question necessitates the comparison of age groups as well as continuous stress scores obtained from different scales for young and old participants. In consequence, we are unable to use either measure as a co-variate to mitigate this possible confound which should be kept in mind when interpreting the results.

In accordance with our above procedure, we ran an additional two stage hierarchical regression model in which we regressed age group, experienced stress score and the interaction term of both on alpha power in the frontal central region (FP1, FPz, FP2, AF3, AF4, F7, F5, F3, F1, Fz, F2, F4, FT7, FC3, FCz, FC2, FC6, FT8) determined as a region of interest in the forgone permutation analysis. For the first step, age as the only independent predictor accounted for 14 % of variance in alpha power ($F[2,109] = 3.5$, $p = 0.041$). Adding the interaction term in the second and third step resulted in a non-significant model ($p = 0.37$). Our regression analysis hereby confirms the main effect of age suggested by the previous permutation test.

Discussion

This study explored whether previously observed stress and age-related electrophysiological changes during cognitive task execution were likewise associated with changes in the system at rest. With respect to the alpha frequency, both age group comparisons revealed significantly reduced alpha power among old compared to young adults. This effect persisted regardless of whether the comparisons were carried out between high or low stress individuals and thus signifies a main effect of age.

Crucially, we observed an effect qualified by both age and stress within the delta frequency range. Old adults with high levels of cumulative life stress manifested higher levels of delta power at rest compared to both old adults with low levels of stress and young adults with high levels of stress. This effect was not present when comparing young low and high stress individuals and the comparison between old and young low stress individuals revealed the opposite pattern: among low stress participants, old adults manifested reduced levels of delta power compared to young adults. Importantly, both the main effect of age in the alpha frequency range and the stress by age interaction effect discovered for the delta frequency remained when reanalysing the data with experienced stress as a continuous rather than a dichotomous grouping variable.

Findings respecting the alpha frequency are in line with investigations into healthy (Busse et al., 2005) and pathological (Babiloni et al., 2015; Koenig et al., 2005) cognitive aging, both of which report decreases of resting alpha power among elderly individuals which manifest independently of age-related slowing of the alpha frequency. The effect we observed emerged predominantly over frontal electrodes. Age-related changes to frontal alpha networks have been reported both during rest and task activity (McEvoy et al., 2001; Kolev et al., 2002; Yordanova et al., 1998) and are considered a prominent characteristic of the ageing EEG. In line with the posterior to anterior shift of electrophysiological activity commonly observed in old age, this finding has been interpreted as a strategic change which enables older adults to maintain cognitive integrity by increasing reliance on frontal/anterior areas of the cortex (McEvoy et al., 2001; Davis et al., 2008). The present alpha results thus correspond to reports on the general slowing of the aging EEG, of which a reduction of resting state alpha power is a prominent characteristic (Klimesch, 1999).

The increase of resting delta power observed among high stress old adults is not what one would expect to find for healthy aging individuals. Past work has reported that normally aging participants exhibit a linear decrease of delta power with advancing years which is significantly reduced compared to young participants (Babiloni et al., 2006). In line with these findings, our comparison between low stress age groups demonstrates reduced delta power among old compared to young adults. Conversely, increases of resting state delta power are a prominent occurrence among elderly individuals suffering from age-related cognitive pathologies such as Alzheimer's, Mild Cognitive Impairment or vascular dementia resulting from progressive cerebral ischemia (Coben et al., 1985; Rae-Grant et al., 1987; Román, 2004). For example, Soininen and colleagues (1989) found that among a subset of elderly patients suffering from AD, progression of the condition over the course of one year was associated with significant increases of resting state delta power while Signorino and colleagues (1995) reported that individuals suffering from vascular dementia exhibited a significant elevation of low frequency power in the delta and theta frequency

ranges. At this stage, it is important to note that for these pathologies, increases of resting delta power often coincide with impaired global cognitive function. We evaluated this in our study using the Mini Mental State Examination (Folstein et al., 1975) on which all our participants scored within the normal range. In addition, we screened participants for a history of stroke, which signifies the most common cause of vascular dementia. Thus, the elevated levels of delta power among high stress old adults are unlikely to signal the presence of a fully developed cognitive pathology. A more plausible interpretation of these findings is as an indication of early stages of pathological development or, in line with our hypothesis, as a marker indexing increased vulnerability towards contracting age-related cognitive pathologies. For example, screening for a history of acute stroke with manifest clinical symptoms does not exclude individuals suffering from chronic cerebral ischemia as a result of stress-induced lifestyle changes which may in time develop into vascular cognitive impairment. In a landmark paper, Llinas and colleagues (1999) proposed an underlying mechanism to account for elevated low frequency power observed across a variety of neuropathologies. Comparing healthy adults to individuals suffering from a range of neurological conditions, the authors reported a global cortical increase of low frequency theta power at rest, which coincided with increased oscillatory coherence between high and low frequencies. They proposed that this phenomenon resulted from aberrant interactions between the thalamus and cortex, brought about by the deactivation of thalamic relay cells through protracted cell membrane hyperpolarisation. According to the authors' theory, the low-threshold spike bursts emitted by these consistently inhibited cells have the propensity to entrain thalamocortical circuits. These in turn interact with feedback loops at the cortical level to produce the increased power in low frequency ranges observed in neurological pathologies. In light of this theory, a further mechanism underlying our low frequency power differences may lie in stress-induced damage to thalamic relay cells. A growing body of work links stress to reduced activation of the thalamus. Reports to this effect highlight that individuals suffering from posttraumatic stress disorder (PTSD) show

reduced blood flow in this particular brain region (Kim et al., 2007; Lanius et al., 2001, 2003; Bremner et al., 1999a). More recently, Yin and colleagues (2011) reported abnormal functional connectivity between the thalamus and cortex in the resting state recordings of PTSD patients and concluded that these may contribute to the underlying pathology of the disorder. Llinas and colleagues' theory coupled with the link between the thalamus and stress highlight a possible cause for the increased low frequency power we observed in old adults with high levels of cumulative life stress. Combined, they advocate the need to investigate stress induced thalamic damage and how this may translate to increased low frequency power observed across the cortex.

The present findings thus highlight that the effects of cumulative experienced stress are associated with changes in the brain's resting state activity and suggest a further indication of the detrimental impact high levels of cumulative stress exert on cognitive aging. This is in line with cross sectional and longitudinal studies reporting the adverse effects of cumulative stress on the cognitive performance of old adults (Dickinson et al., 2011; Peavy et al., 2009). These results also complement our own previous work, which indicates that in addition to cognitive shortcomings, large amounts of stress exposure affect the underlying electrophysiological processing patterns associated with the successful execution of cognitive tasks. It is noteworthy that electrodes demonstrating significantly elevated delta activity among high stress old adults were situated predominantly at frontal and parietal scalp sites. These cortical areas have been highlighted as particularly vulnerable to the hormonal and hypertonic/ischemic effects of stress exposure (Román, 2004; Wignall et al., 2004; Lupien et al., 2005). In addition, they are essential for maintaining high levels of cognitive performance in domains such as memory and perception/inhibition for which our own work has demonstrated a decline as a function of age and stress (Marshall et al., 2015a; Marshall et al., 2016a; Marshall et al., 2016b).

Future Directions and Conclusions

Current findings complement an emerging picture suggesting an adverse effect of cumulative life stress on cognitive integrity in old age. However, as the present data set provides only correlative evidence on the association between life stress and altered resting state patterns in old age, and certain confound variables such as affective disorders were not accounted for, results should be interpreted with caution. At present, only one longitudinal study demonstrates a detrimental effect of stress on cognitive performance which emerges across the lifespan (Pesonen et al., 2013). To enable causative conclusions about the effects of life stress on cognitive aging, work thus needs to be complemented by further longitudinal and intervention studies. In addition to this, several additional limitations must be noted. While life event scales are an established measure of cumulative stress and have been used widely in the field (Dickinson et al., 2011; Comjis et al., 2011; Marshall et al., 2015), they consider neither the subjective estimation of an event's gravity nor whether the event has occurred more than once in an individual's lifetime. While several existing scales include the option of providing additional information about participants' subjective experience of stressful events, none are as exhaustive as the scales chosen for the present study. Future research would thus benefit from devising a stress inventory scale which provided an exhaustive list of stressful life events coupled with a more detailed rating system to ascertain the individual impact of the event and how often it has occurred in an individual lifetime.

In addition, the present study focussed on stressful events commonly encountered in an individual's lifetime and therefore did not include participants who had suffered a traumatic stressful experience or childhood trauma. Moreover, to isolate against the carry-over effects psychiatric disorders may produce in the EEG recordings, we excluded individuals suffering from conditions such as depression or anxiety disorder. Given the link between traumatic stress and the development of psychiatric disorders (Chapman et al., 2004) these measures excluded individuals with the highest stress load and thus limit the generalizability of findings to more common/mild stressful experiences. However, finding

an impact of cumulative life stress on resting power even when excluding extreme cases, highlights the damaging effects of stress by suggesting that even common stressors may have the potential to alter resting state dynamics in old age. In support of this argument, several studies highlight a dose response effect of stressful experiences, reporting that increased numbers of stressful or traumatic incidents throughout the lifespan significantly increase the prevalence of stress-related disorders (Kolassa et al., 2010; Neugenbauer et al., 2009; Neuner et al., 2004; Schauer et al., 2003).

Further additions to the work reported in this paper would lie in exploring cortical structural differences between age and stress groups. The use of neuroimaging would enable further distinction between the different cognitive pathologies suggested in this paper. For example, a greater presence of white matter hyperintensities among high stress elderly participants would point in the direction of a vascular/ischemic impairment, possibly as a result of stress-induced lifestyle choices, rather than an increased vulnerability to conditions such as Alzheimer's or Mild Cognitive Impairment. Additionally, it would be useful to pair electrophysiological recordings with extensive neuropsychological test batteries to explore whether resting state power changes coincide with variations in behavioural test scores. For our present study, we tested older adults' cognitive health using the Mini Mental State Examination. While this test acts as a useful screening tool, it is not sensitive enough to distinguish slight and early cognitive changes among individuals who still operate at a high cognitive level. As our previous work demonstrates that high levels of stress coincide with reduced cognitive performance in old age it would be prudent to extend this research by investigating the extent to which the observed resting state changes coincide with behavioural shortcomings in different cognitive domains. Finally, given individual differences in the way stress affects peoples' wellbeing, an important extension to our work would lie in investigating the role of emotion regulation and coping strategies to explore how they may modulate the effect of cumulative life stress on resting state EEG patterns.

Our results demonstrating increased resting state delta power among old adults with high levels of cumulative life stress shed further light on the way stress may impact on aging cognition. They complement behavioral and electrophysiological work highlighting the negative impact large amounts of lifetime stress exert on cognitive integrity in old age. Investigating age and stress related changes in the system at rest explores this topic from a different angle and deepens our understanding of how stress affects cognitive health by demonstrating that elderly members of the high experienced stress group also manifest electrophysiological resting state patterns which are widely taken to indicate susceptibility towards developing age-related cognitive pathologies (Coben et al., 1985; Rae-Grant et al., 1987; Signorino et al., (1995). Our findings thus complement the literature on how lifetime stress affects health and cognitive integrity in old age and highlight the importance of recognising the impact cumulative life stress has on aging cognition.

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