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Stress evokes stronger medial posterior cingulate deactivations during emotional distraction in slower paced aging

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ABSTRACT

Introduction: Middle-aged offspring from long-lived families are thought to have a slower pace of aging, possibly related to HPA-axis function. Here, we investigated the neural and behavioral effects of social stress in offspring compared to their regular aging partners on emotional distraction during working memory (WM).
Methods: 104 middle-aged participants (53 males) consisting of offspring and their partners underwent the Trier Social Stress Test or a control procedure. Hereafter, a WM task with emotional distracters was performed using fMRI. Saliva cortisol levels were obtained during the procedure.
Results: Partners had higher overall cortisol levels than offspring. In addition, partners had decreased deactivations compared to offspring in the medial posterior cingulate cortex (mPCC) during emotional distraction, which were significantly correlated with lower accuracy during emotional distraction.
Discussion: mPCC-deactivations are known to be modulated by chronological aging, with more deactivations in the young than in the old. Here we show the same pattern in familial longevity versus regular aging after mild stress, with more deactivations related to better accuracy during emotional distraction. Functional mPCC deactivations might thus be related to pace of aging, and can be revealed by inducing mild stress.

1. Introduction

Individual differences in cognitive aging trajectories have been proposed to be the result of the wear and tear of daily hassles, major stressful life events and genetic risk factors (McEwen, 2003). Indeed, daily stress was associated with accelerated cognitive decline in aging in a large (N > 6000) community based population sample (Aggarwal et al., 2014), while a higher accumulation of life-time exposure to stress in elderly was associated with larger impairments in working memory (WM) and the ability to inhibit interference (Marshall, Cooper, Segrave, & Geeraert, 2015). Some older adults, however, appear to cope better with life's stressful circumstances than others. Middle-aged individuals with a familial propensity to reach old age in good health, for instance, show reduced physiological responses to social stress (Jansen, van Heemst, van der Grond, Westendorp, & Oei, 2016) and less cognitive decline compared to age-matched controls (Stijntjes et al., 2013). The present study was aimed at investigating on a behavioral and neural level whether these individuals, who come from long-lived families, are better at coping with emotional distractions when stressed.

Offspring from nonagenarian siblings are considered "enriched for familial longevity", whether due to genetic or epigenetic factors. It has been suggested that these individuals age at a slower pace, making them *biologically* younger than their same age peers (Waaijer et al., 2012). One of the causes of their slower pace of aging might be a more moderate HPA-axis function. First, animal and human aging studies suggest that (over)activity of the hypothalamic-pituitary-adrenal (HPA) axis contributes to an accelerated pace of aging (Aguilera, 2011). For instance, aging is generally associated with increased basal cortisol levels (Deuschle et al., 1997; Nater, Hoppmann, & Scott, 2013; van Cauter, Leproult, & Kupfer, 1996), whereas high basal cortisol levels have been associated with several age-related features of ill health, such as high blood pressure, insulin resistance and physical frailty (Chrousos,

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2000; Kumari et al., 2010; Wallerius, Rosmond, Ljung, Holm, & Bjorntorp, 2003). Middle-aged individuals from long-lived families, however, show somewhat lower basal HPA-activity (Noordam et al., 2012), a lower prevalence of cardiovascular disease (Westendorp et al., 2009) and metabolic syndrome (Rozing et al., 2010) and a lower mortality rate (Schoenmaker et al., 2006) than individuals who are not enriched for familial longevity. Typically, the latter studies (e.g., Rozing et al., 2010; Westendorp et al., 2009) used the partners of these offspring from long-lived families as controls. As the partners are of similar age and have shared the same environment for decades (e.g., SES, major life events, life style) it is less likely that observed differences between offspring and partners are confounded in a major way by environmental factors experienced since young adulthood.

There are also indications of slower cognitive decline in offspring from these same long-lived families compared with their partners, showing better immediate and delayed memory recall and less Stroop interference (Stijntjes et al., 2013). According to the inhibitory deficit hypothesis of aging, the ability to resist interference declines with age, which would in turn negatively affect performance in other aspects of cognition (Hasher & Zacks, 1988). Older adults show exaggerated interference effects when compared to young individuals, which may be caused by deficits in selective attention mechanisms that function to bias task-relevant information in the face of competition (Pettigrew & Martin, 2014). In line with this idea, functional imaging studies in aging showed deficits in cognitive control mechanisms supporting attention, leading to impaired neural suppression of task-irrelevant distracters, associated with impaired WM performance (Gazzaley, Cooney, Rissman, & D'Esposito, 2005; Gazzaley et al., 2008).

Stress also affects the ability to selectively suppress irrelevant information (Oei et al., 2012). At least, when presenting emotional distracters in the delay phase of an item-recognition task, a typical brain activation pattern can be seen of activations in ventral "affective" brain areas, such as the amygdala and right inferior frontal gyrus (RIFG), when contrasting emotional versus neutral distracters, while showing deactivations in dorsal "executive" areas, such as prefrontal and parietal regions of the brain (Dolcos & McCarthy, 2006; Iordan, Dolcos, & Dolcos, 2013). After acute stress, this brain activation pattern changes into *decreased* deactivations in the dorsal "executive" areas, and increased activations in ventral "affective" areas, and impaired WM performance specifically when distractions are emotional (Oei et al., 2012). Decreased WM task-induced deactivations have been found after sleep deprivation, which can also be considered a form of stress (Chee & Choo, 2004) and in studies comparing old versus young adults (Persson, Lustig, Nelson, & Reuter-Lorenz, 2007; Sambataro et al., 2010). If the pace of aging in offspring is indeed slower, it could be expected that they would be less impaired in suppressing distracters compared to other individuals of the same age group and that stress would be less detrimental to them when coping with emotional distractions.

Here, the aim is to investigate the effect of stress on the inhibition of emotional distraction in middle-aged offspring from long-lived families and their partners using fMRI. We hypothesized that stressed offspring would show less interference from emotional distraction on the behavioural level than the partners, associated with smaller decreases in deactivations in dorsal "executive" brain areas. With regard to the ventral "affective" brain areas, we expected smaller RIFG activation in stressed offspring compared to partners, as, according to the meta-analysis of Turner and Spreng (2012), inhibition in older adults is associated with a "young-plus pattern", particularly in the RIFG; This means that older adults activate similar areas as young adults, yet to a greater degree (Turner & Spreng, 2012), areas which were also shown to become more active during stress in young adults during emotional distraction (Oei et al., 2012). With regard to the amygdala, our expectations were less specified: On the one hand, amygdala function has been suggested to show age-related decline and would be less responsive to salient and threatening emotional stimuli, because, relative to young people, aged individuals seem less affected by the emotional impact of negative stimuli and assess these as less negatively arousing (Kaszniak & Menchola, 2012; Weeks & Hasher, 2014). However, an age-related decline in amygdala activation has not consistently been found (Dolcos, Katsumi, & Dixon, 2014; Mather et al., 2004; St Jacques, Dolcos, & Cabeza, 2010).

2. Material and methods

2.1. Participants

Participants were recruited via letters from the pool of participants of the Leiden Longevity Study (LLS). The LLS consists of 421 Caucasian families, enrolled between 2002 and 2006 (Schoenmaker et al., 2006; Westendorp et al., 2009). The LLS families comprise nonagenarians, their male or female offspring and the offspring's partners. To meet the criteria for familial longevity, at least 2 siblings with age ≥ 89 yrs for men and ≥ 91 yrs for women have to be alive. Volunteers from the LLS for the current study were screened before inclusion. Half of the final sample was included because their parents met the criteria for familial longevity ("Offspring"), the other half consisted of the offspring's partners whose parents did not meet the criteria for familial longevity ("Partners"). Other inclusion criteria were: being middle-aged (55–77 years) and having a stable body mass index (BMI) between 19 kg/m^2 < BMI < 33 kg/m^2. Exclusion criteria were: the use of any hormone medication (including oral, nasal and inhalation corticosteroids), a fasting plasma glucose above 7 mmol/L, any significant chronic, renal, hepatic or endocrine disease, or the use of medication known to influence lipolysis, thyroid function, glucose metabolism, GH/IGF-1 secretion or any other hormonal axis. Other exclusion criteria were smoking- and alcohol addiction, extreme diet therapies and current stress-related psychiatric disorders as assessed with the M.I.N.I. International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) and the Geriatric depression scale (GDS-30; Yesavage et al., 1982, with a cut-off score of > 11). Of the 120 volunteers initially included, five were not scanned due to (scanner-) technical problems, one participant had just undergone unexpected surgery, one could not be properly scanned because of an arched back, and one participant became ill during the scan session. After scanning, seven participants were excluded from analyses because of failure to understand the instructions and too many errors (> 44%) in the scanner task, and one participant was excluded because of severe brain atrophy. Structural data of one participant were missing, however, given that all other data were available, this individual was not excluded from the analyses. The final sample thus consisted of 104 healthy middle-aged participants: 61 Offspring (male: n = 31) and 43 partners (male: n = 22). Upon inclusion, couples were randomly allocated to a Stress and Control condition in an experimental design. There was a pre-stress difference in working memory using the subtest Digit Span forward of the Wechsler Adult intelligence Scale (WAIS; Wechsler, 1997), with lower scores in the Stress- compared to the Control condition ($F(1, 102)) = 5.83$, $p = .02$, however, there were no pre-stress differences between groups (Partner vs Offspring) nor Group by Condition (Stress vs Control) interactions in Digit Span-Forward or Backward, state and trait anxiety (STAI; Spielberger, 1983), or psychological functioning using the total score of the Symptom Checklist 90 (SCL-90; Arrindell & Ettema, 1986). (see Table 1 for subject characteristics). Each participant gave signed informed consent in which confidentiality, anonymity, and the opportunity to withdraw without penalty were assured. The study was approved by the Medical Ethics Committee of the Leiden University Medical Center and carried out according to the standards of the Declaration of Helsinki (Declaration of Helsinki, 2013).

Table 1
Subject characteristics of Group (Offspring vs Partners) by Condition (Control vs Stress).

	Partners		Offspring	
	Control n = 25	Stress n = 18	Control n = 28	Stress n = 33
	M ± *SE*	*M* ± *SE*	*M* ± *SE*	*M* ± *SE*
Age (years)	66.44 ± 1.19	65.06 ± 1.15	66.25 ± 1.01	66.21 ± 1.17
BMI (kg/m^2)	27.45 ± 0.71	26.57 ± 0.94	25.40 ± 0.76	25.69 ± 0.60
SCL-90	118.44 ± 3.77	119.72 ± 4.26	114.79 ± 3.41	118.15 ± 3.14
STAI-state	29.46 ± 1.18	30.78 ± 1.37	32.19 ± 1.12	31.00 ± 1.02
STAI-trait	31.58 ± 1.36	31.72 ± 1.56	32.44 ± 1.28	31.63 ± 1.17
DS Forward	9.5 ± 0.44	8.5 ± 0.52	9.21 ± 0.33	8.34 ± 0.30
DS Backward	6.29 ± 0.39	6.11 ± 0.44	6.21 ± 0.27	6.75 ± 0.29
DS total	15.79 ± 0.76	14.61 ± 0.82	15.43 ± 0.60	15.09 ± 0.51
	n (%)	n (%)	n (%)	n (%)
Cardiovascular disease	2 (8)	2 (11)	2 (7)	1 (3)
Hypertension	10 (40)[a]	4 (22.2)[b]	4 (14.3)[c]	7 (21.2)[d]

Note: BMI = Body Mass Index; STAI-trait = Trait version of the State-trait anxiety inventory; SCL–90 = symptom checklist 90; DS = Digit Span. Medication use (n). ACE-inhibitor = angiotensin-converting-enzyme inhibitor; AT2-antagonist = angiotensin 2 receptor antagonist.

[a] b-blockers (1); β-blocker and diuretics (1); β-blocker and calcium channel blocker (1); AT2-agonists (2); AT2-agonists and diuretics (1); AT2-agonists and calcium channel blocker (1); AT2-agonists, diuretics and calcium channel blocker (1); or a combination of diuretics and ACE-inhibitor (2).

[b] β-blockers (1); β-blocker and diuretics (1); ACE-inhibitors (1); diuretics and ACE-inhibitor (1).

[c] ACE-inhibitors (1); diuretics (1); diuretics, calcium channel blocker and ACE-inhibitor (1); AT2-antagonist, β-blocker and diuretic (1).

[d] Diuretics (2); AT2-agonists (1); β-blocker and diuretics (2); calcium channel blocker and ACE-inhibitor (1); β-blocker, ACE-inhibitor and diuretics (1).

3. Materials

3.1. Emotional Sternberg task

WM was measured using an adapted version of the Sternberg item-recognition task (Oei et al., 2012; Sternberg, 1966). In the present version, the task consisted of a total of 180 trials, which lasted no more than 25 min. All trials were of low load (i.e., comparison load 4). Comparison load is defined by the number of targets to hold in WM, multiplied by the number of stimuli in the item-recognition display. In the present version, just one target letter had to be recognized in an item-recognition display that always showed 4 letters. Each trial started with a blue fixation cross (500 ms), followed by the target presentation (1000 ms), a distracter (1500 ms), and a recognition-display (< 2000 ms). Random jitter in between trials ranged from 1500 to 4500 ms. Participants were instructed to ignore the distracter pictures, and to fixate their eyes on a red cross centered in each distracter picture. Participants pressed a "yes" button indicating they had recognized a target, or a "no" button, when no target letter was present. A target was present (present-target trials) in half of the trials, in the other half the target was absent (absent-target trials). Distracters consisted of validated pictures selected from the International Affective Pictures System (Lang, Bradley, & Cuthbert, 2008), of which 30 neutral pictures rated on 9-point Likert scales (1 *very negative*, 9 *very positive*) *M* ± *SD*, valence: 5.09 ± 0.54; arousal (1 *not arousing at all*, 9 *highly arousing*): 3.21 ± 0.77) and 30 negatively arousing pictures (*M* ± *SD*, valence: 2.86 ± 0.93; arousal: 6.22 ± 0.52), that matched in background colour, and complexity, e.g. amount of people or animals in the scene. A third no-distraction category consisted of a fixation cross only. Task stimuli were back-projected on a screen located at the end of the scanner bore via an LCD projector located outside the scanner room. Subjects viewed stimuli on a screen through a mirror located on the head coil. Stimulus software (E-prime-2) was used for stimulus presentation and recording of responses.

3.2. Stress-induction

To induce stress, the Trier Social Stress Task (TSST) was used (Kirschbaum, Pirke, & Hellhammer, 1993). The TSST protocol has consistently proven to raise cortisol levels (Kirschbaum & Hellhammer, 1994). This laboratory stressor consists of a 10-min period in anticipation of a 5-min free speech, and a 5-min arithmetic task (counting backwards from 1033 to zero, in steps of 13) in front of a selection committee of three. As participants also comprised of pensioners or females who never worked, participants were asked to imagine they had applied for a job, or desperately wanted to join a particular club (e.g., choir, or private association) and that they had been invited to convince the committee in a free speech that they were the best man/woman for the job. Both good and bad qualities of the participant had to be brought up in the speech. For the counting backwards part of the TSST, one committee member responded to incorrect answers by saying out loud "incorrect, please start over". In the control condition, participants used the same anticipation period of 10 min to think of a movie to their liking, of which they were informed to having to answer open questions on paper for 5 min, in the same laboratory room, but without audience. Thereafter, they had to count backwards from 50 to zero at a slow pace for 5 min ("Placebo-TSST"; Het, Rohleder, Schoofs, Kirschbaum, & Wolf, 2009).

3.3. Physiological assessments

Salivary cortisol was assessed, using Salivettes (Sarstedt, Germany). Saliva sampling is a stress-free method to assess unbound cortisol (Kirschbaum & Hellhammer, 1994). Saliva samples were stored at −20 °C until assayed at Prof Kirschbaum's laboratory (http://biopsychologie.tu-dresden.de). Cortisol concentrations in saliva were measured using a commercially available chemiluminescence-immunoassay kit with high sensitivity (IBL, Hamburg, Germany). Inter- and intra-assay coefficients of variation were below 10%. Systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), and heart rate (HR, bpm) were recorded using an automatic wrist blood pressure monitor (OMRON, R5-I).

3.4. Scan protocol

Imaging was carried out on a 3 T Philips Achieva MRI scanner (Philips, Best, The Netherlands), using an 32-channel SENSE head coil. For fMRI, T_2^*-weighted gradient echo planar images (EPI) sensitive to BOLD contrast were obtained with the following acquisition parameters: repetition time (TR) = 2.2 s, echo time (TE) = 30 ms, flip angle = 80°, SENSE factor = 3, 38 axial slices, FOV = 220 × 220 mm, 2.75 mm isotropic voxels, 0.25 mm slice gap. A high-resolution

anatomical image (T_1-weighted ultra-fast gradient-echo acquisition; TR = 9.75 ms, TE = 4.59 ms, flip angle = 8°, 140 axial slices, FOV = 224 × 224 mm, in-plane resolution 0.875 × 0.875 mm, slice thickness = 1.2 mm) was acquired for registration purposes. The scan procedure consisted of EPI during the emotional WM task (25 min), the T_1-weighted anatomical scan (6 min), and the high-resolution EPI (1 min), an EPI resting state, to be published elsewhere.

3.5. Procedure

Screening. Volunteers were screened via telephone for present medication use and medical history. The information they provided was subsequently checked using data records obtained from the pharmacy and general practitioner (see Table 1 for medication use).

Participants had to refrain from caffeine, sugar or alcohol containing drinks the evening before the experiment, and were instructed not to eat or drink two hours before arrival time with the exception of water. Participants arrived at 8 h in the morning. After arrival, participants were seated in a quiet room where information was given about the study day and instructions were given with regard to the scan protocol and the emotional WM task. Hereafter, written informed consent was obtained. After participants had changed into the obligatory hospital clothing for scanning, Digit Span was assessed. The start time of the participants was balanced between condition (stress vs. control) and gender to keep morning cortisol levels as even as possible. To this end, lots were drawn by the experimenter, who was blind to the offspring/partner status of the participants. Four types of lots were available: Female receiving stress first, while her husband would be second receiving no-stress, or female first receiving no stress, while her husband would be second and would be receiving stress. Or male receiving stress first, while his wife would receive no stress, or the male would start with no stress, while his wife would be second and be receiving stress. Exactly 35 min after arrival, the TSST protocol started with instructions for the TSST (i.e., to prepare the speech). After 10 min preparation time, participants who started first, were brought to a room, in which the committee was seated, and the TSST protocol was continued for 10 min (Kirschbaum et al., 1993). The committee was also blind to the distinction offspring vs. partner. After the TSST, the participants were brought to the scanner, in which the emotional WM task was delivered, approximately 15 min after the end of the TSST. Saliva was sampled at four times: before ("baseline") and after the preparation phase of the TSST ("pre-speech"), at the end of the TSST, just before entering the scanner ("post-TSST"), and immediately after the scan procedure ("post-scan"). Blood pressure, heart rate and subjective stress were sampled at the same time points. After scanning, participants were seated in front of a PC, to fill out questionnaires. Hereafter, an exit-interview and a debriefing regarding the TSST followed. Participants were then brought to another hospital department for subsequent research (to be published elsewhere).

4. Data processing and analysis

4.1. Cortisol data

We previously published cortisol data of a subsample of males of the present sample (Jansen et al., 2016). However, because the present data included both males and females, we first checked whether gender was a significant factor. As this was not a significant factor, further analyses were done without taking Gender in to account. We then analyzed cortisol using repeated measures ANOVA, with as between-subjects factors Condition (Stress vs. Control) and Group (Offspring vs. Partner) and Time as within-subjects factor, and when appropriate, followed up by *t*-tests at the 4 time points. Blood pressure, heart rate and subjective stress data were analyzed in the same way (see results in the Supplementary material).

4.2. Task data

Reaction times were first checked for errors, misses, and outliers. Errors and misses were scored and removed. Subsequently, outliers were replaced by the mean by Category + 2 standard deviations (Oei, Tollenaar, Spinhoven & Elzinga, 2009). Gender was not a significant factor in these analyses, and was thus witheld from further analysis. Reaction times of correct trials were analyzed using repeated measures ANOVAs with as between-subjects factors Condition (stress vs. control), Group (offspring vs. partner), and as within-subjects factors Target (present vs. absent), and Distracter (neutral vs. emotional). Follow-up analysis of repeated measures ANOVA effects, if relevant, was done with *t*-tests. Greenhouse-Geisser corrections were applied when the sphericity assumption was not met. SPSS (version 20) was used for the analyses.

4.3. FMRI data

FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 6, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl; (Smith et al., 2004)). The following pre-statistics processing was applied: motion correction (Jenkinson, Bannister, Brady, & Smith, 2002); non-brain removal (Smith, 2002); spatial smoothing using a Gaussian kernel of FWHM 5 mm; grand-mean intensity normalisation of the entire 4D dataset by a single multiplicative factor; high pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with σ = 45.0s). Time-series statistical analysis was carried out with local autocorrelation correction (Woolrich, Ripley, Brady, & Smith, 2001). FMRI EPI data were registered to the individual T1-weighted structural scan (Jenkinson et al., 2002; Jenkinson & Smith, 2001), the T1 scan was registered to the 2 mm MNI-152 standard space template using FNIRT nonlinear registration (Andersson, Jenkinson, & Smith, 2007a, 2007b). The resulting registration matrix and warp image were then combined to normalize the EPI data in MNI space.

For each participant, five explanatory variables (EVs) were included in the general linear model: three EVs represented the period between target onset and distracter offset (total length 2.5s) separate for distracter type (Fix/Neu/Emo) on correct trials. Target-recognition periods on correct trials were modelled in one EV, independent of preceding distracter type, with variable durations depending on the response times of the participants. A last EV was included describing error trials, modelling the entire trial from target onset to target-recognition response. Each EV was convolved with a double gamma hemodynamic response function to account for the hemodynamic response. The contrast of interest was Emo > Neu. The images of contrasts of parameter estimates and corresponding variances were then fed into a higher-level mixed effects analysis, carried out with FLAME (FMRIB's Local Analysis of Mixed Effects) (Beckmann, Jenkinson, & Smith, 2003; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). First, the main effect of task was analyzed, using a 1-sample *t*-test, thresholded by initial cluster-forming threshold of $z > 3.1$, and a corrected $p = .05$. Next, a Condition by Group (2 × 2) analysis was done, with 4 EVs: Control Offspring; Control Partner; Stress Offspring; Stress Partner. Whole brain *z* (Gaussianised *T*) statistic images were thresholded by an initial cluster-forming threshold of $z > 3.1$ and a (corrected) cluster significance threshold of $p = .05$ (Worsley, 2001).

5. Results

5.1. Stress cortisol

Gender was not a significant between-subjects factor ($F(1, 83) = 1.22$, $p = .27$, and also did not interact with Group or Condition, and was therefore disregarded in further analyses. There was a significant between-subjects effect of Condition, ($F(1, 88) = 7.83$,

Table 2
Mean cortisol levels (nmol/L) in saliva and standard errors.

	Control			Stress		
	Partner	Offspring	Total	Partner	Offspring	Total
		M ± *SE*			*M* ± *SE*	
Pre-stress	13.32 ± 0.96	12.52 ± 1.09	12.90 ± 0.73	14.83 ± 1.54	12.97 ± 0.90	13.64 ± 0.80
Pre-speech	12.51 ± 0.82	11.23 ± 0.87	11.84 ± 0.60	15.69 ± 2.15	13.24 ± 1.04	14.09 ± 1.01
Post-TSST	12.12 ± 1.01	11.21 ± 1.33	11.65 ± 0.84[a]	20.43 ± 3.09	13.84 ± 1.35	16.36 ± 1.50[a]
Postscan	8.90 ± 0.60	10.42 ± 0.91	9.72 ± 0.57[b]	16.16 ± 2.02	13.51 ± 1.23	14.48 ± 1.08[b]

[a] $p = .006$.
[b] $p < .0005$.

$p = .006$, with higher cortisol levels in the stress group ($M \pm SE = 14.41 \pm 0.71$) than in the control group ($M \pm SE = 11.53 \pm 0.74$) and a significant interaction between Condition and Time ($F(3, 264) = 4{,}37$, $p = .005$). Follow up *t*-tests showed that cortisol levels at baseline did not differ between control and stress ($t_{100} = 0.68$, $p = .50$), while at pre-speech cortisol levels were higher in the Stress condition at trend levels ($t_{78,67} = 1.91$, $p = .055$). After the TSST cortisol levels in the stress condition were significantly higher than in the control condition ($t_{72,71} = 2.74$, $p = .006$). Postscan, cortisol levels between stress and control condition were still significantly different ($t_{72,78} = 3.90$, $p < .0005$, equal variances not assumed in the latter three analyses). Furthermore, a significant between-subjects effect of Group showed that partners had significantly higher overall cortisol levels ($M \pm SE = 13.99 \pm 0.78$) than offspring ($M \pm SE = 11.95 \pm 0.67$), ($F(1, 88) = 3.95$, $p = .05$). There was no significant interaction of Group by Condition ($F(1, 88) = 0.70$, $p = .41$ (see Table 2 for means and standard error).

5.2. Emotional inhibition task: behavioral effects

Reaction times. The RM ANOVA showed that the within-subjects factor Target was significant, ($F(1, 100) = 66.82$, $p < .0005$), with faster RTs during present-target trials, but no significant differences between Groups or Condition or interactions (all *p*'s > .33).

Accuracy. A trend was found for Group by Distracter ($F(1, 100) = 3.70$, $p = .057$. Follow-up *t*-tests showed that offspring were more accurate during emotional trials than during neutral trials ($t_{60} = -2.41$, $p = .02$), whereas there was no difference in accuracy between neutral and emotional trials in partners ($t_{42} = 0.31$, $p = .76$) (see Supplementary Table 2 for reaction times and accuracy scores). Adding Digit Span Forward as a covariate did not change any of the results.

5.3. Emotional inhibition task: functional imaging effects

See Table 3 and Fig. 1 for the main effects of task. The main effects of task in the contrast emo > neu, showed activations comparable to previous studies in young adults, specifically in the amygdala and inferior frontal gyrus (Dolcos & McCarthy, 2006; Oei et al., 2012). Relative deactivations (neu vs. emo) were found in the precuneus and the lateral occipital cortex.

Whole-brain higher level analysis ($z = 3.1$, cluster-corrected) of the Group by Condition interaction in the contrast of interest (Emo > Neu) showed a significant cluster in the medial posterior cingulate cortex (mPCC), extending into the precuneus (peak voxel x,y,z = −12, −52, 40, $p = .008$ (see Fig. 2)). The FSL-tool Featquery was subsequently used to extract mean signal of the neutral and emotional *z*-stats within the functional ROI. As can be seen, the interaction is driven by differences during the stress condition, specifically, partners showing *decreased* deactivation during emotional trials compared to offspring.

Deactivations, particularly in default mode network (DMN) brain areas such as the mPCC, are thought to reflect the reallocation of processing resources to the task at hand, and decreased deactivations as indications of reduced efficiency in doing so (Anticevic et al., 2012; McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003; Sambataro et al., 2010). We therefore tested the correlation between stress-induced deactivations in the mPCC with behavioral performance during emotional trials. Signal from the mPCC ROI during stress was significantly correlated with accuracy of the emotional trials, with the larger the decrease in deactivation, the smaller the accuracy during emotional distraction ($r = -.32$, $p = .025$).

Table 3
Significant clusters and local maxima during emotional distraction.

Region • Local maxima	L/R	Cluster size	x	y	z	Z	*p*
Emo > Neu							
Lingual Gyrus	R	2667	4	−88	−4	6.92	< .0001
• Lingual Gyrus	L		−8	−90	−10	6.66	
• Lateral Occipital Cortex: inferior division	L		−46	−82	8	6.12	
• Occipital Fusiform Gyrus	L		−22	−86	−12	4.97	
Lateral Occipital Cortex, inferior division	R	1032	50	−74	8	5.65	< .0001
Superior Frontal Gyrus		790	−4	52	38	5.59	< .0001
• Frontal Pole	L		−4	64	16	4.49	
• Frontal Pole	R		18	56	28	3.75	
• Paracingulate Gyrus			−6	50	14	3.86	
Frontal pole	L	618	−50	38	0	4.88	< .0001
• Orbitofrontal cortex	L		−50	32	−10	4.05	
• Inferior Frontal Gyrus	L		−52	22	8	4.6	
Orbitofrontal cortex	R	324	34	20	−14	5.14	< .0001
• Orbitofrontal cortex	R		40	28	−40	4.97	
• Inferior Frontal Gyrus	R		50	26	−4	4.47	
Temporal pole	L	284	−44	10	−34	5	< .0002
• Inferior Temporal Gyrus, anterior division	L		−52	−2	−36	4.51	
Amygdala	L	118	−18	−4	−16	3.8	.03
Neu > Emo							
Lateral Occipital Cortex superior division	R	180	40	−68	42	4.55	< .004
Precuneus	R	128	18	−56	20	4.23	< .002

Note: All areas are cluster-corrected significant ($z > 3.1$), $p < .05$; L/R = Left/right in the brain; Voxel size is 2 mm isotropic.

5.4. ROI analysis ventral affective brain areas

Because of our hypotheses of the ventral affective areas, the right amygdala and RIFG, we performed additional ROI-analyses. For the

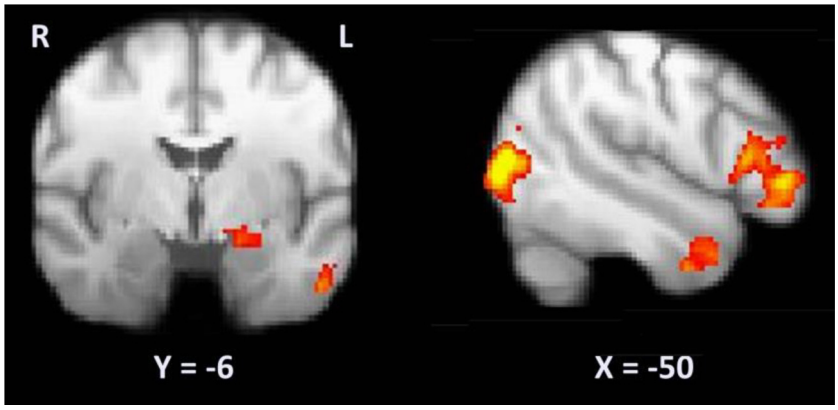

Fig. 1. Brain activation during emotional compared with neutral distraction shows the typical ventral activation pattern in the presence of emotional distraction.
Note. Coronal and sagittal view of clusters of voxels of combined group activations when contrasting emotional vs. neutral distracters; Intensity values in this thresholded *z*-stat map ($z > 3.1$, $p < .05$, cluster-corrected) range from 3.1 (red) to 5 (yellow). Voxel size = 2 mm^3 in MNI-152 Standard Space.

right amygdala and the RIFG we masked using binarized images of the right amygdala and RIFG from the Harvard-Oxford subcortical and cortical probability atlas, set at a probability of 50%, before extracting (emo > neu) signal from these regions using Featquery. Univariate ANOVA with Condition (stress vs. control) and Group (offspring vs. partner) as factors showed no significant differences between Groups, Condition, or any interactions (all *ps* > .1).

6. Discussion

Offspring from long-lived families display a lower prevalence of age-related diseases such as cardiovascular and metabolic diseases, which are generally associated with stress and increased cortisol levels (Dolcos & McCarthy, 2006; Rosmond, 2005; Rozing et al., 2010; Schoenmaker et al., 2006; Westendorp et al., 2009). They also show indications of better resistance against cognitive interference (Stijntjes et al., 2013). As coping with distractions typically deteriorates due to stress ánd aging, we hypothesized that individuals enriched for familial longevity might be less affected by stress, and better at ignoring emotional distraction compared to age-matched controls. We investigated this by inducing social stress in offspring from long-lived families, and their partners of comparable age, and assessed the ability to resist negative emotional and neutral distracters in a working memory task. The neural results of the present study showed that offspring were less affected by stress than their partners, as reflected by smaller stress-induced deactivations in the medial posterior cingulate cortex (mPCC) during emotional distraction. Moreover, smaller stress-induced mPCC deactivations were related to reduced accuracy when distractions were emotional. Although in offspring overall cortisol levels were lower than in their regular aging partners, relative cortisol increases due to stress, however, were not different between the two groups.

We previously reported stress-induced cortisol levels of males of the same sample (Jansen et al., 2016). Here we demonstrate that the general tendency of lower overall cortisol was also evident in female offspring from long-lived families. The more moderate basal HPA-axis activity in offspring from long-lived families is consistent with the findings that regular aging is related to increased cortisol levels, both diurnal (Deuschle et al., 1997; Nater et al., 2013; van Cauter et al., 1996;), and stress-induced (Otte et al., 2005). This overactivity of the HPA-axis is thought to speed up aging (Aguilera, 2011). Due to a

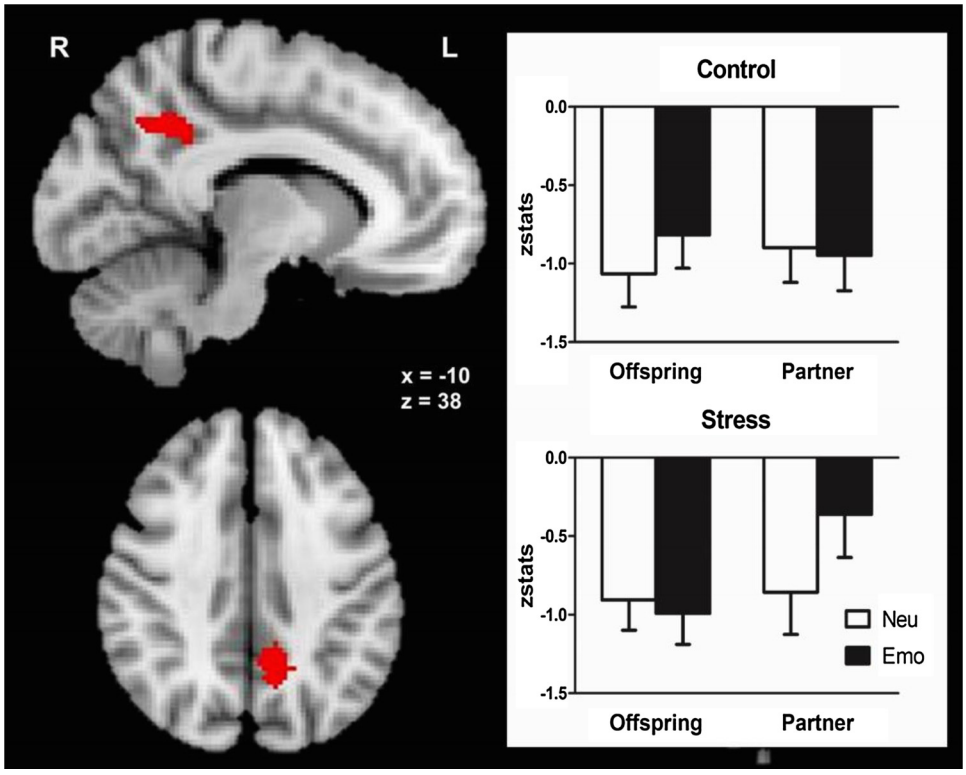

Fig. 2. Significant interaction between Group and Condition during emotional distraction was driven by decreased deactivations during emotional trials in Partners as compared with Offspring in the Stress Condition.
Note. Left panel: Sagittal (top) and axial (bottom) view (thresholded at z > 3.1, $p = .05$, cluster-corrected) of the significant interaction of Group by Condition in the lower level contrast Emo > Neu (MNI-coordinates, x, z = −10, 38). Right panel: BOLD Signal (mean *z*-values ± *SE*) during Neutral and Emotional trials extracted from the medial posterior cingulate cortex (mPCC) ROI of both groups in the Control condition (upper right) and Stress condition (bottom right). Voxel size = 2 mm^3 in MNI-152 Standard Space.

lifetime of adverse neurobiological consequences stress and cortisol are thought to exacerbate cognitive and physical decline particularly in the elderly. The lower basal HPA-axis activity in offspring form long-lived families might be protective against the adverse effects of acute stress, even though the net increase in cortisol does not differ between groups (Jansen et al., 2016).

Remarkably, partners showed smaller stress-induced mPCC deactivations related to reduced accuracy when distractions were emotional. The mPCC is a key region in the "default mode network" (DMN; Raichle et al., 2001) a resting state network of brain regions that are active during rest, but that are generally deactivated during task-processing. As such, DMN deactivations are thought to reflect the suppression of spontaneous brain activities and the reallocation of resources from "default-mode" to attention-demanding task processes (McKiernan et al., 2003). The DMN is suggested to compete with the dorsal attention system (Buckner, Andrews-Hanna, & Schacter, 2008), as these networks are often inversely activated, the more one focuses attention at an externally directed task the more active the dorsal attention network, and the more deactivated the DMN, with the exception of more internally oriented tasks, such as autobiographical tasks, that require DMN activity (e.g., Spreng, Stevens, Chamberlain, Gilmore & Schacter, 2010; Spreng and Schacter, 2012). Modulation of *task-induced* deactivations in the DMN by (chronological) aging has been demonstrated several times: Regular aging compared to young adults showed reduced deactivations specifically in the mPCC (Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Lustig et al., 2003; Spreng and Schacter, 2012), a tendency for decreased DMN functional connectivity with the mPCC as seed (Grady et al., 2010) and lower functional connectivity between mPCC and medial PFC, related to worse performance (Sambataro et al., 2010). Moreover, several fMRI studies showed age-related reduced deactivations in brain areas of the DMN associated with poorer performance of a variety of tasks, including WM tasks (Park, Polk, Hebrank, & Jenkins, 2010; Prakash, Heo, Voss, Patterson, & Kramer, 2012; Persson, Lustig, Nelson, & Reuter-Lorenz, 2007; Sambataro et al., 2010). Older people are thought to suppress the DMN during tasks to a lesser extent than young adults due to reduced cognitive control (Grady et al., 2006; Lustig et al., 2003; Persson et al., 2007). Modulation of task-induced deactivations in the DMN related to stress has also been reported. For instance, with a small group of young chronically stressed participants showing decreased task-induced deactivations in the DMN compared to controls (Soares, Sampaio, Ferreira et al., 2013; Soares, Sampaio, Marques et al., 2013). In the present study, all participants were relatively healthy and middle-aged, and differences in deactivations of the mPCC were only evident when participants were stressed. Given the similarities of the pattern seen in chronological aging and stress, the reduced deactivations related to diminished task accuracy in the partners compared to the offspring, might be suggestive of mPCC-modulation by *biological* aging. At least, it would be consistent with the idea that offspring from long-lived families are biologically younger, or age at a slower rate.

The overall task effects showed similarities with the typical pattern that can be seen during emotional distraction, with robust activations in ventral "affective" brain areas, such as amygdala and IFG. Unlike previous studies in younger adults (Dolcos & McCarthy, 2006) relative deactivations in the dorsal "executive" brain areas were mainly found in posterior parietal regions and appeared small, while relative deactivations in frontal brain areas were even absent, which is more reminiscent of the brain activation pattern during emotional distraction in stressed young adults, who showed decreased deactivations in frontal and parietal areas, and increased activity in ventral affective brain areas (Oei et al., 2012). IFG activations seemed stronger in this middle-aged sample than is usually observed in young adults (e.g. Oei et al., 2012), although we made no direct (statistical) comparison with a group of young adults. Nonetheless, this would be an interesting line of research to pursue in future studies. In aged individuals, greater activations in the RIFG during inhibition would be suggestive of a higher demand to engaging inhibitory control (Turner & Spreng, 2012). Although the RIFG activations were in the expected direction, the differences were not significant. There was also no indication of differences between slower and regular paced aging in the amygdala, and the robustness of the activation does not appear to support the idea of an age-related decline in amygdala function (e.g. Mather et al., 2004), although again, this is speculative, and should be tested in future studies.

Investigating both males and females in a stress study is usually a limitation, because of the known gender differences affecting (measurement) of the hormonal stress response (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999). However, the females from the present sample were all post-menopausal, which at least prevented confounding effects of oral contraceptives. Although gender as a factor did not differ significantly in the present study, this does not imply that (subtle) gender differences in the stress response would not be present after the menopause. By including both males and females of both offspring and partners of offspring, we increased the power to detect differences, because although the total sample was relatively large, the 2×2 design already led to rather small group sizes.

To summarize, the present study showed that middle-aged individuals who are "enriched for familial longevity" do not differ from their same-aged peers in performance on a working memory task with emotional and neutral distracters. Despite this, they show smaller reductions in mPCC deactivations when stressed, which are related to better working memory accuracy when distracted by emotional stimuli. The present findings are suggestive of biological aging effects in a brain area that has been found several times in chronological aging studies. Aging trajectories display great heterogeneity. Efforts in aging research are focussed on the identification and validation of panels of biomarkers that can be applied for classification of adults on biological age and monitoring their responses to preventative or therapeutic strategies (Belsky et al., 2015). Taken together our results suggest that larger stress-induced relative mPCC deactivations are indicative of a slower pace of aging. Future studies into the classification and modulation of aging trajectories might be encouraged to include these measurements as potential biomarkers of biological age.

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Conflicts of interest

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.biopsycho.2018.02.018.

References

Aggarwal, N. T., Wilson, R. S., Beck, T. L., Rajan, K. B., Mendes de Leon, C. F., Evans, D. A., et al. (2014). Perceived stress and change in cognitive function among adults 65 years and older. *Psychosomatic Medicine, 76*, 80–85.

Aguilera, G. (2011). HPA axis responsiveness to stress: Implications for healthy aging.

Experimental Gerontology, 46(2–3), 90–95.
Andersson, L. R., Jenkinson, M., & Smith, S. M. (2007a). *Non-linear optimisation. (Rep. No. FMRIB technical report TR07JA1)*.
Andersson, L. R., Jenkinson, M., & Smith, S. M. (2007b). *Non-linear registration aka spatial normalisation. (Rep. No. FMRIB technical report TR07JA2)*.
Anticevic, A., Cole, M. W., Murray, J. D., Corlett, P. R., Wang, X. J., & Krystal, J. H. (2012). The role of default network deactivation in cognition and disease. *Trends in Cognitive Science, 16*(12), 584–592.
Arrindell, W. A., & Ettema, J. H. M. (1986). *SCL-90. Handleiding bij een multidimensionele psychopathologie-indicator.* Lisse: Swets & Zeitlinger B.V.
Beckmann, C. F., Jenkinson, M., & Smith, S. M. (2003). General multilevel linear modeling for group analysis in FMRI. *Neuroimage, 20*, 1052–1063.
Belsky, D. W., Caspi, A., Houts, R., Cohen, H. J., Corcoran, D. L., Danese, A., et al. (2015). Quantification of biological aging in young adults. *Proceedings of the National Academy of Sciences USA, 112*(30), E4104–E4110.
Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: Anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences, 1124*, 1–38.
Chee, M. W., & Choo, W. C. (2004). Functional imaging of working memory after 24 hr of total sleep deprivation. *Journal of Neuroscience, 24*(19), 4560–4567.
Chrousos, G. P. (2000). The role of stress and the hypothalamic-pituitary-adrenal axis in the pathogenesis of the metabolic syndrome: Neuro-endocrine and target tissue-related causes. *International Journal of Obesity and Related Metabolic Disorders, 24*(Suppl. 2), S50–S55.
World Medical Association (2013). *World medical association declaration of helsinki, Vol. 310*, JAMA2191–2194 (20).
Deuschle, M., Gotthardt, U., Schweiger, U., Weber, B., Korner, A., Schmider, J., et al. (1997). With aging in humans the activity of the hypothalamus-pituitary-adrenal system increases and its diurnal amplitude flattens. *Life Sciences, 61*(22), 2239–2246.
Dolcos, F., & McCarthy, G. (2006). Brain systems mediating cognitive interference by emotional distraction. *Journal of Neuroscience, 26*, 2072–2079.
Dolcos, S., Katsumi, Y., & Dixon, R. A. (2014). The role of arousal in the spontaneous regulation of emotions in healthy aging: A fMRI investigation. *Frontiers in Psychology, 5*, 681.
Gazzaley, A., Cooney, J. W., Rissman, J., & D'Esposito, M. (2005). Top-down suppression deficit underlies working memory impairment in normal aging. *Nature Neuroscience, 8*, 1298–1300.
Gazzaley, A., Clapp, W., Kelley, J., McEvoy, K., Knight, R. T., & D'Esposito, M. (2008). Age-related top-down suppression deficit in the early stages of cortical visual memory processing. *Proceedings of the National Academy of Sciences United States of America, 105*, 13122–13126.
Grady, C. L., Springer, M. V., Hongwanishkul, D., McIntosh, A. R., & Winocur, G. (2006). Age-related changes in brain activity across the adult lifespan. *Journal of Cognitive Neuroscience, 18*, 227–241.
Grady, C. L., Protzner, A. B., Kovacevic, N., Strother, S. C., Afshin-Pour, B., Wojtowicz, M., et al. (2010). A multivariate analysis of age-related differences in default mode and task-positive networks across multiple cognitive domains. *Cerebral Cortex, 20*(6), 1432–1447.
Hasher, L., & Zacks, R. T. (1988). Working memory, comprehension, and afin: A review and a new view. In G. H. Bower (Ed.). *THe psychology of learning and motivation* (pp. 193–225). New York: Academic Press.
Het, S., Rohleder, N., Schoofs, D., Kirschbaum, C., & Wolf, O. T. (2009). Neuroendocrine and psychometric evaluation of a placebo version of the 'Trier Social Stress Test'. *Psychoneuroendocrinology, 34*, 1075–1086.
Iordan, A. D., Dolcos, S., & Dolcos, F. (2013). Neural signatures of the response to emotional distraction: A review of evidence from brain imaging investigations. *Frontiers in Human Neuroscience, 7*, 200.
Jansen, S. W., van Heemst, D., van der Grond, J., Westendorp, R., & Oei, N. Y. (2016). Physiological responding to stress in middle-aged males enriched for longevity: A social stress study. *Stress: The International Journal on the Biology of Stress, 19*, 28–36.
Jenkinson, M., & Smith, S. M. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis, 5*, 143–156.
Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage, 17*, 825–841.
Kaszniak, A. W., & Menchola, M. (2012). Behavioral neuroscience of emotion in aging. *Current Topics in Behavioral Neurosciences, 10*, 51–66.
Kirschbaum, C., & Hellhammer, D. H. (1994). Salivary cortisol in psychoneuroendocrine research: Recent developments and applications. *Psychoneuroendocrinology, 19*, 313–333.
Kirschbaum, C., Pirke, K. M., & Hellhammer, D. H. (1993). The 'Trier Social Stress Test'–a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology, 28*, 76–81.
Kirschbaum, C., Kudielka, B. M., Gaab, J., Schommer, N. C., & Hellhammer, D. H. (1999). Impact of gender, menstrual cycle phase, and oral contraceptives on the activity of the hypothalamus-pituitary-adrenal axis. *Psychosomatic Medicine, 61*, 154–162.
Kumari, M., Badrick, E., Sacker, A., Kirschbaum, C., Marmot, M., & Chandola, T. (2010). Identifying patterns in cortisol secretion in an older population. Findings from the Whitehall II study. *Psychoneuroendocrinology, 35*, 1091–1099.
Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (2008). *International affective picture system (IAPS): Instruction manual and affective ratings. (Rep. No. technical report A-8). The center for research in psychophysiology.* University of Florida.
Lustig, C., Snyder, A. Z., Bhakta, M., O'Brien, K. C., McAvoy, M., Raichle, M. E., et al. (2003). Functional deactivations: Change with age and dementia of the Alzheimer type. *Proceedings of the National Academy of Sciences of the United States of America, 100*, 14504–14509.
Marshall, A. C., Cooper, N. R., Segrave, R., & Geeraert, N. (2015). The effects of long-term stress exposure on aging cognition: A behavioral and EEG investigation. *Neurobiology of Aging, 36*, 2136–2144.
Mather, M., Canli, T., English, T., Whitfield, S., Wais, P., Ochsner, K., et al. (2004). Amygdala responses to emotionally valenced stimuli in older and younger adults. *Psychological Science, 15*, 259–263.
McEwen, B. S. (2003). Interacting mediators of allostasis and allostatic load: towards an understanding of resilience in aging. *Metabolism: Clinical and Experimental, 52*, 10–16.
McKiernan, K. A., Kaufman, J. N., Kucera-Thompson, J., & Binder, J. R. (2003). A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. *Journal of Cognitive Neuroscience, 15*, 394–408.
Nater, U. M., Hoppmann, C. A., & Scott, S. B. (2013). Diurnal profiles of salivary cortisol and alpha-amylase change across the adult lifespan: Evidence from repeated daily life assessments. *Psychoneuroendocrinology, 38*(12), 3167–3171.
Noordam, R., Jansen, S. W., Akintola, A. A., Oei, N. Y., Maier, A. B., Pijl, H., et al. (2012). Familial longevity is marked by lower diurnal salivary cortisol levels: The Leiden Longevity Study. *PLoS One, 7*, e31166.
Oei, N. Y. L., Tollenaar, M. S., Spinhoven, P., & Elzinga, B. M. (2009). Hydrocortisone reduces emotional distracter interference in working memory. *Psychoneuroendocrinology, 34*(9), 1284–1293. http://dx.doi.org/10.1016/j.psyneuen.2009.03.015.
Oei, N. Y. L., Veer, I. M., Wolf, O. T., Spinhoven, P., Rombouts, S. A., & Elzinga, B. M. (2012). Stress shifts brain activation towards ventral 'affective' areas during emotional distraction. *Social Cognitive and Affective Neuroscience, 7*(4), 403–412.
Otte, C., Hart, S., Neylan, T. C., Marmar, C. R., Yaffe, K., & Mohr, D. C. (2005). A meta-analysis of cortisol response to challenge in human aging: Importance of gender. *Psychoneuroendocrinology, 30*(1), 80–91.
Park, D. C., Polk, T. A., Hebrank, A. C., & Jenkins, L. J. (2010). Age differences in default mode activity on easy and difficult spatial judgment tasks. *Frontiers in Human Neuroscience, 19*(3), 75.
Persson, J., Lustig, C., Nelson, J. K., & Reuter-Lorenz, P. A. (2007). Age differences in deactivation: A link to cognitive control? *Journal of Cognitive Neuroscience, 19*, 1021–1032.
Pettigrew, C., & Martin, R. C. (2014). Cognitive declines in healthy aging: Evidence from multiple aspects of interference resolution. *Psychology and Aging, 29*, 187–204.
Prakash, R. S., Heo, S., Voss, M. W., Patterson, B., & Kramer, A. F. (2012). Age-related differences in cortical recruitment and suppression: Implications for cognitive performance. *Behavioural Brain Research, 230*(1), 192–200.
Raichle, M. E., MacLeod, A. M., Snyder, A. Z., Powers, W. J., Gusnard, D. A., & Shulman, G. L. (2001). A default mode of brain function. *Proceedings of the National Academy of Sciences of the United States of America, 98*, 676–682.
Rosmond, R. (2005). Role of stress in the pathogenesis of the metabolic syndrome. *Psychoneuroendocrinology, 30*(1), 1–10.
Rozing, M. P., Westendorp, R. G., de Craen, A. J., Frolich, M., de Goeij, M. C., Heijmans, B. T., et al. (2010). Favorable glucose tolerance and lower prevalence of metabolic syndrome in offspring without diabetes mellitus of nonagenarian siblings: The Leiden longevity study. *Journal of the American Geriatrics Society, 58*, 564–569.
Sambataro, F., Murty, V. P., Callicott, J. H., Tan, H. Y., Das, S., Weinberger, D. R., et al. (2010). Age-related alterations in default mode network: Impact on working memory performance. *Neurobiology of Aging, 31*(5), 839–852.
Schoenmaker, M., de Craen, A. J., de Meijer, P. H., Beekman, M., Blauw, G. J., Slagboom, P. E., et al. (2006). Evidence of genetic enrichment for exceptional survival using a family approach: The Leiden Longevity Study. *European Journal of Human Genetics, 14*, 79–84.
Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., et al. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59*, 22–33.
Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., et al. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage, 23*(Suppl. 1), S208–S219.
Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping, 17*, 143–155.
Soares, J. M., Sampaio, A., Ferreira, L. M., Santos, N. C., Marques, P., Marques, F., et al. (2013). Stress impact on resting state brain networks. *PLoS One, 8*(6), e66500. http://dx.doi.org/10.1371/journal.pone.0066500.
Soares, J. M., Sampaio, A., Marques, P., Ferreira, L. M., Santos, N. C., Marques, F., et al. (2013). Plasticity of resting state brain networks in recovery from stress. *Frontiers in Human Neuroscience, 7*, 919. http://dx.doi.org/10.3389/fnhum.2013.00919.
Spielberger, C. D. (1983). *Manual for the state-trait anxiety inventory (STAI).* Palo Alto, CA: Consulting Psychologists Press.
Spreng, R. N., & Schacter, D. L. (2012). Default network modulation and large-scale network interactivity in healthy Young and old adults. *Cerebral Cortex, 22*(11), 2610–2621. http://dx.doi.org/10.1093/cercor/bhr339.
Spreng, R. N., Stevens, W. D., Chamberlain, J. P., Gilmore, A. W., & Schacter, D. L. (2010). Default network activity, coupled with the frontoparietal control network, supports goal-directed cognition. *Neuroimage, 53*(1), 303–317. http://dx.doi.org/10.1016/j.neuroimage.2010.06.016.
St Jacques, P., Dolcos, F., & Cabeza, R. (2010). Effects of aging on functional connectivity of the amygdala during negative evaluation: A network analysis of fMRI data. *Neurobiology of Aging, 31*(2), 315–327.
Sternberg, S. (1966). High-speed scanning in human memory. *Science, 153*, 652–654.
Stijntjes, M., de Craen, A. J., van, H. D., Meskers, C. G., van Buchem, M. A., Westendorp, R. G., et al. (2013). Familial longevity is marked by better cognitive performance at middle age: The Leiden Longevity Study. *PLoS One, 8*, e57962.
Turner, G. R., & Spreng, R. N. (2012). Executive functions and neurocognitive aging:

Dissociable patterns of brain activity. *Neurobiology of Aging, 33*(4), 813–826.
van Cauter, E., Leproult, R., & Kupfer, D. J. (1996). Effects of gender and age on the levels and circadian rhythmicity of plasma cortisol. *The Journal of Clinical Endocrinology & Metabolism, 81*(7), 2468–2473.
Waaijer, M. E., Parish, W. E., Strongitharm, B. H., van, H. D., Slagboom, P. E., de Craen, A. J., et al. (2012). The number of p16INK4a positive cells in human skin reflects biological age. *Aging Cell, 11*, 722–725.
Wallerius, S., Rosmond, R., Ljung, T., Holm, G., & Bjorntorp, P. (2003). Rise in morning saliva cortisol is associated with abdominal obesity in men: A preliminary report. *Journal of Endocrinological Investigation, 26*(7), 616–619.
Wechsler, D. (1997). *Wechsler adult intelligence scale* (3rd ed.). San Antonio: The Psychological Corporation.
Weeks, J. C., & Hasher, L. (2014). The disruptive – And beneficial – Effects of distraction on older adults' cognitive performance. *Frontiers in Psychology, 5*(February), 133. http://dx.doi.org/10.3389/fpsyg.2014.00133.
Westendorp, R. G., van, H. D., Rozing, M. P., Frolich, M., Mooijaart, S. P., Blauw, G. J., et al. (2009). Nonagenarian siblings and their offspring display lower risk of mortality and morbidity than sporadic nonagenarians: The Leiden Longevity Study. *Journal of the American Geriatrics Society, 57*, 1634–1637.
Woolrich, M. W., Ripley, B. D., Brady, M., & Smith, S. M. (2001). Temporal autocorrelation in univariate linear modeling of FMRI data. *Neuroimage, 14*, 1370–1386.
Woolrich, M. W., Behrens, T. E., Beckmann, C. F., Jenkinson, M., & Smith, S. M. (2004). Multilevel linear modelling for FMRI group analysis using Bayesian inference. *Neuroimage, 21*, 1732–1747.
Worsley, K. J. (2001). Statistical analysis of activation images. In P. Jezzard, P. M. Matthews, & S. M. Smith (Eds.). *Functional MRI: An introduction to methods* (pp. 251–270). New York: Oxford University Press Inc.
Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., et al. (1982). Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research, 17*(1), 37–49.