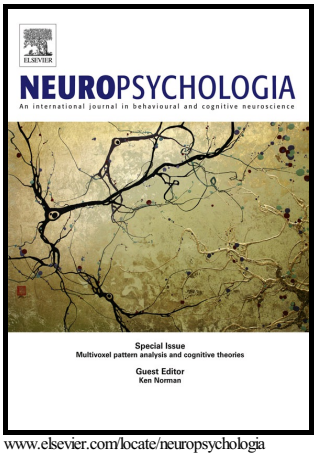

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Age-related alterations in functional connectivity patterns during working memory encoding of emotional items

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Running head: Aging and Emotional Encoding

Abstract

Previous findings indicate age-related differences in frontal-amygdala connectivity during emotional processing. However, direct evidence for age differences in brain functional activation and connectivity during emotional processing and concomitant behavioral implications is

lacking. In the present study, we examined the impact of aging on the neural signature of selective attention to emotional information during working memory (WM) encoding. Participants completed an emotional WM task in which they were asked to attend to emotional targets and ignore irrelevant distractors. Despite an overall reduction in accuracy for older relative to younger adults, no behavioral age effect was observed as a function of emotional valence. The functional connectivity patterns of left ventrolateral prefrontal cortex showed that younger adults recruited one network for encoding of both positive and negative emotional targets and this network contributed to higher memory accuracy in this cohort. Older adults, on the other hand, engaged two distinct networks for encoding of positive and negative targets. The functional connectivity analysis using left amygdala further demonstrated that older adults recruited one single network during encoding of positive as well as negative targets whereas younger adults recruited this network only for encoding of negative items. The engagement of amygdala functional network also contributed to higher memory performance and faster response times in older adults. Our findings provide novel insights into the differential roles of functional brain networks connected to the medial PFC and amygdala during encoding of emotionally-valenced items with advancing age.

Keywords: Aging, Emotion, Working Memory, Functional Connectivity, PLS, amygdala, fMRI

Aging is characterized by an overall decline in several cognitive domains, including working memory (WM) and episodic memory. Behavioral and neural evidence has suggested that attentional deficits in suppressing task-irrelevant information underlie decline in WM performance with advancing age (Gazzaley & D'Esposito, 2007). However, despite overall age-related cognitive impairment in inhibiting task-irrelevant information, emotional processing is typically well preserved in aging (Reuter-Lorenz & Lustig, 2005). According to one dominant

theory, the socioemotional selectivity theory (SST), limited time perception in late adulthood leads to a motivational shift, and subsequent changes in processing of emotional information (Carstensen et al., 1999). Consistent with this account, a number of behavioral studies have demonstrated that older adults show a processing bias for positive, compared to negative information in attention (Allard & Isaacowitz, 2008; Mather & Carstensen, 2003, 2005; Samanez-Larkin et al., 2009), decision making (Lockenhoff & Carstensen, 2007; Löckenhoff & Carstensen, 2004), and memory (Charles et al., 2003; Mather & Knight, 2005; Ziaei et al., 2015). This processing bias is often referred to as the positivity effect (For a review see Reed et al. (2014)). It has been argued that the positivity effect relies on top-down attentional control subserved by the prefrontal cortex (Mather, 2012). However, there is limited understanding of the underlying neural correlates involved in the positivity effect.

In addition to behavioral support for the positivity effect in aging, neuroimaging studies have reported changes in activity patterns of regions involved in emotional processing, such as the amygdala and lateral PFC. More specifically, age-related increased recruitment of PFC, along with decreased amygdala activity is the most consistent finding across studies (for reviews see Mather (2012); Nashiro et al. (2012)). In addition to regional activation differences, age-related alterations in the functional connectivity between amygdala and PFC regions have been reported. For instance, St Jacques et al. (2010)) showed that the functional connectivity between the amygdala and ventral anterior cingulate cortex was greater during evaluation of negative items in older compared to younger adults. Moreover, during the processing of positive relative to negative stimuli, older adults showed a stronger connectivity between medial PFC and retrosplenial cortex when engaged in deep processing (semantic elaboration), whereas younger adults demonstrated the opposite pattern (Ritchey et al., 2011a). The findings of prefrontal -

amygdala functional connectivity during processing of emotional items suggest that older adults, more so than their younger counterparts, may engage in regulatory mechanisms, particularly during processing of negative emotions. Given that emotional processes are widely distributed over multiple functionally interacting brain regions (Pessoa, 2008), it is reasonable to suggest that the process of encoding emotional items are supported by large-scale brain networks rather than isolated brain areas. Therefore, understanding the functional brain networks of such highly complex processes will provide insights into how emotional and cognitive operations are affected by increasing age in both healthy and clinical populations. Only a few studies, however, have investigated age-related changes in functional brain connectivity during emotional processing and the results have been inconclusive. The primary aim of this study is to investigate the impact of aging on functional brain network connectivity between PFC and amygdala and the rest of the brain during WM encoding of emotional items.

In order to identify age-related differences in neural activation and functional connectivity patterns associated with selective attention during encoding of emotional items in WM, both univariate and multivariate (spatial-temporal partial-least-squares, PLS) analyses were applied. First, we aimed to investigate age-related differences in behavior and brain activation by instructed attention to emotional targets during WM encoding; second, to examine the functional connectivity pattern between *lateral PFC* and the rest of the brain in response to task-relevant emotional items, and third, to explore the functional connectivity pattern between the *amygdala* and the rest of the brain during instructed attention to task-relevant emotional items.

In order to achieve these aims, we first identified activity patterns associated with instructed attention to emotional target items across age groups using whole-brain univariate statistics. Key regions implicated in selective attention during WM encoding were subsequently used for seed-

behavioral PLS to examine whether functional connectivity patterns involved in WM encoding were modulated by emotional valence, if functional connectivity differed between age groups, and whether functional connectivity was related to task performance. Given previous evidence for a positivity effect in older adults, we hypothesized that younger and older adults would show differential recruitment of brain networks in response to positive and negative target items. If younger and older adults show age-invariant functional network engagement from each of the seed regions, results from the seed PLS analysis should reveal a common circuitry with a possibility for quantitative differences. Alternatively, if younger and older adults engage distinct networks that support emotional processing, then results from the seed PLS analysis should reveal separate networks that are differentially connected to the seed regions as a function of emotional valence.

Methods and Materials

Participants

Sixteen healthy younger adults and 15 healthy older adults participated in this study. Three younger and two older participants were excluded from the analysis due to extensive movement in the scanner and brain signal losses. Therefore, analyses were conducted on the data from 13 younger adults (9 females; *M* = 22.6, *SD* = 1.69; range = 23-26 years) and 13 older adults (9 females; *M* = 68.23, *SD* =3.7 years; age range = 64-74). Younger participants were undergraduate students recruited from Stockholm University and older adults were community volunteers. All participants were right-handed, Swedish speakers, with no history of neurological or psychiatric problems, and had normal or corrected-to-normal vision using MRI compatible glasses. All participants were screened for claustrophobia, neurological and psychiatric medications, and MRI compatibility. Additionally, older adults were screened for cognitive

impairments using Mini Mental State Examination (MMSE; Folstein et al. (1975)). All participants took part in two separate test sessions; one for behavioral assessments, and one for the fMRI scanning. Informed consents were obtained from all participants. The investigation was approved by the Ethical Review Board in Stockholm. Participants were paid 800 SEK (~ $95 USD) for their participation and were debriefed after they completed the second session.

Materials

Stimuli consisted of seven hundred eighty six pictures that were drawn from the International Affective Pictures Systems (IAPS; Lang et al., 2008). Based on the IAPS rating system, 312 were rated as negative (valence: M = 2.83, SD = 1.7, arousal: M = 5.54, SD = 2.17), 312 as positive (valence: M = 6.79, SD = 1.73; arousal: M = 4.83, SD = 2.3), and 162 as neutral (valence: M = 4.87, SD = 1.26; arousal: M = 2.79, SD =2.0). No significant differences were found between the arousal levels of positive and negative pictures ($p > .05$). Pictures were presented against a black background using E-prime 2.0 (Psychology Software Tools, Pittsburgh, PA, USA), and were presented at a 600 × 800-pixel resolution.

Procedure

The study consisted of two sessions; first a behavioral testing session which took place at the Department of Psychology at Stockholm University, and second, an fMRI session which took place at the MRI facility at the Karolinska hospital on a separate day. Both sessions were conducted within a week. During the behavioral testing session, participants completed the color-word Stroop test (Jensen & Rohwer, 1966), a complex short-term memory tests (operation span; Unsworth et al. (2005), and an emotion regulation questionnaire (Gross & John, 2003). Older adults also completed the MMSE. In addition, practice runs of the emotional WM tasks were performed in preparation for the scanning session. During the second session, and prior to MR

scanning, participants were verbally instructed on how to perform the task, and also performed a practice run until they were familiarized with the task.

Experimental design

A modified version of a visual WM task developed by Gazzaley et al. (2005a) was used to investigate age-related changes in brain networks involved in selective attention to emotional items. Participants first received an instruction to either attend to negative or positive pictures (5 sec), while ignoring irrelevant distractors. Then, three sequential screens, each composed of a pair of pictures were presented (2.5 sec for each pair separated by a 0.5 sec fixation cross). Presentation of all three screens were followed by a fixation cross (maintenance phase; 4 sec), and finally a WM probe (retrieval phase; 2 sec). Trials were separated by an intertrial interval (ITI) with a variable length (42% ITIs of 1.5 sec, 28% ITIs of 3 sec, 14% ITIs of 4.5 sec, 12% ITIs of 6 sec, and 4% ITIs of 7.5 sec), allowing for an independent estimation of the BOLD response on a trial-by-trail basis (Huettel et al., 2014).

A full description of the task is provided elsewhere (Ziaei et al., 2014). In short, five different conditions were used: (1) attend to negative pictures/ignore positive pictures, (2) attend to negative pictures/ignore neutral pictures, (3) attend to positive pictures/ignore negative pictures, (4) attend to positive pictures/ignore neutral pictures, (5) and passive viewing (Fig. 1). During encoding, pairs of emotional-neutral (positive-neutral or negative-neutral pairs) or emotional-emotional (positive-negative or negative-positive) pictures were presented, and participants were instructed to focus on the relevant target and ignore the irrelevant item (Figure 1). During retrieval, an emotional picture (with either positive or negative valence) was presented. Participants were instructed to respond with their index finger if the probe matched one of the previously presented pictures, and press with their middle finger if the probe did not

match any of the previously presented pictures. All responses were collected using a scanner compatible response box (Lumitouch, Inc.). The valence of the retrieval cue (probe item) and the target always matched. Thus, if participants were instructed to attend to positive pictures (target item), the probe also had positive valence. Fifty novel and 50 previously-shown images were used as probes. For the passive viewing condition, 50 % of the probes were positive and 50% were negative. Neutral pictures were never used as probes. For each condition, participants performed 20 trials in four different blocks (5 trials in each block) in two separate runs. The order of conditions was counterbalanced between participants.

[Insert Figure 1 about here]

Recognition memory task: After scanning, participants performed a self-paced recognition memory task that included images that were included in the WM target set, but were not used as probes in the WM task. One-hundred and thirty pictures (100 previously shown pictures; 20 pictures from each condition) intermixed with 30 novel stimuli (10 from each of positive/negative/neutral categories) were chosen for the recognition memory task. For each picture, participants were asked to indicate whether the picture had been presented previously during the WM scanning task, and also, for each picture, were asked to rate the confidence of their responses using a 4-point scale (one of four responses: sure old, unsure old, unsure new, sure new). The hit rates for WM and recognition memory is presented in Supplementary Figure 1 & Table 1.

Image Acquisition, Preprocessing, and Analysis

Magnetic resonance imaging was performed using a 3-Tesla General Electric scanner MR750 equipped with a 32 channel head coil. Acquisition of functional data was achieved using a gradient echo-planar imaging sequence (37 transaxial slices, odd–even interleaved, 2 mm in

plane resolution, gap: 0.5 mm, repetition time [TR]: 2000 ms, echo time [TE]: 30 ms, flip angle: 80°, field of view: 25 × 25 cm, voxel size: 2 × 2 × 2 mm). In order to allow for progressive saturation of the fMRI-signal, 10 dummy scans were collected, and discarded prior to experimental image acquisition. High-resolution T1-weighted structural images were also collected with a 3D fast spoiled gradient echo sequence (180 slices, with a 1 mm thickness, TR = 8.2 ms, TE = 3.2 ms, flip angle: 12°, field of view: 25 × 25 cm). The emotional WM task was presented to the participants on a computer screen, seen through a mirror mounted on the head coil. Participants were using headphones and earplugs to dampen scanner noise, and cushions inside the head coil minimized head movements.

All fMRI data were preprocessed using the statistical parametric mapping software (SPM8, Welcome Department of Imaging Neuroscience, University College London, UK) implemented in MATLAB 2010b (Mathworks Inc., MA). Following slice timing correction, motion correction was done using the INRIAlign toolbox (Freire et al., 2002). Following coregisteration, the "New Segment" procedure was used to segment the T1 image into gray matter (GM) and white matter (WM). The "DARTEL" toolbox was used to create a custom group template from the segmented GM and WM images (Ashburner, 2007). In addition, deformation from the group-specific template to each of the subject-specific GM/WM images was computed (i.e. flow field). Finally, the coregistered fMRI images and segmented GM/WM images were nonlinearly normalized, subject by subject, to the sample-specific template (using a subject-specific flow field), affine aligned into the Montreal Neurological Institute (MNI) template, and finally smoothed using an 8 mm FWHM Gaussian kernel. At the end, a correction was applied to remove noise in the data using the voxel-level linear model (Macey et al., 2004). The artifact repair toolbox

(http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html) was also utilized to correct for movement. None of the participants required more than 3% repair from all volumes.

Whole-brain univariate analysis: Functional MRI data was collected in two separate runs. Each run contained 10 trials of each condition (see above) with a total time of approximately 30 min. The order of runs was counterbalanced across participants. Given our aim of investigating brain networks associated with encoding and corresponding memory performance, only the encoding phase was modeled in the framework of the general linear model (GLM) as implemented in SPM8. Blocked sustained responses were modeled with a boxcar function, whereas event-related transient responses were modeled as delta functions based on trial onset. All regressors of interest were convolved with the hemodynamic response function (HRF). Onsets of all trials were included in the analyses. In order to account for in-scanner movement, three translational [x y z] and three rotational (pitch, roll, and yaw) regressors obtained from the realignment step were included as covariates of no interest in the individual fixed effect analyses. Single-subject statistical contrasts were set up using the GLM, and group data were analyzed in a random-effects model that differentiated between conditions and effects of age. Statistical parametric maps were generated using *t* statistics to identify regions activated according to the model. All results are reported in MNI space. Unless otherwise specified, whole-brain analyses were employed when no regional a-priori hypothesis was considered; in these cases, only effects surviving a family-wise error (FWE) corrected (cluster and/or height) level of $P = .05$.

Partial least squares (PLS) analyses: To investigate multivariate relations between brain activation and behavioral performance, along with experimentally induced functional connectivity in relation to aging, seed-PLS analysis was conducted (McIntosh et al., 1996; McIntosh et al., 2004). For a detailed tutorial of PLS, see Krishnan et al. (2011). PLS analyses

were used to extend the univariate analyses by using a network-level approach. In contrast to univariate analyses, which assess the significance of each voxel separately, PLS identifies activity patterns across the brain in relation to the experimental manipulation of interest. As the activation patterns identified by PLS reflects activity changes across all regions of the brain simultaneously, there is no need for multiple comparison correction. Moreover, PLS is a data-driven approach which decomposes the data into a set of patterns that capture the most amount of variance in the data, rather than using prior assumptions by imposing contrasts between conditions of interest.

For this study, we were primarily interested in identifying brain networks involved in WM encoding of emotional targets. Therefore, we collapsed across conditions with emotional and neutral distractors resulting in three conditions; instructed attention to positive target items (positive condition), instructed attention to negative target items (negative condition), and passive viewing (passive). A cross-correlation matrix was computed as the correlation between behavior (accuracy and RT), the temporal signature of the seed region, and activity in all other brain voxels across participants within each experimental condition (young-positive, young-negative, young-passive, old-positive, old-negative, and old-passive). This cross-correlation matrix was then subjected to singular value decomposition (SVD) to identify a set of orthogonal latent variables (LVs), which represent linear combinations of the original variables. The first LV accounts for the largest covariance of the data, with progressively smaller amount for each subsequent LV. The first set of saliencies of each LV represent the pattern of covariance of behavioral performance, seed voxel, and the rest of the brain across experimental conditions. Additionally, the brain score reflects how strong each subject contributes to the pattern expressed in each LV.

The statistical significance of each LV was assessed using permutation tests that involve reordering the rows of the data matrix and recalculating the LVs of the reordered matrix using a SVD approach. The number of times a singular value exceeds the original singular value yields the probability of significance of original LVs. In the present study, 500 permutations were performed. In addition, stability of voxel saliencies contributing to each LV was determined using bootstrap estimation of standard errors (SEs), using 100 bootstrap samples. The Bootstrap Ratio (BR) was computed, and voxels with BR > 3 (approximately a Z-score of 3, corresponding to $p < 0.0001$, two-tailed) were considered as reliable. All reliable clusters comprised at least 50 contiguous voxels. In addition, the upper and lower percentiles of the bootstrap distribution were used to generate 95% confidence intervals (CIs) around the brain and correlation scores respectively to facilitate interpretation. For example, brain/correlation scores were considered unreliable when CIs crossing zero and two groups were considered significantly different from each other if the CIs did not overlap.

We identified two seed regions for seed-behavior PLS analysis; the left amygdala (-30 -6 -10) and the left VLPFC (-38 16 26). The selection of both of these seeds was based on two criteria; first reliable task-related activation for instructed attention to emotional items in the univariate whole-brain analysis, and, second, converging evidence from previous studies demonstrating the role of amygdala and VLPFC in emotional processing. The VLPFC has been shown to be involved in emotion regulation (Buhle et al., 2014), attention to emotional stimuli (Lindquist et al., 2012), and deep processing of emotional stimuli among older adults (Ritchey et al., 2011a). The amygdala also has been reported as a key region involved in emotional processes in a number of neuroimaging and brain lesion studies (for instance see (Adolphs, 1999; Lindquist et al., 2012; Pessoa & Adolphs, 2010; Wager et al., 2015). In addition to the analyses reported

here, we also conducted functional connectivity analyses with only correct trials using the amygdala and VLPFC as seeds. These results are generally in agreement with the reported findings here, but are presented in the Supplementary results for transparency.

Results

Behavioral Findings

Signal detection theory was used to calculate memory accuracy scores by subtracting false alarms from hits. Due to extreme values (1- extreme bias in favor of yes to all conditions or 0 - extreme bias in favor of no responses), all data were put through loglinear transformation using the approach proposed by Stanislaw and Todorov (1999). The loglinear approach involved adding 0.5 to the number of hits and FAs and adding 1 to the number of signal and noise trials before calculating the hit and FA rates. Thus, memory accuracy scores were computed as loglinear hits – loglinear false alarms.

Working memory performance[1]: First, we tested whether instructed attention to specific emotional targets had an impact on WM accuracy. As predicted, results from a 5 (conditions) by 2 (age groups) repeated measure ANOVA revealed a significant main effect of condition ($F(4,96) = 7.36$, $p < .01$, $\eta_p^2 = .23$), showing higher WM accuracy in conditions with instructed attention, compared to passive viewing (all *ps*< .05*)*. No significant differences were found between instructed attention conditions (all *ps* > .05). The main effect of age was also significant, showing that older adults had lower accuracy compared to younger adults ($F(1,24) = 15.27$, $p < .01$, $\eta_p^2 = .38$; Fig. 2). The age group by condition interaction did not reach significance ($F(4,96) = 1.09$, $p = .36$, $\eta_p^2 = .04$; Fig. 2A).

[1] The WM performance was also analyzed using nonparametric statistics. A Mann-Whitney test indicated that older adults had lower WM accuracy compared to younger adults in all conditions (all *ps* < .005).

Next, we examined the role of instructed attention on reaction times (RTs) using a 5 (condition) by 2 (age group) repeated measure ANOVA. There was a significant reduction in RTs for instructed attention compared to passive viewing in across age groups ($F(4,88) = 3.07$, $p = .02$, $\eta_p^2 = .12$), but the age by condition interaction was not significant ($F(4,88) = .14$, $p = .96$, $\eta_p^2 = .01$). As expected, older adults responded slower relative to younger adults ($F(1,22) = 44.72$, $p < .01$, $\eta_p^2 = .67$). No significant differences were found between instructed attention conditions (all *p*s > .05; Fig. 2B).

Recognition memory performance: We further investigated whether instructed attention during encoding influenced off-line recognition memory performance. First, a 5 (conditions) by 2 (age groups) repeated measure ANOVA analysis revealed a significant main of condition ($F(4,88) = 4.52$, $p < .05$, $\eta_p^2 = .17$), showing that recognition memory accuracy was higher for instructed attention conditions compared to passive viewing (all *p*s < .05), with the exception of the condition where participants selectively attended to positive items while ignoring neutral items ($p = .17$). Neither the main effect of age nor the age by condition interaction was significant (*F*s < 1; Fig. 2C).

[Insert Figure 2 about here]

fMRI Findings

Univariate whole brain analysis

To investigate brain correlates associated with processing of emotional items during selective attention, we contrasted all conditions in which participants were instructed to attend to emotional targets with the passive viewing condition (*instructed attention > passive viewing*) across both groups using a full factorial model in SPM. A network of fronto-parietal regions, including bilateral ventrolateral prefrontal cortex (VLPFC), anterior cingulate cortex (ACC), insula, bilateral parietal cortex, and left amygdala, was found to be associated with instructed

attention to emotion during WM encoding. These findings are consistent with prior literature reporting increased fronto-parietal activation during instructed attention (Corbetta & Shulman, 2002a; Desimone & Duncan, 1995; Gazzaley & Nobre, 2012). The reverse contrast (*passive viewing > instructed attention*) showed significant activation in a set of regions known to be part of the default-mode network (DMN); including angular gyrus, inferior parietal cortex, midcingulate cortex, precuneus, and posterior cingulate cortex (Buckner et al., 2008; Raichle et al., 2001). This finding is in line with previous research indicating enhanced suppression of the DMN with task difficulty/effort across a variety of cognitive tasks (Buckner et al., 2008; Mazoyer et al., 2001; Shulman et al., 1997).

Next, we investigated age-related differences in brain activation identified from the whole-brain analysis across participants. These comparisons were masked by the overall activation pattern for task-positive (instructed attention > passive viewing) and task-negative (passive viewing > instructed attention) brain activation patterns across participants. Brain activation associated with instructed attention to emotion for younger adults was compared to the corresponding pattern for older adults. Older adults showed less recruitment in a sub-set of the task-positive fronto-parietal regions, along with reduced DMN activation compared to younger adults (Fig. 3).

To further investigate the role of amygdala, this region showed to be significant at a peak-level threshold during all instructed attention conditions relative to passive viewing. Therefore, for the following functional connectivity analysis, the coordinates acquired from univariate analysis were used (-30 -6 -10).

[Insert Figure 3 about here]

Seed-Behavioral PLS Findings

Although results from the univariate analysis revealed that the left amygdala and the VLPFC was part of the network which was more activated during instructed attention relative to passive viewing across the two age groups, it is still plausible that the networks that are functionally connected to these regions might differ between age groups. Using seed-behavioral PLS, we therefore mapped brain network functional connectivity with each seed region (VLPFC and amygdala), and examined potential modulation of these networks as a function of target item's emotional valence, and whether age-related changes in functional connectivity as well as brain – behavior correlations differed between younger and older adults.

Left VLPFC (-38 16 26)

The left VLPFC seed analysis resulted in two significant LVs. LV1 (p =.000) accounted for 34% of the covariance in the data, and showed a positive seed and positive memory accuracy correlation during encoding of negative items among older adults. Although both younger and older adults engaged this network (LV1; Fig. 4B, overlapping CIs across green and purple bars for VLPFC during negative condition), the correlation with seed was reliable only in older adults, (i.e. purple bar's CI in the younger group crosses zero). This network also revealed a negative correlation with WM reaction time for both positive and negative items among older adults, indicating that older adults who responded faster engaged this network (yellow regions) to a larger extent. Critically, the correlation with RT was remarkably different across the two groups (non-overlapping CIs across purple and green bars for RT). Regions that were positively connected to the seed region (and facilitated faster response in older group; regions in yellow) included right insula, right inferior parietal lobule (IPL), bilateral inferior frontal gyrus (IFG), right superior frontal gyrus (SFG), and right middle temporal gyrus (Fig. 4A & Table 2). Regions

with a negative functional connectivity (anticorrelated; regions in blue) with the seed region included right cerebellum, right middle occipital gyrus, and right precentral gyrus. No reliable correlation was found for seed, memory accuracy, or RT in the younger group in any of the conditions (CIs cross zero).

The second LV (p = .010) accounted for 14% of the covariance, and revealed a network which was positively correlated with the VLPFC during encoding of both positive and negative items among younger adults. This network also facilitated WM accuracy for positive and negative items in this group. This network which was positively connected to the seed region among younger adults for both conditions (regions in yellow) included left IFG, left superior medial gyrus, left middle temporal gyrus, left middle frontal gyrus, left inferior temporal gyrus, left superior parietal lobule (SPL), right hippocampus, right parahippocampus, bilateral fusiform gyrus (FG), right cerebellum, and left thalamus (Fig. 5A). This particular network was also engaged during encoding of positive, but not negative items, in the older adults' group. The engagement of this network was related to slower response time and lower WM accuracy for negative items among older adults (Fig. 5 & Table 2). Note that, although both younger and older adults reliably and similarly engaged the network for attending to positive items (LV2; Fig. 5B, overlapping CIs across purple and green bars for positive conditions), the correlation with accuracy differed considerably between the two groups (non-overlapping CIs across purple and green bars for accuracy). Regions that were anticorrelated with the seed (regions in blue) included right IFG, right superior temporal gyrus (STG), and right occipital gyrus (Fig. 5 & Table 2).

[Insert Figures 4&5 & Table 2 about here]

Left Amygdala (-30 -6 -10)

One significant LV was identified when the left amygdala was used as a seed. This LV (p= .0001) accounted for 44% of the covariance in the data and exhibited a network that showed a positive seed correlation during encoding of both positive and negative items in the older group but only for encoding of negative items in the younger group. This network, that included left middle temporal gyrus, right IFG, right superior and middle frontal gyrus, right insula, right hippocampus and right superior medial gyrus (yellow regions, Fig. 6A), was also engaged by older adults who showed higher accuracy and faster RTs for both positive and negative items. Note that, although both younger and older adults engaged this network (LV1; Fig. 6B, overlapping CIs across green and purple bars for the amygdala during positive condition), the correlation with the seed region was reliable in the older, but not for the younger adults (i.e. purple bar's CI in the younger adults crosses zero). For younger adults, however, this network was only correlated with the seed during encoding of negative items (Fig. 6 & Table 3). No reliable correlation was found for RT or memory accuracy among younger adults (CIs cross zero).

Taken together, results from the left VLPFC seed functional connectivity analyses showed that, for older adults, VLPFC was connected to two separate networks during WM encoding of positive and negative items. One network facilitated faster response times in older adults in both conditions (LV1), and memory accuracy for negative items only. Younger adults, on the other hand, engaged one network for both encoding of positive and negative items, and this network was positively correlated with performance (LV2). Results from the functional connectivity analysis using the amygdala as a seed revealed that older adults recruited a single network during encoding of both positive and negative items which facilitated faster response times and memory accuracy for both positive and negative items. Younger adults, on the other hand, only recruited

this network for encoding of negative items and this network did not contribute to their behavioral performance.

[Insert Figure 6 & Table 3 about here]

Discussion

The present study was designed to investigate age-related changes in brain functional activity and connectivity associated with instructed attention to emotional valence during WM encoding. We specifically aimed to identify the functional brain networks connected to the left VLPFC and the left amygdala during encoding of positive or negative items. The behavioral results showed that instructed attention to items with a specific emotional valence, relative to passive viewing, resulted in enhanced WM and recognition memory accuracy, along with faster reaction times. Whole-brain analyses across age groups demonstrated increased activation of a fronto-parietal network during instructed attention, relative to passive viewing, and activation of the default-mode network. Older adults exhibited reduced activation in a subset of the fronto-parietal task positive regions, along with reduced DMN activation, relative to their younger counterparts. Functional connectivity analyses using VLPFC as a seed was related to activation in two separate networks, which were involved in processing of positive and negative items among older adults. Younger adults, however, engaged one network connected to VLPFC during encoding of both emotional targets, and this network contributed to memory accuracy in this age group. Amygdala functional connectivity was associated with network engagement during encoding of both positive and negative items in older adults but only negative items among younger adults. These results indicate that specific brain networks are differentially engaged by younger and older adults, and are also differently modulated by emotional valence.

Behavioral Findings

In line with previous findings (Gazzaley et al., 2005b), enhanced memory performance during instructed attention compared to passive viewing was found for working and recognition memory in both age groups, while older adults had overall worse performance compared to younger adults. This finding suggests that enhanced attention to task-relevant information during encoding improves performance both in the short- and long-term, and indicate beneficial effects from instructed attention during WM encoding.

While there was a general effect of improved performance for instructed attention, we did not find any evidence for a positivity effect in older adults. While this was somewhat unexpected, this finding is line with some previous evidence that have not been able to demonstrate a positivity effect ((Grühn et al., 2005; Kensinger et al., 2002), for a review see Ziaei and Fischer (2016)). Reed and colleagues (2014) have argued that the lack of positivity effect in some experiments could be due to the experimental instructions and task characteristic. However, using a similar paradigm with a larger sample size, Ziaei et al. (2015) recently reported a significant positivity effect in older, relative to younger adults in recognition memory. Thus, one potential explanation for the lack of a positivity effect in the current study may be lack of statistical power due to the small sample size. Indeed, the positivity effect is typically rather small (Ruffman et al., 2008), and a small sample size might reduce the possibility for detecting this effect in the behavioral data.

Whole-Brain Analysis

In line with previous neuroimaging studies, instructed attention compared to passive viewing, revealed increased activation in a fronto-parietal network, including IFG, ACC, insula, and the parietal cortex (Yarkoni et al., 2009). The role of fronto-parietal network engagement

during top-down modulation of attention is well documented in studies of selective attention (Corbetta & Shulman, 2002b; Yarkoni et al., 2009). A likely role for fronto-parietal network engagement is in directing attention to and processing of relevant items, and filtering out task irrelevant information. Similar to the present findings, a number of studies have also linked fronto-parietal network engagement to top-down attentional processes during WM encoding, which may result in subsequent enhancement of WM accuracy and faster RTs (for a review, see Gazzaley and Nobre (2012). Our findings corroborate and extend these previous observations to the emotional domain by showing the role of the fronto-parietal circuit during encoding of emotional information.

Within the fronto-parietal network, older adults exhibited reduced activation in a sub-set of these regions, such as bilateral IFG, bilateral parietal cortex, bilateral anterior insula, and bilateral fusiform gyrus. While reduced frontal engagement in older adults during WM *retrieval* has been suggested to account for age-related decline in WM performance (e.g. (Rypma & D'Esposito, 2000), the link between frontal activation during *encoding* and age-related decline in WM performance is relatively unknown. Given the importance of fronto-parietal activation for selective attention in WM tasks, the observed age-related reduction of activity in task relevant regions suggest a link between impaired encoding-related attentional processes, and emotional WM performance in older adults, which is supported by prior findings (Ferri et al., 2013; Gazzaley et al., 2005b).

Similarly, the reverse contrast (passive viewing > instructed attention) yielded activation in regions which are known to be parts of the DMN. In line with previous WM and episodic memory findings (Ferri et al., 2013; Persson et al., 2007; Sambataro et al., 2010), reduced

default-mode activation in older adults might indicate impaired ability in suppressing task-irrelevant information during WM encoding.

Functional Connectivity with VLPFC

Functional connectivity results with left VLPFC as a seed revealed that this region was functionally connected to one network among older adults during instructed attention to negative items. The first network (LV1), which was functionally connected to the VLPFC for encoding of negative items in older adults included left amygdala, right middle frontal gyrus, bilateral IFG, right superior frontal gyrus, and bilateral middle temporal gyrus. Engagement of this network is in line with a number of studies in younger adults, and suggests a role of VLPFC in regulation of negative emotion (Ochsner & Gross, 2005; Phan et al., 2005), and that such regulatory functions may engage cognitive control processes. For instance, Wager and colleagues (2008) demonstrated that VLPFC – subcortical connectivity predicted reappraisal success. St Jacques et al. (2010) also showed increased activity of the PFC in response to the evaluation of negative items, and stronger connectivity between PFC, amygdala, and hippocampus was found for subsequently remembered negative items. The involvement of PFC regions during instructed attention to negative emotion is also in line with findings from a recent meta-analysis on emotion regulation (Buhle et al., 2014) that reported increased activity in cognitive control regions, including medial and lateral PFC, posterior parietal cortex, along with modulation of amygdala activation, in emotion regulation tasks. Although there were no explicit regulatory instructions in this experiment, in a process model of emotion regulation, attentional deployment has been highlighted as a core function of emotion regulation strategies, and may influence emotional responding by redirecting attention within a given situation (Gross & Thompson, 2007). Consequently, recruitment of a cognitive control network during WM encoding of negative

emotions by older adults might indicate that they were engaged in regulatory processes, and that this recruitment is selective for negative emotions. Thus, current findings provide neuroimaging support for previous behavioral findings showing enhanced ability for older adults in regulating negative emotions (Charles & Carstensen, 2007; Scheibe & Carstensen, 2010).

Moreover, another network, that included left IFG, left superior medial frontal gyrus, right hippocampus, left FG, right cerebellum, left middle temporal gyrus, left SPL, and the left thalamus was functionally connected to the VLPFC during encoding of positive items for both age groups (LV2). Although some regions did overlap with the brain regions from LV1 (see above), most of the regions were uniquely associated with instructed attention to positive items. This suggests that in older adults, two, at least partially, separate networks were involved in WM encoding of negative and positive items respectively. The involvement of frontal and hippocampal regions during encoding of positive information is in line with previous studies on episodic memory indicating age-differential connectivity for encoding of positive and negative information (Addis et al., 2010). Our findings indicate that, unlike younger adults, older adults recruit additional specific anterior PFC regions for processing of positive items which might result in increased memory performance.

Younger adults, on the other hand, recruited one single network for encoding of both positive and negative items (LV2). This finding suggests that younger adults may be less influenced by emotional valence of the targets during encoding. Although there was no significant positivity bias in the behavioral data among older adults, the engagement of differential brain networks for processing positive and negative items in the older group suggest that at the brain network level, older adults engage two separate functional networks connected to VLPFC during encoding of positive and negative items. The lack of behavioral evidence for a

positivity bias along with a brain functional segregation between positive and negative information suggest that the neural changes might provide a more sensitive measures relative to behavioral performance in identifying age by valence interactions (Ritchey et al., 2011b).

Functional Connectivity with Amygdala

Functional network connectivity with the amygdala was characterized by engagement in superior temporal gyrus, ACC, superior medial gyrus, angular gyrus, and the thalamus for older adults during encoding of both positive and negative items. Most likely, recruitment of this network is influenced by the increased cognitive control effort required for instructed attention during WM encoding, regardless of emotional valence. The lack of age-related differences in modulation of the amygdala network by valence among older adults provide evidence for functional preservation of the amygdala functionality in aging (Ritchey et al., 2011b; St Jacques et al., 2009b; St Jacques et al., 2010; Wright et al., 2006). Although a majority of studies have reported amygdala activation for negative emotions such as fear, sadness, and anger (for extensive reviews see (Lindquist et al., 2012; Phelps & LeDoux, 2005; Sander et al., 2005; Wager et al., 2015), Hamann (2003), for instance, proposed that the amygdala codes for arousing stimuli irrespective of valence. Thus, our current findings do not seem to support age-related alterations in amygdala activity for different emotionally-valenced information (St Jacques et al., 2009a), but rather suggest that amygdala, and by extension, its network, is engaged during encoding of emotional items irrespective of valence.

Brain-Behavior Relationships

Ventrolateral PFC functional network connectivity was associated with faster response times and higher accuracy for negative items in older adults. The fact that faster and more accurate older adults recruited a wide-spread network that included frontal and parietal regions to

a larger extent, adhere to the view that frontal regions are core components of an executive control network that are also involved in effortful emotionally task-related activity. This is also in line with prior findings showing recruitment of frontal regions during cognitive effortful tasks (Cabeza, 2002; Davis et al., 2008). One possibility for this pattern of activity is that RTs reflect effort or time-on-task effects (Yarkoni et al., 2009), and faster individuals and individuals with higher accuracy may engage this fronto-parietal brain regions in order to perform the task appropriately.

Moreover, another VLPFC-related functional network was found to be related to memory accuracy in younger adults for WM encoding both positive and negative items. This particular network included lateral and medial frontal regions that have a known role in cognitive control (such as left IFC and ACC), and memory processes (such as the hippocampus). Increased functional connectivity between the VLPFC and ACC as well as the hippocampus was associated with enhanced performance for both positive and negative items among younger adults. The ACC plays a critical role in executive control via a distributed attentional network. Indeed, it has been suggested that the ACC is part of a core system for maintaining a task-set relevant for goal-directed behavior (Dosenbach et al., 2008). Previous studies have also shown that ACC activation is positively correlated with successful attention shifting (Kondo et al., 2004). At a more general level, activation in these regions has repeatedly been associated with behavioral performance across task domains (Eriksson et al., 2011; Kim, 2011; Walsh et al., 2011). Therefore, it seems that younger adults, relative to older adults, recruited a less distributed network during WM encoding of emotional targets, irrespective of valence, although the cognitive processes associated with functional connectivity in this network remains to be specified.

Finally, three methodological limitations of this study have to be acknowledged. First, it has to be noted that our results reported in this paper included all trials during the encoding phase. The reason for including all trials was that the primary focus of this paper was to examine age differences in attentional processes during WM encoding of positive and negative emotions, and not on the successful encoding of individual emotional items. Given that older and younger adults did not show any positivity or negativity preference behaviorally, we decided to analyze all trials included in each condition. We did, however, conduct additional analyses using *only correct trails* which is reported as supplementary material. Importantly, we were able to replicate the results for the brain networks connected to the amygdala also when only correct trials were considered. The pattern of the VLPFC network was slightly different from the analyses reported with all trials, but these supplementary analyses still corroborate our original findings suggesting that older adults recruit one brain network for encoding of negative items which resembles the emotion regulation network and one additional network for encoding of only positive items in older group relative to younger adults. Second, the arousal and valence ratings for pictures were drawn from IAPS. Evidence indicates that there might be age-related differences in arousal ratings of IAPS pictures (Grühn & Scheibe, 2008). Future studies are required to investigate how brain activation and memory performance is modulated by subjective ratings of the pictures. Finally, the use of eye-tracking during the task would provide helpful insights into the attentional mechanisms underlying instructed attention during WM encoding (please refer to Ziaei et al. (2015) for more information on the eye-tracking data). Additionally, given that there was no significant difference between neutral and emotional distractors, we pooled them together for this study. Future research is needed to investigate the age-related changes in processing emotional and neutral distractors.

Taken together, the seed PLS analyses demonstrated differential frontal functional connectivity networks for WM encoding of positive and negative items in older adults, while younger adults recruited a single network regardless of emotional valence. Amygdala functional connectivity revealed a single network which was engaged during encoding of both positive and negative items among older adults, suggesting that this network subserves a different function relative to the networks connected to VLPFC seed. Although there was lack of a behavioral positivity effect, the functional connectivity findings highlight the engagement of cognitive control regions during encoding of negative items, perhaps as a way to down regulate negative emotions, and a separate and more localized network during encoding of positive items among older adults. These findings imply that older adults' preference for positive items might stem from differential engagement of brain networks during processing of both positive and negative items, relative to their younger counterparts. Mapping age differences in frontal-amygdala functional connectivity will contribute to further understanding of the changes in emotion-cognition interactions in normal aging which can be used as makers for diagnosis of clinical disorders that are characterized by aberrant emotional dysfunction.

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Figure legends

Figure 1. Experimental design. The task includes five conditions; (1) attend to negative pictures/ignore neutral pictures, (2) attend to negative pictures/ignore positive pictures, (3) attend to positive pictures/ignore neutral pictures, (4) attend to positive pictures/ignore negative pictures, and (5) passive viewing of the pictures. During retrieval, participants were asked to decide whether the probe was a part of the previously presented target set or not.

Figure 2. Working memory and recognition memory performance for older and younger adults. Accuracy performance is based on loglinear hits – loglinear false alarms (FA). Bars represent 1 standard error of the mean (SEM). The results indicated that older adults were less accurate and slower relative to younger adults. Additionally, both age groups were faster and more accurate in responding during instructed attention relative to passive viewing. Panel A represents working memory accuracy, panel B represents working memory reaction times, and panel C represents long-term memory accuracy.

Figure 3. Whole-brain univariate analysis. (A) Represents the activation in all conditions vs. passive viewing (yellow color). Regions in green represent areas with reduced activation in older adults compared to younger adults. (B) Regions in blue color shows increased activation in

passive viewing vs. all conditions. Areas in green reflect reduced deactivation in older adults relative to younger adults.

Figure 4. Seed-PLS results using left VLPFC as a seed (LV1). Panel A represents a pattern of whole brain activity in LV1. For LV1, regions shown in yellow indicate greater activity for instructed attention to negative items in older adults only. Panel B represents brain scores from LV1 indicating significant correlations between the brain regions connected to the left VLPFC and behavioral performances, such as RTs and accuracy, during negative conditions among older group (Green bars). Error bars denote 95% confidence intervals for the correlations calculated using the bootstrap procedure. All reported regions have BSR $\geq$ 3. L = left hemisphere, R = right hemisphere

Figure 5. Seed-PLS results using left VLPFC as a seed (LV2). Panel A represents the whole brain functional connectivity associated with LV2. Regions depicted in yellow color reflect areas with greater activity during encoding of positive items in older adults, and encoding of both positive and negative items in the younger group. Panel B represents the brain scores indicating the positive correlation between the brain networks connected to VLPFC during encoding of both emotional items and higher accuracy during retrieval of positive and negative items among younger adults (purple bars). Error bars denote 95% confidence intervals for the correlations calculated using the bootstrap procedure. All reported regions have BSR $\geq$ 3. L = left hemisphere, R = right hemisphere.

Figure 6. Seed-PLS results using left amygdala as a seed. Panel A represents the functional connectivity pattern for LV1. Panel B represents a correlation between activity in left amygdala, RTs, accuracy, and the scores representing activity in regions seen in panel A. Error

bars denote 95% confidence intervals for the correlations calculated using the bootstrap procedure. All reported regions have BSR ≥ 3. L = left hemisphere, R = right hemisphere.

Table 1. Descriptive and inferential statistics for the background measures for younger and older adults.

Measures	Older adults	Younger adults	Inferential statistics	
	Mean (SD)	*Mean (SD)*	*t*	*df*
Age	68.23 (3.7)	22.53 (1.71)		
Gender	9 females, 4 males	9 females, 4 males		
MMSE	27.61 (1.19)	-		
Emotion Regulation Questionnaire				
Reappraisal	24.30(9.25)	30.23 (7.06)	1.83	24
Suppresssion	10.00(3.87)	11.38 (5.28)	0.76	24
Stroop test (in ms)				
Congruent	1428 (261.11)	842.72 (183.60)	6.62*	24
Incongruent	1650.95 (308.76)	1034.30 (209.60)	5.98*	24
Neutral	1313.85 (184.80)	817.99 (168.19)	7.15*	24
Stroop effect	222.11 (149.54)	191.58 (75.25)	1.43	24

Operation span	20.1 (13.4)	46.9 (20.9)	3.69*	24
Working memory				
FA for negative items	0.06 (0.09)	0.03 (0.01)	1.30	24
FA for positive items	0.06 (0.12)	0.03 (0.02)	0.98	24
Hits for positive items	0.63 (0.18)	0.84 (0.14)	3.35**	24
Hits for negative items	0.66 (0.18)	0.88 (0.07)	4.03**	24
Recognition memory				
Hits for positive	0.55 (0.08)	0.52 (0.15)	0.54	22
Hits for negative	0.64 (0.12)	0.54 (0.15)	1.78	22
FA for positive	0.32 (0.13)	0.34 (0.20)	0.28	22
FA for negative	0.37 (0.17)	0.32 (0.17)	0.62	22

*= $p < .05$, ** = $p < .01$; MMSE = Mini Mental State Examination. Stroop effect in ms refers to incongruent minus congruent trials

Table 2

Peak coordinates for clusters from the functional connectivity (PLS) analysis using VLPFC (-38 16 26) as a seed region.

Regions	Hem	MNI coordinates[XYZ]	BR	Cluster size (in voxels)
LV1				
Middle Occipital Gyrus	R	[42 -80 0]	4.95	1604
Cerebellum	R	[40 -66 -24]	4.74	153
Precentral Gyrus	R	[14 -22 72]	4.29	62
Cerebellum	R	[12 -74 -16]	3.90	95
Inferior Frontal Gyrus	R	[46 26 2]	-5.88	398
Medial Temporal Gyrus	R	[64 -46 8]	-5.58	1033
Rolandic Operculum	R	[52 4 16]	-5.23	156
Inferior Parietal Cortex	R	[52 -52 30]	-5.08	842
Insula lobe	R	[38 12 -6]	-4.50	171
Superior Frontal Gyrus	R	[28 56 10]	-4.36	169
LV2				
Inferior Frontal Gyrus	L	[-40 18 26]	8.19	430
Superior Medial Gyrus	L	[-2 50 38]	6.17	101
Parahippocampus	R	[20 -22 -24]	5.26	295
Middle Frontal Gyrus	R	[32 30 38]	4.76	74
Hippocampus	R	[28 -24 -8]	4.75	50
Cerebellum	R	[44 -64 -26]	4.69	369
Fusiform Gyrus	L	[-34 -48 -22]	4.68	213
Middle Temporal Gyrus	L	[-48 -20 -14]	4.54	219
Middle Frontal Gyrus	L	[-38 16 46]	4.49	148
Superior Parietal Lobe	L	[-20 -78 52]	4.46	76
Thalamus	L	[-14 -30 -2]	4.45	72
Middle Frontal Gyrus	L	[-20 28 52]	4.42	72
Inferior Temporal Gyrus	L	[-54 -54 -6]	4.13	147
Fusiform Gyrus	R	[20 -48 -14]	3.94	117

Superior Occipital Gyrus	R	[28 -68 32]	-5.42	1101
Superior Temporal Gyrus	R	[52 -26 8]	-5.00	413
Inferior Frontal Gyrus	R	[54 20 10]	-4.14	74

Hem = hemisphere, BA = Broadmann Area, BR = Bootstrap Ratio

Table 3

Regions	Hem	MNI coordinates XYZ	BR	Cluster size (in voxels)
LV1				
Middle Temporal Gyrus	L	[-50 -50 6]	9.06	24241
Inferior Frontal Gyrus	R	[58 12 14]	6.44	657
Postcentral Gyrus	R	[64 -14 24]	6.41	111
Superior Frontal Gyrus	R	[26 16 38]	6.04	683
Middle Frontal Gyrus	R	[36 54 6]	5.89	404
Superior Medial Gyrus	R	[6 56 0]	5.15	424
Insula Lobe	R	[44 8 -6]	4.91	169
Hippocampus	R	[28 -8 -18]	4.37	308
Superior Medial Gyrus	R	[0 48 18]	3.20	97
Precentral Gyrus	L	[-60 8 28]	-6.46	257
Middle Temporal Gyrus	R	[42 -72 8]	-5.84	2250
Cerebellum	R	[14 -80 -20]	5.09	211
	L	[-12 -52 -10]	-4.60	67
Middle Frontal Gyrus	L	[-42 56 4]	-3.90	69

Middle Occipital Gyrus	L	[-32 -88 8]	-3.87	578
Fusiform Gyrus	L	[-28 -50 -18]	-3.56	100
Cuneus	R	[8 -94 24]	-3.55	50
Middle Temporal Gyrus	L	[-68 -22 0]	-3.50	54

Peak coordinates for clusters from the functional connectivity (PLS) analysis using amygdala (-30 -6 -10) as a seed region.

Hem = hemisphere, BA = Broadmann Area, BR = Bootstrap Ratio

Highlights

- Older adults recruit a fronto-parietal network during encoding of *negative* emotion.
- Older adults recruit separate frontal regions for encoding of *positive* emotions.
- Young adults recruited one vlPFC network for encoding of *positive* & *negative* items.
- Age-related cortical-subcortical shift was found for encoding of emotional items.
- Positivity bias in aging may stem from fronto-parietal cognitive control network.

Figure 1

Figure 2

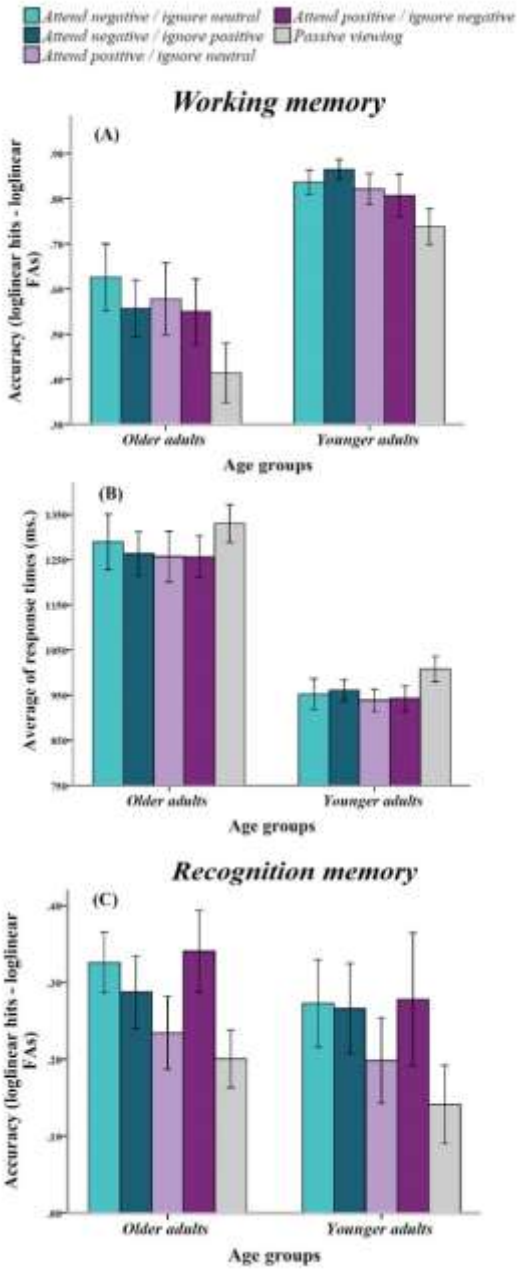
Attend negative / ignore neutral
Attend negative / ignore positive
Attend positive / ignore neutral
Attend positive / ignore negative
Passive viewing
Working memory
(A)
Accuracy (loglinear hits - loglinear FAs)
Older adults
Younger adults
Age groups
(B)
Average of response times (ms.)
Older adults
Younger adults
Age groups
Recognition memory
(C)
Accuracy (loglinear hits - loglinear FAs)
Older adults
Younger adults
Age groups

Figure 3

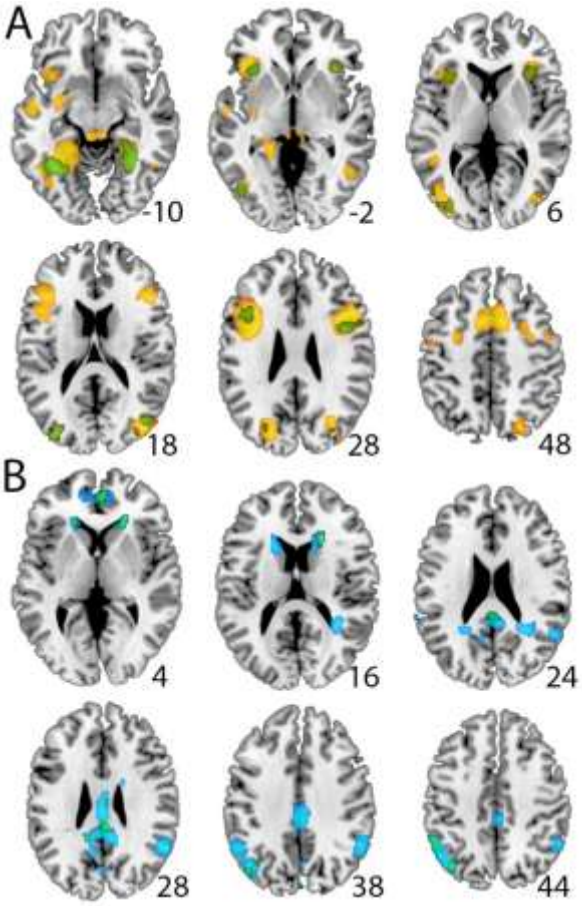

Figure 4

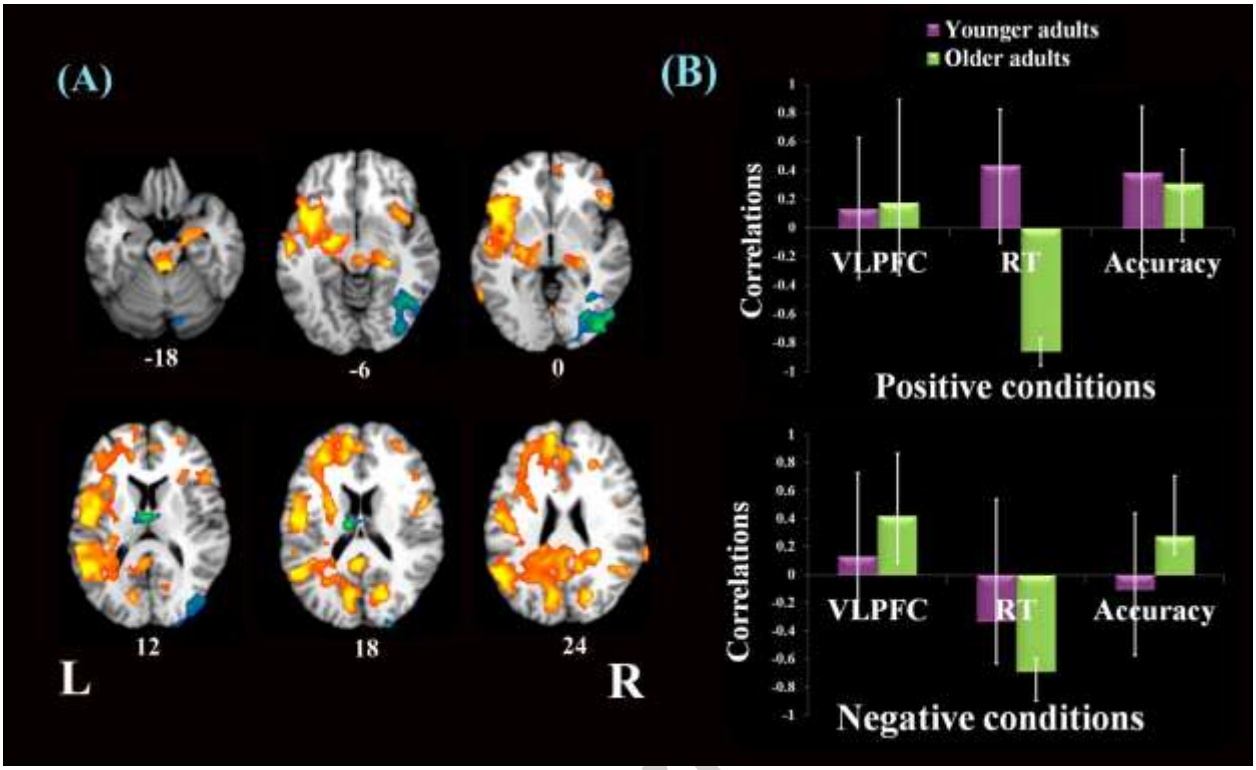

Figure 5

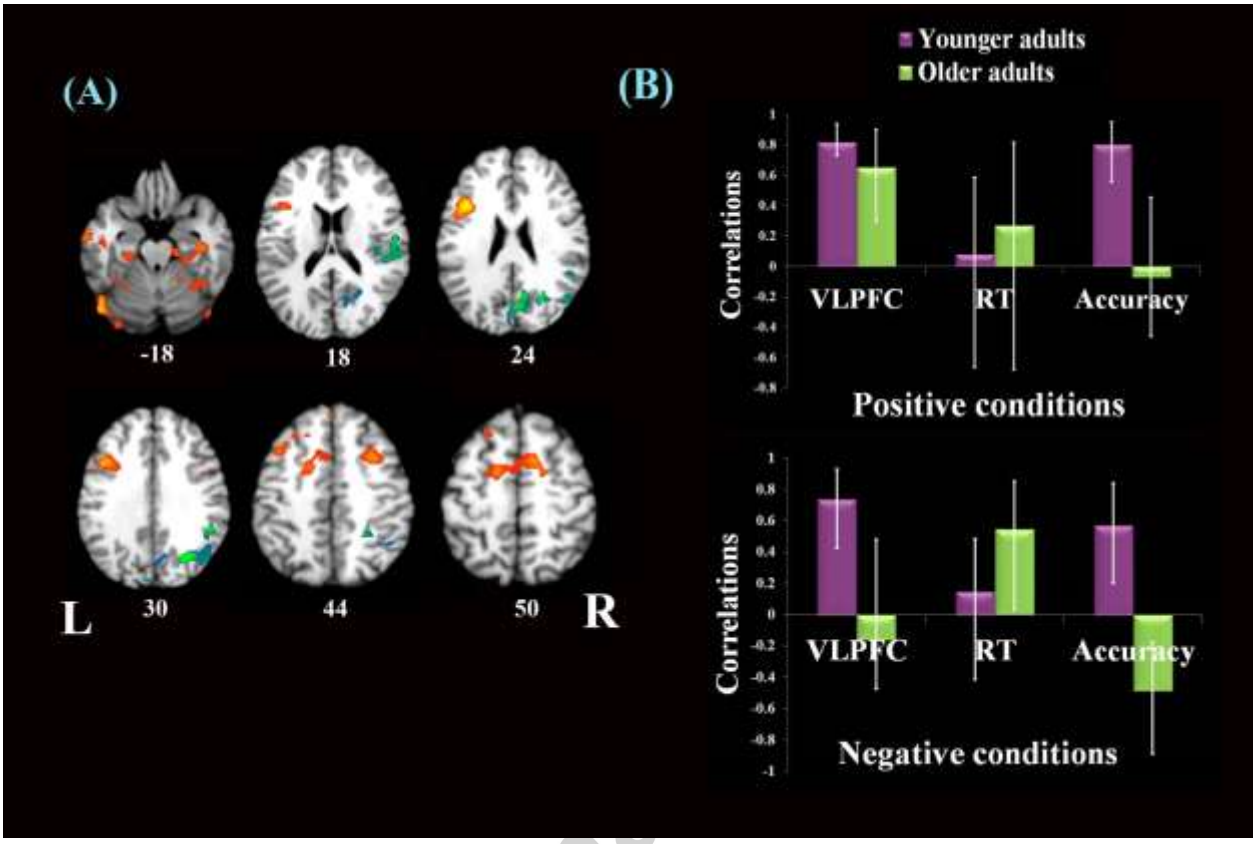

Figure 6