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Compensatory Brain Activity during Encoding among Older Adults with Better Recognition Memory for Face-Name Pairs: An Integrative Functional, Structural, and Perfusion Imaging Study

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Abstract

Many neuroimaging studies interpret the commonly reported findings of age-related increases in frontal response and/or increased bilateral activation as suggestive of compensatory neural recruitment. However, it is often unclear whether differences are due to compensation or reflective of other cognitive or physiological processes. This study aimed to determine whether there are compensatory age-related changes in brain systems supporting successful associative encoding while taking into account potentially confounding factors including age-related differences in task performance, atrophy, and resting perfusion. Brain response during encoding of face-name pairs was measured using functional magnetic resonance imaging in 10 older and nine young adults and was correlated with memory performance. During successful encoding, older adults demonstrated increased frontal and decreased occipital activity as well as greater bilateral involvement relative to the young. Findings remained significant after controlling for age-related cortical atrophy and hypoperfusion. Among the older adults, greater response was associated with better memory performance. Cognitive aging may involve recruitment of compensatory mechanisms to improve performance or prevent impairment. Results extend previous findings by suggesting that age-related alterations in activation cannot be attributed to the commonly observed findings of poorer task performance, reduced resting perfusion, or cortical atrophy among older adults.

Keywords

Magnetic resonance imaging; Aging; Cognition; Frontal lobe; Neuropsychology; Paired associate learning

INTRODUCTION

Due to increasing longevity and chronic age-related diseases as primary causes of morbidity and mortality, aging has recently been recognized as among the greatest public health concerns. Maintaining good cognitive functioning is an important contributor to quality of life and functional independence (Depp, Vahia, & Jeste, 2010). There is heterogeneity in rate, severity, and type of cognitive change that occurs in aging and some older adults maintain a very high level of cognitive performance (Wilson et al., 2002). Research focusing on successful cognitive aging rather than age-related cognitive decline may yield valuable insights into how to enhance cognitive functioning of older adults (Rowe & Kahn, 1997).

Neuroimaging techniques are useful in elucidating the neural correlates of successful cognitive aging. A recent review of functional brain imaging studies of successful cognitive aging (Eyler, Sherzai, Kaup, & Jeste, 2011) observed that positive associations between brain activation and performance were often reported in frontal regions, which is consistent with theories that increased activation, especially in the prefrontal cortex (PFC), reflects compensatory processing. Two such theories are (1) the hemispheric asymmetry reduction in older adults, or HAROLD model, in which bihemispheric involvement is thought to emerge to help counteract age-related neurocognitive deficits (Cabeza, 2002) and (2) the “posterior–anterior shift in aging,” or PASA pattern, which suggests that older adults might rely on strategies mediated by PFC to compensate for declines in sensory processing mediated by posterior regions (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008).

Despite the popularity of interpreting increased frontal activation in older adults as suggestive of compensatory neural recruitment, alternative explanations including dedifferentiation of cognitive processes (Li & Lindenberger, 1999), decreased transcallosal inhibition (Logan, Sanders, Snyder, Morris, & Buckner, 2002), or increased neural noise (Welford, 1965) have been posited. Given this, standardized criteria to use when determining whether such differences are indeed related to compensatory recruitment have been proposed (Han, Bangen, & Bondi, 2009). This model advocates considering issues related to brain regions, activation patterns, and behavioral performance and thus was termed the Region-Activation-Performance (RAP) model. Regarding the consideration of brain regions, observed differences in brain response may be influenced by differential atrophy and, therefore, structural data should be considered. In terms of activation patterns, resting state cerebral blood flow (CBF) or other measures of cerebrovascular functioning should be integrated with functional magnetic resonance imaging (fMRI) data given that changes in the cerebrovascular system commonly occur in aging and may influence the blood-oxygenation-level-dependent (BOLD) signal thereby complicating the interpretation of findings of age-related differences in fMRI response (Bangen et al., 2009; D’Esposito, Deouell, & Gazzaley, 2003). Finally, the model advocates explicit cognitive task control (e.g., ensuring equivalent performance between groups) so that group differences in brain activation cannot be attributed to factors including effort and task difficulty.

The present study involved a scanner task assessing face-name associative encoding, an ability that is relevant to daily functioning and has been shown to decline in normal aging (Sperling, 2007). Forming novel face-name associations is a type of learning that is thought to be difficult because it requires forming associations across verbal and visual modalities and because first names are typically arbitrarily given and, therefore, are not particularly facilitative of forming associations (Sperling et al., 2003). Furthermore, the ability to form novel associations among individual units of information may have broader implications for cognitive functioning and may be particularly sensitive to early cognitive decline (e.g., Fowler, Saling, Conway, Semple, & Louis, 2002).

For many of the studies that have aimed to understand age-related changes in memory processes and how this may relate to individual differences in everyday memory performance, interpretation of findings was limited by a variety of factors including (1) poorer cognitive performance among older relative to young adults, (2) characterization of individuals as cognitively healthy older adults based solely on scanner task performance, (3) comparison of the mean activation pattern of a group of young participants to that observed in a group of older adults without any examination of individual differences among older adults, (4) no direct assessment of the relationship between activation patterns and behavioral performance to assist in the interpretation of any age-related differences in task-related activity as reflecting possible compensatory mechanisms, (5) no examination of differential atrophy between age groups, and (6) no measurement of resting CBF or cerebrovascular functioning.

The present study aimed to examine whether there are compensatory age-related changes in brain systems supporting successful associative encoding while addressing these concerns. While it would be difficult to address all of the limitations discussed above in one study, we paid particular attention to the following issues: (1) using a scanner task in which performance between age groups was comparable as well as performing analyses restricted to successful memory encoding in an effort to rule out group differences in effort or task difficulty, (2) characterizing our participants *via* cognitive and emotional functioning assessments completed outside of the scanner, (3) examining differences between age groups but also within-group activation patterns and their relationship with behavioral measures to assess individual differences among older adults, (4) directly correlating performance on the scanner task and degree of brain activation to help aid in the interpretation of findings as consistent with compensation, (5) obtaining cortical thickness measurements to examine whether the age groups differed in terms of cortical atrophy, and (6) collecting resting CBF data to determine whether age-related differences in perfusion existed and should be considered when interpreting fMRI activation results.

We predicted that (1) consistent with the PASA pattern, older adults would demonstrate increased frontal activation accompanied by decreased posterior response relative to young adults; (2) consistent with the HAROLD model, older adults would demonstrate greater bilateral activation in frontal regions compared to the young adults; (3) supporting the potential engagement of compensatory mechanisms among older adults, greater frontal activation would be associated with better memory abilities; and (4) after taking into account potentially confounding variables outlined in the Region-Activation-Performance model (including cortical thickness and resting cerebral blood flow) age-related differences in activation would remain.

METHODS

Participants

Ten healthy older adults and 11 young adults were recruited from a larger pool of individuals participating in ongoing research studies as well as the local university community. Potential participants completed a telephone screen to ensure they were eligible based on the following exclusionary criteria: history of left-handedness, neurological disorders (e.g., stroke), psychiatric disorders, substance use disorders, and MRI contraindications (e.g., pacemaker). Furthermore, each participant reported no history of illegal drug use. Participation involved (1) clinical interview, (2) neuropsychological assessment, and (3) neuroimaging exam. Older participants were characterized as healthy and unimpaired based on (1) the absence of disability, (2) good cognitive functioning (i.e., no cognitive impairment), and (3) good emotional functioning (i.e., no history of a psychiatric disorder). No individual was excluded based on performance on measures

administered during study participation. Two young adults were excluded for completing only two of the four functional scans. All data were collected in accordance with UCSD institutional review board-approved procedures and with the guidelines of the Helsinki Declaration.

Neuropsychological Assessment

Participants underwent a neuropsychological assessment including measures of global cognitive functioning, learning and memory, executive functioning, working memory, and language (Table 1). One young and one older participant did not complete the standardized neuropsychological measures.

Face-name Associative Encoding Task

The scanner task was adapted from work published by Sperling and colleagues (2003; Figure 1). Participants viewed face-name pairs and were instructed to “study each person’s face and name and try to remember both.” Before scanning, participants practiced the task using different stimuli than those presented during scanning. During the scan session, participants completed four runs of the task. Thirty face-name pairs were viewed per run and each pair was presented twice within the same run. No stimuli were repeated across runs resulting in a total of 120 face-name pairs viewed across the entire experiment. To ensure adequate attention, participants were instructed to indicate whether each face-name pair was “new” (i.e., not previously seen) or “old” (i.e., previously seen) *via* a handheld button box. Each pair was presented for four seconds. Trials consisting of a cross-hair fixation that varied in length between 0.5 and 9 s were interspersed throughout each run.

Immediately following scanning, participants completed a forced-choice recognition test (Figure 2). Individual faces were presented and participants were prompted to select among three name choices for each face, which included (1) the accurate name, (2) a name that had been paired with a different face during scanning, and (3) a name that had not been presented during scanning. These option types were selected to ensure specificity of the face-name associations. The recognition task consisted of 140 face-name pairs including all 120 pairs presented during scanning and 20 distracter pairs including faces that were not presented during scanning. Accuracy (i.e., hit rate) and reaction time were calculated for the scanner task and the post-scanning recognition task to determine performance level on encoding and longer-term recognition memory of face-name pairs.

Scanning Procedure

Participants were scanned in a General Electric Signa Infinity EXCITE 3.0 Tesla whole body imager with an eight-channel receive-only head coil. Functional images were obtained with a one-shot gradient echo EPI scan: 24 cm FOV, 64 × 64 matrix, 4 mm × 4 mm in-plane resolution (the exception were four participants whose scan resolutions ranged from 3.75 mm × 3.75 mm × 4 mm to 4 mm × 4 mm × 5 mm), TR = 2000 ms, TE = 32 ms, flip angle = 90°. Thirty 4-mm-thick oblique slices were acquired. Field maps were collected to correct for distortions in EPI images due to inhomogeneities in the static magnetic field. A T1-weighted anatomical scan was acquired at 1 mm³ resolution using either a fast spoiled gradient-echo or magnetization-prepared rapid gradient-echo pulse sequence. A resting state pulsed arterial spin labeling scan was acquired using a modified flow-attenuated inversion recovery pulse sequence to collect twenty 6-mm-thick contiguous oblique slices (Wong, 2005). CBF data were not collected for three participants and were unusable for one participant due to technical difficulties. Linear interpolation was used to substitute missing mean CBF values for these four individuals, which included two older adults and two young adults. For conversion of CBF to absolute units (millimeters of blood per 100 g tissue/min), a cerebral spinal fluid (CSF) reference scan was acquired.

Data Analysis

Group comparisons on demographic, cognitive, scanner task, motion, anatomical, and cerebral blood flow variables—Independent samples *t* tests compared the means of the young and older adults on demographic, neuropsychological, scanner task and post-scanning recognition task performance, motion during functional scans, cortical thickness, and CBF. Each set of analyses comparing the age groups on the same dependent variable was treated as an omnibus test with Bonferroni corrections for multiple comparisons separately applied for each. The resulting α values controlling for multiple comparisons ranged from .004 to .05 and are included in the description of results for each group of tests.

Functional neuroimaging data—Functional imaging data were analyzed with the Analysis of Functional Neuroimaging (AFNI) software package (Cox, 1996). Field map and slice timing corrections were applied to the EPI images. Each participant's anatomical and EPI datasets were aligned to the center image of the functional time series. After this automated motion correction, the time series was examined for uncorrected motion outliers, and time-points with motion obvious on visual inspection were excluded. The mean number of excluded time points due to excessive motion was 24 (standard deviation = 32), which represents 3.3% of the data. The four functional runs were concatenated into a single time series. The first two images of each run were excluded to eliminate images collected before attainment of a steady state. Grand mean scaling was performed so that each voxel time series had a mean of 100. Functional images were spatially smoothed to a resolution of approximately 6 mm full-width at half-maximum. The T1-weighted anatomic images and functional datasets were warped to the coordinates of the atlas of Talairach and Tournoux (1988) and resampled at a 4 mm³ resolution.

The association between measured BOLD signal and the face-name associative encoding task was calculated with multiple regression using the AFNI 3dDeconvolve program. The following predictors were included in the model: a constant, a linear trend, three parameters indicating the degree of motion correction performed in three rotational angles, and stimulus functions indicating whether the presented face-name pairs were remembered (i.e., correctly recognized during the post-scanning recognition task). Linear contrasts between remembered versus all other trials were calculated from these models allowing us to isolate processing during successful encoding and, thus, equate performance across individuals.

Voxel-wise task-related whole brain response was examined using between- and within-group *t* tests with the fit coefficient averaged across the four runs serving as the dependent variable. Regions were considered activated if each voxel was significant at $p < .05$ and the cluster contained at least 31 contiguous voxels. This threshold/voxel combination protected a whole-brain probability of false positives of $p < .05$.

CBF data were processed using AFNI, FMRIB Software Library (Smith et al., 2004), and in-house MATLAB scripts. To minimize the effects of motion, the AFNI 3D volume registration program was used to co-register the ASL time series with the middle time point. The anatomical images were skull stripped and segmented into gray, white, and CSF compartments. The T1-weighted image and partial volume segmentations were aligned with the ASL volume and resampled to the resolution of the ASL data. A mean CBF image was formed from the average signal difference of the control and tag images (Wong, 2005) and converted to absolute units with use of the CSF image (Chalela et al., 2000). The resulting image was spatially smoothed with a Gaussian kernel of 4 mm full-width at half-maximum. Voxels with negative perfusion values were replaced with zero. The gray matter segmentation was applied to the CBF data to extract mean global gray matter perfusion values.

Correlations between brain response and cognitive performance—To assist in the interpretation of observed clusters of activity during face-name encoding, we calculated the Pearson's correlation between mean brain response (i.e., fit coefficient) in clusters of significant activity identified during between-group analyses and both accuracy on the post-scanning recognition task and performance on standardized memory measures administered outside of the scanner (i.e., WMS-III Verbal Paired Associates Delayed Recall and CVLT-II Total Recognition Discriminability).

Structural neuroimaging data—The cortical surface was reconstructed and parcellated into various regions of interest using FreeSurfer (Buckner et al., 2004; Dale, Fischl, & Sereno, 1999). Mean global cortical thickness was calculated by averaging the thickness of each hemisphere, with each hemisphere's contribution to the average weighted by the surface area of the hemisphere.

Hierarchical regression including perfusion and cortical thickness

measurements—To examine the contribution of resting CBF and cortical thickness to observed group differences in activation, hierarchical regression analyses were performed. Mean fit coefficient values for each participant were extracted from the clusters of significant between-group differences and served as the dependent variables. Mean resting global CBF and cortical thickness were entered as predictor variables on step one and age group was entered on step two.

Posterior–anterior shift—To determine whether results were supportive of a posterior–anterior shift in brain response, correlations were performed between the mean fit coefficients extracted from the frontal and occipital clusters of significant age-related differences in activity for the remembered face-name pairs.

Laterality index—To examine hemispheric laterality of successful memory encoding and determine whether our data were consistent with the HAROLD model, a laterality index was calculated. AFNI's 3dLRflip program was used to create a left hemisphere region of interest (ROI) homologous to the right frontal cluster identified through the between-group analyses of the remembered trials. Mean fit coefficients and counts of positively responsive voxels for each participant were extracted for the left and right hemisphere ROIs. The following laterality index formula was used: $(LH - RH) / (LH + RH)$, where LH and RH represent left and right hemisphere task-related activity, respectively. Negative laterality index values indicate right hemisphere dominance whereas positive values represent left hemisphere dominance (Seghier, 2008).

RESULTS

Demographic and Cognitive Variables

The two age groups did not significantly differ in terms of years of education, sex distribution, or raw score or demographically corrected neuropsychological performance (all p values > 0.12 , no p values less than the Bonferroni corrected significance level of $p = 0.004$; Table 1). All mean demographically corrected neuropsychological scores were within the normal range (i.e., all standard scores > 100 ; all T-scores > 45 ; all z -scores > -0.5). In addition, all older adults reported a minimal level of depression (Geriatric Depression Scale scores ranged from 0 to 7) and a minimal degree of anxiety (Beck Anxiety Inventory scores ranged from 0 to 4).

FMRI Scanner Task and Post-Scanning Recognition Task Performance

There were no significant differences between age groups in terms of accuracy and reaction time on the face-name associative encoding task during scanning (no p values less than the Bonferroni corrected significance level of $p = 0.013$; Table 2). On the post-scanning recognition task, the age groups did not differ in terms of accuracy; however, the older adults demonstrated a trend toward longer response latencies relative to the young participants ($t = -2.24$, $p = .04$; Table 2).

Motion—There were no significant between group differences in overall degree of motion, as demonstrated by the motion correction indices computed by the automated algorithm (no p values less than the Bonferroni corrected significance level of $p = 0.025$).

Cortical thickness—Older adults demonstrated reduced mean cortical thickness compared to the young participants ($t = 2.99$; $p = .008$; Table 1). When each hemisphere was analyzed individually, older adults showed reduced cortical thickness in both right ($t = 3.04$; $p = .007$) and left hemispheres ($t = 2.90$; $p = .01$).

Resting cerebral blood flow—At rest, older adults showed significantly reduced mean global gray matter CBF relative to their young counterparts ($t = 3.05$; $p = .007$; Table 1). When the two hemispheres were examined separately, older adults showed reduced CBF in both right ($t = 2.96$; $p = .009$) and left hemispheres ($t = 3.05$; $p = .007$). When those participants with substituted CBF values were excluded, results remained qualitatively and statistically very similar.

FMRI Data

Within-group analysis for encoding of remembered face-name pairs versus all other trials—When whole brain voxel-wise within-group t test analyses were performed for encoding-related activation to remembered face-name pairs there were several regions of significant task-related brain response (Table 3; Figure 3). Young adults showed significant response in several regions including bilateral parahippocampal gyrus, fusiform gyrus, thalamus, superior and medial frontal gyri, cingulate, angular gyrus, parietal lobule, occipital cortex, and cerebellum. Older adults showed activation during remembered trials in a large region spanning bilateral medial frontal gyrus, precentral gyrus, postcentral gyrus, cingulate gyrus, hippocampus, fusiform gyrus, superior parietal lobule, thalamus, and culmen. In addition, they showed less response (deactivation) during remembered trials in regions including bilateral precuneus, left cuneus, posterior cingulate and cingulate as well as in bilateral medial frontal gyrus and anterior cingulate.

Between-group analyses for encoding of remembered face-name pairs versus all other trials—When the young and older adults were statistically compared, older adults demonstrated increased activation in anterior regions including right superior frontal, middle frontal, inferior frontal gyri and right anterior cingulate. In contrast, the older adults showed decreased activity relative to the young adults in a posterior cluster including bilateral cuneus and lingual gyrus.

Correlations between brain response and cognitive performance—With the exception of a trend toward a negative association between accuracy on the post-scanning recognition task and left lingual gyrus activation in the older adults ($r = -.65$; $p = .04$), task-related brain response determined from the between-group analyses was not related to accuracy or reaction time on the scanner task or the post-scanning recognition task for either age group (no p values less than the Bonferroni corrected significance level of $p = 0.013$). When task-related brain response was correlated with memory performance on a paired-

associate task administered outside of the scanner, there was a positive association between performance and right superior frontal activation for older adults ($r = .79$; $p = .01$; Figure 4) but not for young adults ($r = -.62$; $p = .10$). An analysis involving a Fisher r -to- z transformation indicated that the difference between these correlation coefficients was statistically significant ($z = 3.23$; $p = .001$). There were no trends toward a significant relationship between the response in the posterior cluster and performance on this paired-associate learning task (older adults, $r = -.16$; $p = .68$; young adults, $r = .46$; $p = .26$) or for either cluster and performance on the word-list learning task (no p values less than the Bonferroni corrected significance level of $p = 0.013$).

Hierarchical regression including perfusion and cortical thickness measurements

—Two separate hierarchical regression models with the fit coefficients for each of the two observed significant clusters of between-group differences in task-related brain response for encoding of remembered face-name pairs serving as the dependent variable demonstrated that age group but neither resting CBF nor cortical thickness predicted task-related fMRI activation. Specifically, for the anterior cluster, when resting CBF and cortical thickness were entered on step 1, the model was not significant ($F_{2,16} = 1.23$; $p = .32$; $\Delta R^2 = .13$; CBF: $\beta = -.28$; $p = .31$; cortical thickness: $\beta = -.14$; $p = .61$). However, when age group was entered on step 2, the model was statistically significant ($F_{3,15} = 7.21$; $p = .003$; $\Delta R^2 = .46$; age: $\beta = .93$; $p = .001$). Similarly, for the posterior cluster, when resting CBF and cortical thickness were entered on step 1, the model was not significant ($F_{2,16} = .95$; $p = .41$; $\Delta R^2 = .11$; CBF: $\beta = .34$; $p = .23$; cortical thickness: $\beta = -.02$; $p = .95$). In contrast, when age group was entered on step 2, the model was statistically significant ($F_{3,15} = 6.22$; $p = .006$; $\Delta R^2 = .45$; age, $\beta = -.92$; $p = .001$).

Anterior–posterior shift—Across all participants, degree of frontal and posterior task-related activity were negatively correlated ($r = -.47$; $p = .04$). However, this correlation was no longer statistically significant when the two age groups were examined separately (p values $> .05$). Qualitatively, older adults demonstrated greater anterior relative to posterior activity whereas the younger adults showed increased posterior compared to frontal activity (Figure 5).

Laterality index—Applying the laterality index to the left and right frontal ROIs indicated that young and older adults differed in their demonstrated pattern of hemispheric laterality during the encoding of face-name pairs that were later remembered (Figure 6). Using the mean of positive fit coefficients as the dependent variable, analyses revealed that older adults demonstrated greater bilateral involvement compared to the young adults who showed greater left relative to right hemisphere involvement ($t = 2.46$; $p = .03$, older adult mean = $-.02$, younger adult mean = $.21$). There were no significant associations between laterality index and accuracy on the scanner task or memory performance outside of the scanner (no p values less than the Bonferroni corrected significance level of $p = 0.013$).

DISCUSSION

To summarize, results support our four predictions related to the neural correlates of successful memory encoding in aging. First, during the successful encoding of face-name pairs, older adults demonstrated greater task-related brain response in right frontal regions compared to young adults. In contrast, they demonstrated decreased task-related activity relative to the young in posterior regions including the lingual gyrus and cuneus. Consistent with the PASA pattern (Davis et al., 2008), these findings suggest that older adults demonstrate a shift from posterior to anterior involvement during successful memory encoding. Second, analysis of laterality indices provided support for the HAROLD model given that for the older adults the laterality index for the mean fit coefficient was near zero,

a value indicating complete bilaterality. Third, findings support the potential engagement of compensatory mechanisms among older adults given that greater frontal activation was associated with better memory abilities and age-related alterations were observed despite equivalent accuracy on the post-scanning recognition task and analysis of only those items that were correctly remembered. Fourth, hierarchical regression analyses demonstrated that reduced global resting CBF and cortical thickness cannot account for the observed age-related differences in brain response during successful memory encoding.

Our finding that older adults demonstrated reduced task-related activity in posterior regions relative to young adults during the encoding of face name pairs is consistent with previous studies examining age-related differences in memory encoding. Such studies often report a tendency for older adults to demonstrate weaker activation in posterior regions which show greater engagement in young adults (e.g., Cabeza et al., 1997; Grady et al., 1995), suggesting that encoding deficits may contribute to episodic memory decline in normal aging (Minati, Grisoli, & Bruzzone, 2007). Age-related decreases in activation could be due to a variety of factors including reduced spatial extent of activation, increased variability or asynchrony in neuronal population firing, neurotransmitter dysfunction, reduced neuronal metabolic activity, or disruptions in network connectivity (Hedden & Gabrieli, 2004).

Many studies address age-related differences in the neural correlates of memory encoding but do not differentiate among subgroups of older adults or restrict analyses to successfully encoded stimuli and, therefore, do not examine successful cognitive aging *per se*. Individual differences among older adults may relate to a variety of factors including life experience, genetics, cognitive strategies, and vulnerability to neuropathology. In particular, it has been proposed that variability in normal aging may be related to differences in the integrity of prefrontal cortex. Examining individual differences and how activation patterns relate to behavioral performance are critical to understanding the functional significance of age-related differences in brain response and distinguishing between normal and pathological aging (Hedden & Gabrieli, 2004).

Our finding of increased frontal activity among older adults was observed in the context of (1) analyses restricted to successfully encoded items providing support for the notion that age-related differences in brain response are not due to task difficulty; (2) comparable performance on scanner task and post-scanning recognition task as well as additional neuropsychological measures administered outside of the scanner further ruling out confounds between age and cognitive performance; (3) a positive association between degree of frontal activation and performance on an associative encoding task performed outside of the scanner among older adults suggesting that increased activation may benefit performance; and (4) analyses accounting for age-related differences in global measures of resting CBF and cortical atrophy ruling out any potential confounds related to these variables. Importantly, we took into account guidelines for interpreting group differences in fMRI response as compensation outlined in the Region-Activation-Performance model (Han et al., 2009) including considering issues related to differential atrophy, resting CBF, and task difficulty. Taken together, the observed increased frontal activation in older adults appears to be consistent with a compensatory mechanism evoked to maintain/improve performance.

Furthermore, this finding of increased right frontal activation among the older adults during successful encoding is consistent with previous studies reporting that increased right frontal engagement is correlated with better verbal list learning abilities among healthy older adults (Johnson, Saykin, Flashman, McAllister, & Sparling, 2001) as well as findings that older adults at risk for cognitive decline demonstrate greater activation in several right hemisphere regions while viewing previously encoded word pairs (Han et al., 2007). Regarding the

latter, the authors concluded that additional activation in frontotemporal regions provided evidence for the recruitment of executive functions and semantic memory processes to compensate for episodic memory encoding deficits. However, in contrast to the many studies demonstrating associations between greater frontal activation and better performance across older adults, some studies explicitly examining subsequent memory (Duverne, Motamedinia, & Rugg, 2009; Miller et al., 2008) have reported that reduced lateralization of prefrontal activity was observed for those older adults with poorer memory performance. The authors argued that such findings suggest that preservation of memory abilities among older adults does not rely on greater bilateral prefrontal involvement. Of note, the present study differs from those of Duverne and colleagues and Miller and colleagues given that the older adults included in their samples performed significantly less accurately than young adults on post-scanning recognition measures suggesting that findings may be related to differential performance. Furthermore, these studies did not assess atrophy or resting CBF.

There are limitations that need to be considered when interpreting the present findings and that should be addressed in future studies. First, as is often the case in neuroimaging studies, our sample size was relatively small, which may have resulted in a lack of statistical power to detect differences. However, given that significant findings were demonstrated in the context of a relatively small sample size, these findings are likely robust. Second, our sample was generally relatively well-educated and medically healthy, which may limit generalizability. Third, there was an unequal ratio of men to women in our sample. However, the young and older adult age groups did not differ in terms of sex distribution and *post hoc* analyses found no significant differences in brain response based on sex. Finally, future fMRI studies integrating simultaneous measurements of CBF and BOLD response to cognition as well as a separate hypercapnic challenge (e.g., CO₂ inhalation) in both younger and older participants might reduce the potential ambiguity of interpreting BOLD signal differences between groups by disentangling the relative contribution of vascular versus neuronal components to the fMRI signal and how these may change with age (Wierenga & Bondi, 2007).

In closing, fMRI study of memory encoding combined with assessment of individual differences represents a promising approach for further elucidating the neural correlates of successful cognitive aging. The present study extends previous findings by providing support for the notion that age-related alterations in activation cannot be attributed to the commonly observed findings of poorer task performance, reduced resting CBF, or cortical atrophy among older adults. Furthermore, these findings provide support for compensatory mechanisms possibly involving right frontal regions. The compensatory hypothesis suggests the potential for lifelong plasticity (e.g., Reuter-Lorenz, 2002) and highlights the potential utility of cognitive interventions in aging (Papp, Walsh, & Snyder, 2006). Further research is necessary to clarify longitudinal cognitive, neuroanatomical, and neurophysiologic changes that occur in successful cognitive aging in an effort to prevent cognitive decline and maintain quality of life among older adults.

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Fig. 1.

The event-related fMRI paradigm involved the presentation of face-name pairs (each shown twice during the experiment) as well as periods of a cross-hair fixation interspersed throughout the task. Participants were instructed to indicate whether each face-name pair was “new” (i.e., not previously seen) or “old” (i.e., previously seen).

- 1) Martin
- 2) Guy
- 3) Mitchell

Fig. 2.
Example of post-scanning forced-choice recognition test stimuli. Individual faces were presented and participants were prompted to select among three name choices for each face.

Fig. 3.

Whole brain response to remembered face-name pairs overlaid onto a high-resolution anatomical image. The top panel shows the within-subject t tests for older adults (a) and young adults (b), with warm colors representing areas more active during the viewing of remembered face-name pairs than all other trials and cool colors representing areas more active during all other trials compared to remembered face-name pairs. Axial slices span from 12 inferior to 60 superior in 8-mm increments. The bottom panel (c) shows the independent-samples t test comparison of older adults to young adults, with warm colors representing areas of greater task-related brain response among older adults and cool colors representing areas of greater task-related brain response among young adults. Sagittal slices span from 14 left to 31 right in 5-mm increments. Results have been clustered and thresholded so as to protect a whole-brain probability of false positives less than or equal to 0.05. Images are presented in radiological view.

Fig. 4.

Scatterplot of the correlation between performance on a standardized memory measure administered outside of the scanner and right frontal activation during the successful encoding of face-name pairs for the older adult participants.

Fig. 5. Anterior versus posterior activity during successful memory encoding according to age group. The anterior and posterior regions were identified through the between-group analyses of the remembered trials. The anterior region included right superior frontal, middle frontal, and inferior frontal gyri, as well as anterior cingulate. The posterior cluster included bilateral cuneus and lingual gyrus.

Fig. 6. Lateralization of frontal activity during successful memory encoding according to age group.

Table 1

Participant characteristics

Variables	Age group		<i>t</i> or χ^2 value	<i>p</i> value
	Young adults, <i>n</i> = 9* mean (<i>SD</i>)	Older adults, <i>n</i> = 10** mean (<i>SD</i>)		
Demographics				
Age, yrs	26.89 (1.97)	75.60 (7.09)	–	–
Education, yrs	17.44 (2.56)	17.70 (1.70)	–.26	.80
Women/men	6/3	7/3	.02	.88
Global cognition				
ANART Verbal IQ	115.20 (8.37)	107.20 (40.99)	.56	.58
Learning and memory				
WMS-III LM immediate recall (T)	65.38 (10.29)	51.20 (22.44)	1.65	.12
WMS-III LM delayed recall (T)	64.63 (10.34)	54.50 (23.61)	1.13	.28
WMS-III VPA immediate recall (T)	57.13 (8.68)	45.60 (22.40)	1.37	.19
WMS-III VPA delayed recall (T)	55.13 (6.62)	49.50 (23.67)	.72	.49
CVLT-II List 1–5 total recall (T)	63.88 (9.80)	56.70 (24.60)	.77	.45
CVLT-II long delay free recall (z)	.88 (.83)	–.05 (3.29)	.77	.45
CVLT-II Recognition Discriminability (z)	.75 (.53)	–.25 (3.26)	.85	.41
Executive functioning				
WCST-48, categories	3.50 (1.41)	1.70 (3.97)	1.22	.24
WCST-48, total errors (T)	47.63 (8.28)	46.00 (22.84)	.19	.85
Working memory				
WAIS-III Letter-Number Sequencing (T)	58.25 (12.59)	47.10 (21.59)	1.29	.22
Language				
WAIS-III Vocabulary (T)	57.00 (6.48)	51.20 (22.79)	.69	.50
Emotional functioning				
GDS	–	2.11 (2.57)		
BAI	–	1.78 (2.47)		
Mean bilateral cortical thickness (mm)				
Left hemisphere	2.42 (.07)	2.27 (.13)	2.99	.008
Right hemisphere	2.42 (.08)	2.27 (.13)	2.90	.01
	2.42 (.07)	2.28 (.12)	3.04	.007

Variables	Age group		<i>t</i> or χ^2 value	<i>p</i> value
	Young adults, <i>n</i> = 9* mean (SD)	Older adults, <i>n</i> = 10** mean (SD)		
Mean whole brain CBF (milliliters of blood per 100 g tissue/min)	68.33 (17.85)	48.50 (9.82)	3.05	.007
Left hemisphere	69.73 (18.03)	49.29 (10.61)	3.05	.007
Right hemisphere	66.55 (17.76)	47.49 (9.48)	2.96	.009

* One young did not complete the standardized neuropsychological measures and, given this, analyses involving these variables included 8 young adults. All other analyses for which results are reported in this table included 9 young adults.

** One older adult did not complete the standardized neuropsychological measures and, therefore, analyses involving these variables included 9 older adults. All other analyses for which results are reported in this table included 10 older adults.

ANART VIQ = American National Adult Reading Test Verbal Intelligence Quotient estimate; WMS-III = Wechsler Memory Scale – Third Edition (Wechsler, 1997b), LM = Logical Memory subtest, VPA = Verbal Paired Associates subtest; CVLT-II = California Verbal Learning Test – Second Edition (Delis, Kramer, Kaplan, & Ober, 2000); WCST-64 = Wisconsin Card Sorting Test-64 card version (Kongs, Thompson, Iverson, & Heaton, 2000); WAIS-III = Wechsler Adult Intelligence Scale – Third Edition (Wechsler, 1997a); GDS = Geriatric Depression Scale (Yesavage et al., 1983); BAI = Beck Anxiety Inventory (Beck & Steer, 1993); CBF = cerebral blood flow.

Table 2
Performance on the fMRI face-name associative encoding scanner task and post-scanning recognition task

Variables	Age group		<i>t</i>	<i>p</i> value	η^2		
	Young adults, <i>n</i> = 8 for scanner task and <i>n</i> = 9 for recognition task mean (<i>SD</i>)	Older adults, <i>n</i> = 10 mean (<i>SD</i>)					
Scanner Task							
Accuracy (% correct)	91.44	(5.16)	88.05	(5.68)	1.31	.21	.09
Reaction Time (ms)	1348.56	(229.21)	1388.67	(290.76)	-.32	.75	< .01
Post-scanning Recognition Task							
Accuracy (% correct)	67.27	(14.35)	57.67	(10.91)	1.65	.12	.13
Reaction Time (ms)	4276.93	(1754.00)	5797.65	(1093.78)	-2.24	.04	.22

Table 3
Clusters of significant brain response for within and between subjects for viewing subsequently remembered face-name pairs

Direction of response	Hemisphere	Subregions	Volume (mm ³)	Coordinates* of maximum intensity voxel	t-score for maximum intensity voxel	η^2 (Mean $\pm$ SEM)
Young Adults (<i>n</i> = 59)						
<i>Remember > All other trials</i>	R & L	L & R thalamus, R parahippocampus, R & L culmen, L & R lentiform nucleus, R fusiform	106752	18L, 29P, 20S	9.33	0.54 $\pm$ 0.00
	R & L	L fusiform, L parahippocampus, L & R Declive, R & L lingual gyrus, R & L cuneus, L middle occipital gyrus, L & R culmen	28096	34L, 57P, 16I	5.92	0.51 $\pm$ 0.00
	R & L	L & R superior frontal, L & R medial frontal, L & R cingulate	9152	6R, 7A, 52S	6.96	0.56 $\pm$ 0.01
	R	R superior parietal lobule, R angular gyrus, R inferior parietal lobule, R precuneus, R middle occipital gyrus	7552	30R, 61P, 40S	6.41	0.55 $\pm$ 0.01
	R	R middle frontal gyrus, R inferior frontal gyrus, R precentral gyrus	4864	38R, 23A, 24S	4.95	0.49 $\pm$ 0.01
	L	L superior parietal lobule, L inferior parietal lobule, L angular gyrus, L precuneus	4416	30L, 53P, 48S	7.81	0.53 $\pm$ 0.01
	L	L postcentral gyrus, L inferior parietal lobule	3328	50L, 29P, 40S	4.99	0.51 $\pm$ 0.01
<i>All other trials > Remembered</i>	No significant clusters of activity					
Older adults (<i>n</i> = 10)						
<i>Remembered > All other trials</i>	R & L	L & R culmen, L & R medial frontal gyrus, precentral gyrus, L & R postcentral gyrus, L & R medial frontal gyrus, L & R cingulate gyrus, L & R thalamus, L & R fusiform gyrus, L & R hippocampus, L & R parahippocampus, L & R superior parietal lobule	289600	2R, 49P, 16I	10.86	0.50 $\pm$ 0.00
<i>All other trials > Remembered</i>	R & L	R & L anterior cingulate, R & L medial frontal gyrus,	9024	6R, 43A, 16S	-5.94	0.49 $\pm$ 0.01
Old versus young adults						
<i>Old > Young</i>	R	R middle frontal gyrus, R superior frontal gyrus, R inferior frontal gyrus, R anterior cingulate, R medial frontal gyrus	2432	22R, 51A, 12S	3.90	0.45 $\pm$ 0.01
<i>Young > Old</i>	R & L	L & R lingual gyrus, L & R cuneus	4032	10L, 73P, 4S	-2.95	0.25 $\pm$ 0.00

* From Talairach & Tournoux (1988).

L = left; R = right; A = anterior; P = posterior; S = superior; I = inferior.