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Prefrontal Gray Matter Volume Mediates Age Effects on Memory Strategies

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Abstract

Age differences in the strategies that individuals spontaneously use to learn new information have been shown to contribute to age differences in episodic memory. We investigated the role of prefrontal structure in observed age effects on self-initiated use of memory strategies. The relationships among age, prefrontal regional gray matter volumes, and semantic and serial clustering during free recall on the California Verbal Learning Test - II were examined across the adult lifespan. Semantic clustering was negatively correlated with age and positively correlated with gray matter volumes in bilateral middle and left inferior frontal regions across the adult lifespan. Gray matter volumes in these regions mediated the effects of age on semantic clustering. Forward serial clustering was also negatively correlated with age. However, forward serial clustering was not significantly positively correlated with gray matter volumes in any region of lateral prefrontal cortex. These results suggest that bilateral middle and left inferior frontal regions support self-initiated semantic memory strategy use across the adult lifespan. They also suggest that age differences in prefrontal gray matter volume are a significant contributor to age differences in self-initiated use of elaborative memory strategies.

Keywords

aging; clustering; MRI; recall; semantic; serial

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1. Introduction[1]

Episodic memory is one of the domains of cognition susceptible to decline with age (for a review see Balota et al., 2000). For example, older adults' ability to recall studied information is impaired relative to younger adults' when they are told to learn new information, but are not explicitly instructed how to do so (unsupported intentional encoding) (Hultsch et al., 1990; Murphy et al., 1997; Sanders et al., 1980). Prior research suggests that age differences in self-initiated use of memory strategies contribute to age differences in episodic memory (Hertzog et al., 1998; Kirchhoff et al., 2012a; Perfect and Dasgupta, 1997; Verhaeghen and Marcoen, 1994; for a review see Kirchhoff et al., 2012b). Self-initiated memory strategy use is the self-selection and intentional use of specific sets of cognitive processes to learn or retrieve information.

One of the techniques that has been used to compare self-initiated memory strategy use in younger and older adults is clustering analyses of word retrieval order. In a common variant of this technique (e.g., see Hazlett et al., 2010), a list of words is studied and retrieved multiple times. The word list is presented in the same order during each encoding trial, and words are studied using unsupported intentional encoding. The word list contains words from multiple semantic categories (e.g., animals, vegetables, furniture, etc.). However, words from the same category are not presented consecutively (unblocked presentation). Following each encoding trial, participants are asked to say or write as many words as they can remember from the list in any order (free recall). The order in which the words are recalled is then examined to assess strategic processing.

Forward serial clustering occurs when participants recall words in the same order as they were presented in during encoding (Pellegrino et al., 1974). Given that word rehearsal order during encoding of word lists has been shown to be reflected in word output order during free recall (Rundus, 1971), forward serial clustering is thought to be a measure of participants' use of memory strategies during encoding and/or retrieval that facilitate retrieval of word order (e.g., rehearsal of word order during encoding). Prior research suggests that healthy aging may not significantly affect forward serial clustering (Murphy et al., 1997).

Semantic clustering occurs when participants report words from the same semantic category consecutively during free recall (Bousfield, 1953). It is thought to be a measure of participants' use of semantic memory strategies during encoding and/or retrieval (e.g., rehearsing words from the same semantic category together during encoding). In support of this, categorical clustering during encoding has been shown to lead to categorical clustering during free recall (Schmitt et al., 1981; Weist, 1972). Lower semantic clustering has been reported for older than younger adults following unsupported intentional encoding (Gutchess et al., 2006; Jacobs et al., 2001; Murphy et al., 1997; Sanders et al., 1980), suggesting that older adults are less likely than younger adults to self-initiate semantic strategies during encoding and/or retrieval. Consistent with this, Sanders and colleagues

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[1]Abbreviations
CVLT-II, California Verbal Learning Test – II; FDR, false discovery rate; MMSE, Mini-Mental Status Exam; MPRAGE, magnetization prepared rapid gradient echo; ROI, region of interest

(1980) found that older adults rehearsed words by category less frequency than younger adults when they were instructed to verbalize their thoughts during unsupported intentional encoding of an unblocked categorized word list. Importantly, Schmitt and colleagues (1981) found that explicitly instructing older adults to use a semantic categorization strategy during encoding can increase their use of this strategy, their semantic clustering during free recall, and the number of words they are able to recall. This suggests that age differences in elaborative memory strategy use are driven primarily by age differences in the ability to self-initiate elaborative memory strategies, instead of the ability to implement them or benefit from their use.

Self-initiated memory strategy use in younger and older adults has also been compared using retrospective self-reports. In these studies, encoding strategy use was assessed after unsupported intentional encoding by asking participants to answer open-ended strategy use questions (Devolder and Pressley, 1992; Hertzog et al., 1998, 2010; Naveh-Benjamin et al., 2007), to indicate how frequently they used different encoding strategies on rating scales (Brooks et al., 1993; Kirchhoff et al., 2012a; Verhaeghen and Marcoen, 1994), or to indicate what strategy they used to encode each stimulus (Dunlosky and Hertzog, 2001; Rowe and Schnore, 1971). These assessments of self-initiated memory strategy use have revealed that older adults more frequently report not using any strategies to learn words during encoding than younger adults (Devolder and Pressley, 1992; Kirchhoff et al., 2012a; Rowe and Schnore, 1971). Older adults are also less likely to report using elaborative encoding strategies than younger adults (Brooks et al., 1993; Hertzog et al., 1998, 2010; Naveh-Benjamin et al., 2007; Verhaeghen and Marcoen, 1994). However, instructing or training older adults to use elaborative encoding strategies can increase their self-reported use of these strategies and improve their memory performance (Kirchhoff et al., 2012a; Naveh-Benjamin et al., 2007). This further suggests that age differences in memory strategy use are driven primarily by age differences in the ability to self-initiate effective memory strategies.

Currently, relatively little is known regarding what drives age differences in self-initiated use of memory strategies. One factor that may be a significant contributor to these age differences is age differences in prefrontal function. Prefrontal cortex plays a central role in supporting self-initiated use of elaborative memory strategies. Individuals with prefrontal lesions are less likely than healthy controls to cluster words by semantic category during free recall (Baldo et al., 2002; Gershberg and Shimamura, 1995; Hildebrandt et al., 1998). They are also more likely to report not using any strategies during intentional encoding than healthy controls (Gershberg and Shimamura, 1995). However, individuals with prefrontal lesions can effectively use elaborative strategies during encoding and retrieval when they are explicitly instructed to do so (Gershberg and Shimamura, 1995; Hirst and Volpe, 1988). In healthy younger adults, positive correlations have been reported between semantic clustering and gray matter volume in the left inferior frontal gyrus and gyrus rectus (Matsui et al., 2008). Associations with semantic clustering are not limited to structural measures of brain volume in healthy individuals, but extend to functional measures of brain activity patterns as well. For example, Savage and colleagues (2001) demonstrated that activity during intentional encoding in right orbitofrontal and ventromedial frontal cortex is positively correlated with subsequent semantic clustering during free recall. Positive correlations have also been found between semantic clustering and a combined measure of brain activity during intentional encoding and free recall in right medial and bilateral dorsolateral and inferior frontal cortex (Hazlett et al., 2004; Nohara et al., 2000). Self-report measures of strategic processing have also revealed that self-initiated use of verbal and visual encoding strategies engages prefrontal regions (verbal: medial superior, right superior, and left inferior regions; visual: right superior and inferior regions) (Kirchhoff and Buckner, 2006).

While prefrontal cortex supports self-initiated use of elaborative memory strategies, it may not play a necessary role in self-initiation of the relatively simple memory strategies that lead to high levels of forward serial clustering during recall. Prior research suggests that forward serial clustering is not impaired in individuals with prefrontal lesions (Alexander et al., 2003; Baldo et al., 2002; Stuss et al., 1994). In addition, studies that have examined the neural correlates of forward serial clustering in healthy younger and middle-aged adults have not found positive correlations between forward serial clustering and prefrontal structure or activity patterns (Hazlett et al., 2000, 2004; Matsui et al., 2008; Rannikko et al., 2012).

Consistent with the hypothesis that age differences in prefrontal function play a significant role in age differences in self-initiated use of memory strategies, prefrontal cortex is one of the brain regions most affected by aging (for reviews see Gunning-Dixon et al., 2009; Raz and Rodrigue, 2006). Negative associations between age and prefrontal gray and white matter volumes have been reported in both cross-sectional adult lifespan and longitudinal research (Driscoll et al., 2009; Jernigan et al., 2001; Raz et al., 1997, 2005; Resnick et al., 2003). Aging has also been shown to be associated with increases in white matter hyperintensity volume (Burgmans et al., 2010; Gunning-Dixon and Raz, 2003; Sachdev et al., 2007) and decreases in white matter fractional anisotropy (Head et al., 2004; Michielse et al., 2010; Pfefferbaum et al., 2005; Salat et al., 2005) in prefrontal cortex.

To date, few studies have examined the neural correlates of self-initiated memory strategy use in healthy older adults. Kirchhoff and colleagues (2012a) examined the effects of semantic encoding strategy training on older adults' brain activity patterns during intentional encoding. They found that training-related changes in recognition were positively correlated with training-related changes in brain activity in medial superior and left dorsolateral and inferior prefrontal cortex. Hazlett and colleagues (2010) examined the relationship between semantic clustering and a combined measure of brain activity during intentional encoding and free recall across the adult lifespan (i.e., 20s to 80s). They found a positive correlation between semantic clustering and activity in left inferior prefrontal cortex in women, and a negative correlation between semantic clustering and activity in left inferior and orbital prefrontal cortex in men. To our knowledge, the contribution of age effects on prefrontal structure to age effects on self-initiated memory strategy use has not been directly explored.

The goal of the present research was to investigate whether prefrontal structure mediates age effects on self-initiated use of memory strategies. The relationships among age, prefrontal regional gray matter volumes, and clustering during free recall on the California Verbal Learning Test – II (CVLT-II; Delis et al., 2000) were examined. We hypothesized that prefrontal regional gray matter volumes would be positively correlated with semantic but not forward serial clustering across the adult lifespan. We also hypothesized that prefrontal regional gray matter volumes would mediate the effects of age on semantic clustering.

2. Material and Methods

2.1 Participants

Demographic, cognitive assessment, strategy use, memory performance, and regional gray matter volume data came from an archival dataset of structural brain images and neuropsychological assessments of one hundred and fifty healthy adults (96 female, 54 male) aged 18 to 91 (M = 55.1, SD = 22.2). Participants were initially recruited from the Washington University Psychology Department's older adult subject pool and the St. Louis community. All participants were right-handed native English-speakers. They were screened for neurologic illness, head injury, and medical conditions that might produce cognitive impairment (e.g., cerebrovascular disease, Parkinson's disease, etc.). Participants were also screened for gross cognitive status using the Mini-Mental Status Exam (MMSE; Folstein et al., 1975). Individuals included in this study had a MMSE score of 27 or higher. Educational history was assessed using a seven-point scale on which one indicated that a person had not completed high school or a GED and seven indicated that a person had a M.D., J.D., Ph.D. or other advanced degree. Participants' demographic characteristics are summarized in Table 1. Study procedures were approved by Washington University's Human Studies Committee, and informed consent was obtained in accordance with its guidelines.

2.2 Assessments of cognitive function, strategy use, and memory performance

Scores on the MMSE were used as a measure of gross cognitive status. The vocabulary subtest of the Shipley Institute of Living Scale (Shipley, 1940) was used as a measure of participants' semantic processing ability. Immediate recall of word list A from the CVLT-II (Delis et al., 2000) was used to assess participants' strategy use and memory performance. Participants were read a list of sixteen words (four words per semantic category) and were asked to verbally recall the words on the list in any order immediately after the last word on the list was read. Participants' responses were transcribed by the experimenter. This study-test cycle was repeated for five trials. The same list of words was presented in the same order during the study phase of all five trials. Words from the same category were never presented consecutively. Participants' semantic strategy use during encoding and/or retrieval was measured by averaging the Chance Adjusted Semantic Clustering scores (Delis et al., 2000; Stricker et al., 2002) for each of the five immediate memory trials. The Chance Adjusted Semantic Clustering score for a trial equaled the number of correct semantic clusters – ((the number of correctly recalled words – 1)/5). A semantic cluster occurred whenever a participant recalled a correct word immediately following another correct word from the same category. The possible score range for Chance Adjusted Semantic Clustering was −3.0 to 9.0. Participants' forward serial strategy use during encoding and/or retrieval was measured by averaging the Chance Adjusted Serial Clustering scores (Delis et al., 2000; Stricker et al., 2002) for each of the five immediate memory trials. The Chance Adjusted Serial Clustering score for a trial equaled the number of correct serial clusters – ((the number of correctly recalled words – 1)/16). A serial cluster occurred whenever a participant recalled a correct word immediately following another correct word in the same order as their presentation on word list A. The possible score range for Chance Adjusted Serial Clustering was −.93 to 14.06. Memory performance was measured by averaging the number of words correctly recalled during each of the five immediate memory trials.

2.3 Image acquisition and processing

A high resolution, T1-weighted sagittal magnetization-prepared rapid gradient echo (MPRAGE) scan (TR = 9.7 ms, TE = 4 ms, flip angle = 10°, TI = 20 ms, voxel size = 1 × 1 × 1.28 mm, slices = 128) was acquired using a Siemens 1.5 Tesla Vision MRI scanner (Erlangen, Germany). Cushions and a thermoplastic mask were used to minimize head movement during scanning. The MRI scan sessions occurred within an average of 12 days (SD 22 days) of the assessments of cognitive function, strategy use, and memory performance.

2.4 Regional volumetry

Regional gray matter volumes were generated using the Freesurfer image analysis suite (version 5.0; http://surfer.nmr.mgh.harvard.edu/) (Desikan et al., 2006; Fischl et al., 2002, 2004a). Freesurfer implements an automated labeling procedure in which each voxel in a T1-weighted image is assigned a neuroanatomical label based on probabilistic information derived from a manually labeled training set. Regional gray matter volumes generated using this procedure have been shown to have a high correspondence with manually traced volumes (Fischl et al., 2004b). Regions of interest (ROIs) were identified using the Desikan-Killiany atlas within Freesurfer and included superior, caudal middle, rostral middle, inferior, medial orbital, and lateral orbital frontal regions bilaterally (see Figure 1 for location of ROIs). Volumes were adjusted for intracranial volume using a covariance approach (Buckner et al., 2004; Mathalon et al., 1993).

2.5 Analytic approach

2.5.1 Outlier Analysis—The demographic, cognitive assessment, strategy use, recall, and regional gray matter volume data were first examined for multivariate outliers by calculating a Mahalanobis D^2 score for each participant (Lattin et al., 2003). The Mahalanobis D^2 score p values were > 0.001 for all participants, indicating that there were no multivariate outliers. The data were also examined for univariate outliers. Two participants had serial clustering scores greater than 4 standard deviations above the mean. The pattern of results did not differ when these values were included versus excluded. The results reported here include these values.

2.5.2 Missing data—The Shipley vocabulary score for one participant was missing. It was replaced using regression imputation via likelihood estimation. The expectation-maximization algorithm in SPSS (version 20) was used to estimate the missing vocabulary score based on all the other data (i.e., all age, sex, education, MMSE, vocabulary, forward serial clustering, semantic clustering, recall, and regional gray matter volume data points).

2.5.3 Covariates—Zero-order correlations between sex, education, gross cognitive status, semantic processing ability, and all predictor and outcome variables were examined (α = 0.05, one-tailed). There were significant zero-order correlations between sex, gross cognitive status, and semantic processing ability and at least one predictor or outcome variable. Therefore, these variables were treated as covariates in statistical analyses. Education was not significantly correlated with any predictor or outcome variable (all *p*s > 0.1), and therefore was not included as a covariate in statistical analyses.

2.5.4 Partial Correlation Analyses—Age, sex, gross cognitive status, semantic processing ability, forward serial clustering, semantic clustering, recall, and regional gray matter volume data were transformed into *z* scores. These z scores were used in all data analyses. Partial correlation analyses of the relationships among age, strategy use, recall, and regional gray matter volumes that controlled for sex, gross cognitive status, and semantic processing ability were conducted. A one-tailed α of 0.05 was used as the statistical significance threshold for these partial correlations because we had *a priori* hypotheses regarding the directions of the relationships among these variables based on prior literature. Partial correlation analyses in which regional gray matter volume was a variable were corrected for multiple comparisons using a False Discovery Rate (FDR) correction (Benjamini and Hochberg, 1995). Partial correlations between age and forward serial and semantic clustering were used to investigate the effects of age on self-initiated use of serial and semantic strategies. The relationship between age and prefrontal structure was examined using partial correlations between age and regional gray matter volumes. Partial correlations between regional gray matter volumes and forward serial and semantic clustering scores were used to investigate what prefrontal regions support self-initiated use of serial and semantic strategies across the adult lifespan.

2.5.5 Hierarchical Linear Regression Analyses—To examine whether the relationships between brain structure and self-initiated strategy use vary as a function of age, hierarchical linear regression analyses were conducted. Specifically, the effect of age on the relationship between gray matter volume and clustering was examined for prefrontal ROIs in which there were significant partial correlations between gray matter volume and clustering. Separate regression models were created for each ROI. Sex, gross cognitive status, and semantic processing ability covariates were entered in the first steps of hierarchical linear regression models predicting clustering. Age and regional gray matter volume were entered in the second steps. Age and regional gray matter volume data were then multiplied together to create interaction terms, and these interaction terms were entered into the models in the third steps. A significant interaction term would indicate that age moderates the relationship between gray matter volume and self-initiated strategy use within a region.

Hierarchical linear regression analyses were also conducted to examine whether the relationships between brain structure and self-initiated strategy use vary as a function of sex in the prefrontal ROIs in which there were significant partial correlations between gray matter volume and clustering. Gross cognitive status and semantic processing ability covariates were entered in the first steps of these analyses. Sex and regional gray matter volume were entered in the second steps, and sex and regional gray matter volume interaction terms were entered in the third steps. A significant interaction term would indicate that sex moderates the relationship between gray matter volume and self-initiated strategy use within a region. An alpha of 0.05 (two-tailed) with a FDR multiple comparisons correction was used as the statistical significance criterion for all of the hierarchical linear regression analyses.

2.5.6 Mediation Analyses—The INDIRECT mediation analysis software program developed by Preacher and Hayes (2008; http://afhayes.com/spss-sas-and-mplus-macros-and-code.html) was used to examine whether regional gray matter volumes mediated age effects on self-initiated strategy use. This program uses bootstrapping to estimate indirect effects and to test whether they are significantly different from zero by generating confidence intervals. Standardized residuals controlling for sex, gross cognitive status, and semantic processing ability were used in these mediation analyses.

3. Results

3.1 Relationships among age, strategy use, and recall

Participants' scores on the MMSE, Shipley vocabulary subtest, and CVLT-II are summarized in Table 1. Analyses of the relationships among age, self-initiated strategy use, and recall revealed that age was negatively correlated with forward serial clustering ($pr = -.21$, $p < 0.01$), semantic clustering ($pr = -.16$, $p < 0.05$), and recall ($pr = -.55$, $p < 0.001$). There was not a significant relationship between forward serial clustering and recall ($pr = .09$, $p > 0.1$). In contrast, semantic clustering was positively correlated with recall ($pr = .48$, $p < 0.001$). Semantic and forward serial clustering were negatively correlated with each other ($pr = -.60$, $p < 0.001$).

3.2 Volumetric correlates of self-initiated strategy use across the adult lifespan

Analyses of the relationships among age, regional gray matter volumes, and self-initiated strategy use revealed that age was negatively correlated with gray matter volumes in all ROIs (Table 2). Forward serial clustering was not significantly positively correlated with gray matter volume in any ROI. In contrast, semantic clustering was significantly positively correlated with gray matter volume in left caudal middle, left inferior, and right rostral middle frontal regions (Figure 2).

To examine whether age moderated the relationships between gray matter volume and semantic clustering in left caudal middle, left inferior, and right rostral middle frontal cortex, hierarchical linear regression analyses were conducted with semantic clustering as the dependent variable. The first steps of these models, which contained sex, gross cognitive status, and semantic processing ability, were significant (all ROIs: $\Delta R^2 = .10$, $F(3, 146) = 5.13$, $p = 0.002$). The second steps of these models, which contained age and volume, were also significant (left caudal middle: $\Delta R^2 = .04$, $F(2, 144) = 3.62$, $p = 0.029$; left inferior: $\Delta R^2 = .04$, $F(2, 144) = 3.46$, $p = 0.034$; and right rostral middle: $\Delta R^2 = .06$, $F(2, 144) = 4.80$, $p = 0.010$). Importantly, the age x volume interactions in the third steps of these models were not significant in any of these regions (left caudal middle: $\Delta R^2 = .01$, $F(1, 143) = .77$, $p = 0.381$; left inferior: $\Delta R^2 = .00$, $F(1, 143) = .33$, $p = 0.569$; and right rostral middle: $\Delta R^2 = .00$, $F(1, 143) = .33$, $p = 0.568$), indicating that age did not moderate the positive relationships between gray matter volume and semantic clustering in these ROIs.

Hierarchical linear regression analyses were also conducted to examine whether sex moderated the relationships between gray matter volume and semantic clustering in left caudal middle, left inferior, and right rostral middle frontal cortex. Semantic clustering was the dependent variable in these analyses. The first steps of the hierarchical linear regression models, which contained gross cognitive status and semantic processing ability, were significant (all ROIs: $\Delta R^2 = .04$, $F(2, 147) = 3.13$, $p = 0.047$). The second steps of these models, which contained sex and volume, were also significant (left caudal middle: $\Delta R^2 = .09$, $F(2, 145) = 7.56$, $p = 0.001$; left inferior: $\Delta R^2 = .10$, $F(2, 145) = 7.95$, $p = 0.001$; and right rostral middle: $\Delta R^2 = .11$, $F(2, 145) = 9.42$, $p = 0.000$). However, the sex x volume interactions in the third steps of these models were not significant in any of these regions (left caudal middle: $\Delta R^2 = .00$, $F(1, 144) = .06$, $p = 0.804$; left inferior: $\Delta R^2 = .01$, $F(1, 144) = 1.93$, $p = 0.167$; and right rostral middle: $\Delta R^2 = .01$, $F(1, 144) = 1.30$, $p = 0.256$), which demonstrates that sex also did not moderate the positive relationships between gray matter volume and semantic clustering in these ROIs

3.3 Prefrontal mediation of age effects on self-initiated semantic strategy use

We found negative correlations between age and prefrontal regional gray matter volumes and between age and semantic clustering. In addition, we found positive correlations between prefrontal regional gray matter volumes and semantic clustering. This pattern of results suggests that prefrontal regional gray matter volumes may mediate age effects on self-initiated semantic strategy use. To formally test this, we used a mediation analysis technique developed by Preacher and Hayes (2008). The direct effect of age on semantic clustering controlling for gray matter volume, and the indirect effect of age on semantic clustering mediated by gray matter volume, were estimated in the bilateral middle and left inferior frontal ROIs with significant partial correlations between gray matter volume and semantic clustering using 20,000 bootstrap samples. The results of these mediation analyses are presented in Table 3 and Figure 3. The direct effects of age on semantic clustering were non-significant when controlling for gray matter volume in all three ROIs. In addition, the 95% bias-corrected and accelerated bootstrap confidence intervals for the indirect effects of age on semantic clustering mediated by gray matter volume did not contain zero in all three ROIs, indicating that the indirect effects were significant. This pattern of results demonstrates that gray matter volume was a significant mediator of the age effect on semantic clustering in bilateral middle and left inferior frontal cortex.

4. Discussion

In this research, we examined the relationships among age, prefrontal regional gray matter volumes, and clustering during free recall. Semantic clustering was negatively correlated with age and positively correlated with gray matter volumes in bilateral middle and left inferior frontal regions across the adult lifespan. Gray matter volumes in these regions mediated the effects of age on semantic clustering. Forward serial clustering was also negatively correlated with age. However, forward serial clustering was not significantly positively correlated with gray matter volume in any prefrontal region. The implications of these results are discussed below.

Consistent with prior reports of age differences in semantic clustering (Gutchess et al., 2006; Jacobs et al., 2001; Murphy et al., 1997; Sanders et al.,1980), we found a negative correlation between age and semantic clustering. Importantly, prefrontal regional gray matter volumes were shown to mediate the effect of age on semantic clustering. This novel finding suggests that age differences in prefrontal gray matter volume are a significant contributor to age differences in self-initiated use of elaborative memory strategies. White matter damage in prefrontal regions is also associated with aging (Gunning-Dixon and Raz, 2003; Head et al., 2004; Jernigan et al., 2001; Resnick et al., 2003), and episodic memory function in older adults has been linked to white matter integrity (Charlton et al., 2010; Kennedy and Raz, 2009). Therefore, future research should explore whether age differences in prefrontal white matter integrity also contribute to age differences in self-initiated use of elaborative memory strategies.

Gray matter volumes in the middle frontal gyrus were positively correlated with semantic clustering bilaterally in the present research. Hierarchical regression analyses revealed that age did not moderate the relationship between gray matter volume and semantic clustering in these dorsolateral prefrontal regions. This suggests that the middle frontal gyrus supports self-initiated semantic memory strategy use across the adult lifespan. Consistent with this, Hazlett and colleagues (2004) reported that activity in the vicinity of the middle frontal gyrus during intentional encoding and free recall was positively correlated with semantic clustering in healthy younger and middle-aged adults. Cognitive training-related changes in activity in the vicinity of the left middle frontal gyrus during encoding have also been shown to be positively correlated with cognitive training-related changes in self-initiated semantic encoding strategy use in healthy older adults (Kirchhoff et al., 2012a).

Prior research suggests that the middle frontal gyri may support self-initiated use of elaborative memory strategies by supporting relational processing during encoding. Blumenfeld and colleagues (2011) found that when healthy younger adults performed an encoding task that required them to form visual relationships between pairs of unrelated concrete nouns (i.e., forming interactive visual images of the object referents), bilateral activity in the middle frontal gyrus during encoding predicted their subsequent associative recognition of the word pairs. Fletcher and colleagues (1998) compared brain activity during intentional encoding of categorized word lists in conditions that differed in the amount of self-initiated semantic relational processing that they required. Participants' brain activity was greater in the left middle frontal gyrus when they were required to process the meaning of words in relationship to each other to identify the categories present in a list than when they were told what categories would be present in a list before encoding. Consistent with this finding, greater activity has been reported in both the left and right middle frontal gyri during encoding when healthy younger and middle-aged adults were instructed to use a semantic categorization strategy to memorize unblocked categorized word lists than during unsupported intentional encoding (Miotto et al., 2006; Savage et al., 2001). Greater activity has also been reported in the middle frontal gyrus bilaterally during intentional encoding after healthy younger adults were trained to use a method of loci mnemonic (Bower, 1970) than before (Kondo et al., 2005; Nyberg et al., 2003). Use of this mnemonic involves visualizing each item of a to-be-remembered list in a familiar location during encoding, thereby requiring the formation of relationships between items and locations. If the middle frontal gyri do play a central role in relational processing during encoding, our finding that gray matter volumes in the middle frontal gyri mediate age effects on semantic clustering suggests that age differences in self-initiated use of elaborative memory strategies may be driven in part by age differences in relational processing during encoding.

Gray matter volume in the left inferior frontal gyrus was also positively correlated with semantic clustering in the present research. Age did not moderate this relationship, suggesting that the left inferior frontal gyrus also supports self-initiated semantic memory strategy use across the adult lifespan. Consistent with this, positive correlations have been reported between semantic clustering and gray matter volume (Matsui et al., 2008) and activity (Nohara et al., 2000) in healthy younger adults, and between semantic clustering and activity in women across the adult lifespan (Hazlett et al., 2010), in the left inferior frontal gyrus. Activity in this region during intentional encoding has also been shown to increase following semantic strategy training in healthy younger and middle-aged adults (Miotto et al., 2006). Prior research suggests that the left inferior frontal gyrus plays a central role in controlled semantic processing (Badre et al., 2005; Gold et al., 2006; Meinzer et al., 2012). Therefore, it likely supports self-initiated semantic memory strategy use by processing the meaning of studied words during encoding and/or retrieval. Importantly, gray matter volume in the left inferior frontal gyrus was positively correlated with semantic clustering in the present research when participants' scores on a vocabulary test were partialled out of the volumetric and clustering data. This suggests that the positive correlations between gray matter volume and semantic clustering in this region were driven by individual differences in self-initiation of semantic strategy use instead of individual differences in semantic processing ability.

We also found a negative correlation between forward serial clustering and age. This suggests that age may lead to reductions in use of memory strategies that facilitate retrieval of word order. This finding was unexpected given that prior research has not found significant negative associations between age and forward serial clustering (Hazlett et al., 2010; Murphy et al., 1997). However, the sample size of the present dataset was much larger than the sample sizes of previous studies that have examined the effects of age on forward serial clustering, which may explain why the negative relationship between age and forward serial clustering in the present research differs from the results of prior studies.

We hypothesized that there would not be a significant positive relationship between prefrontal regional gray matter volumes and serial clustering across the adult lifespan in this dataset. A limitation of doing so is that it is not possible to definitively prove a null hypothesis. However, consistent with our hypothesis, prefrontal regional gray matter volumes were not significantly positively correlated with forward serial clustering in the present research. While there may be many reasons for the lack of significance, this finding is consistent with prior research that has either found no significant relationships (Hazlett et al., 2000; Rannikko et al., 2012), or negative relationships, between prefrontal structure or activity (Hazlett et al., 2004; Matsui et al., 2008) and forward serial clustering. Interestingly, negative correlations between prefrontal structure or activity and forward serial clustering occurred in regions that also had significant positive correlations between gray matter volume (left inferior prefrontal cortex; Matsui et al., 2008) or activity (left dorsolateral prefrontal cortex; Hazlett et al., 2004) and semantic clustering. Forward serial and semantic clustering are typically negatively correlated (Savage et al., 2001). Therefore, the associations between forward serial clustering and prefrontal structure or activity in these studies may have actually been driven by prefrontal support of self-initiated semantic memory strategy use. Overall, the lack of significant positive correlations between prefrontal structure or function and forward serial clustering in the present and prior research, and the lack of serial clustering impairments following prefrontal lesions (Alexander et al., 2003; Baldo et al., 2002; Stuss et al., 1994), suggest that prefrontal cortex does not play an essential role in supporting the self-initiated strategic processes that lead to relatively high levels of forward serial clustering. Future research is needed to identify the brain regions that do play a necessary role in those strategic processes.

The present research used clustering analyses of word retrieval order to investigate the neural correlates of self-initiated memory strategy use across the adult lifespan. An advantage of using this strategy assessment technique is that it is an objective measure of self-initiated memory strategy use. In addition, it is the most common method of assessing self-initiated memory strategy use in the prefrontal lesion (e.g., Alexander et al., 2003; Baldo et al., 2002; Gershberg and Shimamura, 1995; Hildebrandt et al., 1998; Stuss et al., 1994) and neuroimaging research (e.g., Hazlett et al., 2004, 2010; Matsui et al., 2008; Nohara et al., 2000; Savage et al., 2001) that has investigated the neural correlates of self-initiated strategic processing. However, this strategy assessment method has multiple limitations. It is not possible to determine from clustering analyses alone which specific encoding and retrieval strategies younger and older adults have used to study and retrieve words. For example, self-initiated use of multiple different semantic strategies during encoding could lead to semantic clustering during recall (e.g., rehearsal of words grouped by semantic category, story formation, sentence generation, thinking about the personal relevance of words, etc.). Therefore, clustering analyses cannot be used to identify the brain regions that support self-initiated use of specific memory strategies. In addition, serial and semantic clustering during recall could reflect self-initiated strategy use during encoding, recall, or both. Therefore, it is not possible to determine whether the positive correlations between semantic clustering and prefrontal regional gray matter volumes in the present research are driven by self-initiated strategic processing during encoding, recall, or both. Finally, clustering analyses of word retrieval order are likely not pure measures of intentional use of memory strategies. For example, retrieval of words grouped by semantic category during recall could be driven by an individual's purposeful use of category information learned during encoding to facilitate recall. Alternatively, semantic clustering during recall could result from retrieval of one member of a semantic category automatically triggering recall of other members of the category. Therefore, clustering during recall may at least in part reflect automatic retrieval of associations formed during encoding. Importantly, prior research has shown that the order in which individuals spontaneously rehearse categorized and unrelated word lists during encoding is reflected in their clustering scores during recall (Weist, 1972). This demonstrates that clustering during recall is a valid measure of self-initiated memory strategy use, albeit an imperfect one. Future research that examines the relationships among age, prefrontal structure, and self-reported spontaneous encoding and retrieval strategy use is needed to identify the brain regions that support self-initiated use of specific encoding and retrieval strategies across the adult lifespan, and to identify which prefrontal regional brain volumes mediate age effects on the use of specific encoding and retrieval strategies.

Another limitation of the present research is that mediation analyses were conducted on cross-sectional data. Statistical simulations have suggested that mediation analyses of cross-sectional data in aging research can both overestimate and underestimate the true relationships between longitudinal changes in hypothesized mediator variables and outcome variables (Lindenberger et al., 2011). Therefore, longitudinal research needs to be conducted to further investigate the role of age differences in prefrontal gray matter volumes in age differences in self-initiated use of elaborative memory strategies.

Currently, it is unknown whether reductions in prefrontal gray matter volume are associated with reductions in memory strategy-related activity in affected regions across the adult lifespan, or whether reductions in prefrontal gray matter volume are associated with increases in memory strategy-related activity in affected regions within some age groups. Therefore, future research should examine the relationships among prefrontal regional gray matter volumes, prefrontal brain activity levels during encoding and retrieval, and elaborative strategy use within a longitudinal adult lifespan sample. Future research is also needed to explore whether age differences in bilateral middle and left inferior frontal gray matter volumes are significant contributors to age differences in self-initiated strategic processing within other cognitive domains.

5. Conclusions

Age differences in self-initiated memory strategy use contribute to age differences in episodic memory. This research suggests that bilateral middle and left inferior frontal regions support self-initiated semantic memory strategy use across the adult lifespan. It also suggests that age differences in gray matter volume in these regions are a significant contributor to age differences in self-initiated use of semantic memory strategies during encoding and/or retrieval of episodic memories.

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References

Alexander MP, Stuss DT, Fansabedian N. California Verbal Learning Test: performance by patients with focal frontal and non-frontal lesions. Brain. 2003; 126:1493–1503. [PubMed: 12764068]

Badre D, Poldrack RA, Paré-Blagoev EJ, Insler RZ, Wagner AD. Dissociable controlled retrieval and generalized selection mechanisms in ventrolateral prefrontal cortex. Neuron. 2005; 47:907–918. [PubMed: 16157284]

Baldo JV, Delis D, Kramer J, Shimamura AP. Memory performance on the California Verbal Learning Test-II: findings from patients with focal frontal lesions. J. Int. Neuropsychol. Soc. 2002; 8:539–546. [PubMed: 12030307]

Balota, DA.; Dolan, PO.; Duchek, JM. Memory changes in healthy older adults.. In: Tulving, E.; Craik, FIM., editors. The Oxford Handbook of Memory. Oxford University Press; New York: 2000. p. 395-409.

Benjamini, Y.; Hochberg, Y. J. R. Statist. Soc. Vol. B57. 289-300: 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing..

Blumenfeld RS, Parks CM, Yonelinas AP, Ranganath C. Putting the pieces together: the role of dorsolateral prefrontal cortex in relational memory encoding. J. Cog. Neurosci. 2011; 23:257–265.

Bousfield WA. The occurrence of clustering in the recall of randomly arranged associates. J. Gen. Psychol. 1953; 49:229–240.

Bower GH. Analysis of a mnemonic device: modern psychology uncovers the powerful components of an ancient system for improving memory. Am. Scientist. 1970; 58:496–510.

Brooks JO, Friedman L, Gibson JM, Yesavage JA. Spontaneous mnemonic strategies used by older and younger adults to remember proper names. Memory. 1993; 1:393–407. [PubMed: 7584279]

Buckner RL, Head D, Parker J, Fotenos AF, Marcus D, Morris JC, Snyder AZ. A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. Neuroimage. 2004; 23:724–738. [PubMed: 15488422]

Burgmans S, van Boxtel MPJ, Gronenschild EHBM, Vuurman EFPM, Hofman P, Uylings HBM, Jolles J, Raz N. Multiple indicators of age-related differences in cerebral white matter and the modifying effects of hypertension. Neuroimage. 2010; 49:2083–2093. [PubMed: 19850136]

Charlton RA, Barrick TR, Markus HS, Morris RG. The relationship between episodic long-term memory and white matter integrity in normal aging. Neuropsychologia. 2010; 48:114–122. [PubMed: 19699215]

Delis, DC.; Kramer, JH.; Kaplan, E.; Ober, BA. California Verbal Learning Test. Second Edition. Pearson Education, Inc.; San Antonio: 2000.

Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage. 2006; 31:968–980. [PubMed: 16530430]

Devolder PA, Pressley M. Causal attributions and strategy use in relation to memory performance differences in younger and older adults. Applied Cog. Psychol. 1992; 6:629–642.

Driscoll I, Davatzikos C, An Y, Wu X, Shen D, Kraut M, Resnick SM. Longitudinal pattern of regional brain volume change differentiates normal aging from MCI. Neurology. 2009; 72:1906–1913. [PubMed: 19487648]

Dunlosky J, Hertzog C. Measuring strategy production during associative learning: the relative utility of concurrent versus retrospective reports. Memory Cognit. 2001; 29:247–253.

Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron. 2002; 33:341–355. [PubMed: 11832223]

Fischl B, Salat DH, van der Kouwe AJW, Makris N, Ségonne F, Quinn BT, Dale AM. Sequence-independent segmentation of magnetic resonance images. Neuroimage. 2004a; 23:S69–S84. [PubMed: 15501102]

Fischl B, van der Kouwe A, Destrieux C, Halgren E, Ségonne F, Salat DH, Busa E, Seidman LJ, Goldstein J, Kennedy D, Caviness V, Makris N, Rosen B, Dale AM. Automatically parcellating the human cerebral cortex. Cereb. Cortex. 2004b; 14:11–22. [PubMed: 14654453]

Fletcher PC, Shallice T, Dolan RJ. The functional roles of prefrontal cortex in episodic memory: encoding. Brain. 1998; 121:1239–1248. [PubMed: 9679776]

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J. Psychiatr. Res. 1975; 12:189–198. [PubMed: 1202204]

Gershberg FB, Shimamura AP. Impaired use of organizational strategies in free recall following frontal lobe damage. Neuropsychologia. 1995; 13:1305–1333. [PubMed: 8552230]

Gold BT, Balota DA, Jones SJ, Powell DK, Smith CD, Andersen AH. Dissociation of automatic and strategic lexical-semantics: functional magnetic resonance imaging evidence for differing roles of multiple frontotemporal regions. J. Neurosci. 2006; 26:6523–6532. [PubMed: 16775140]

Gunning-Dixon FM, Brickman AM, Cheng JC, Alexopoulos GS. Aging of cerebral white matter: a review of MRI findings. Int. J. Geriatr. Psychiatry. 2009; 24:109–117. [PubMed: 18637641]

Gunning-Dixon FM, Raz N. Neuroanatomical correlates of selected executive functions in middle-aged and older adults: a prospective MRI study. Neuropsychologia. 2003; 41:1929–1941. [PubMed: 14572526]

Gutchess AH, Yoon C, Luo T, Feinberg F, Hedden T, Jing Q, Nisbett RE, Park DC. Categorical organization in free recall across culture and age. Gerontology. 2006; 52:314–323. [PubMed: 16974103]

Hazlett EA, Buchsbaum MS, Hsieh P, Haznedar MM, Platholi J, LiCalzi EM, Cartwright C, Hollander E. Regional glucose metabolism within cortical Brodmann areas in healthy individuals and autistic patients. Neuropsychobiology. 2004; 49:115–125. [PubMed: 15034226]

Hazlett EA, Buchsbaum MS, Jeu LA, Nenadic I, Fleischman MB, Shihabuddin L, Haznedar MM, Harvey PD. Hypofrontality in unmedicated schizophrenia patients studied with PET during performance of a serial verbal learning task. Schizophr. Res. 2000; 43:33–46. [PubMed: 10828413]

Hazlett EA, Byne W, Brickman AM, Mitsis EM, Newmark R, Haznedar MM, Knatz DT, Chen AD, Buchsbaum MS. Effects of sex and normal aging on regional brain activation during verbal memory performance. Neurobiol. Aging. 2010; 31:826–838. [PubMed: 19027195]

Head D, Buckner RL, Shimony JS, Williams LE, Akbudak E, Conturo TE, McAvoy M, Morris JC, Snyder AZ. Differential vulnerability of anterior white matter in nondemented aging with minimal acceleration in dementia of the Alzheimer type: evidence from diffusion tensor imaging. Cerebral Cortex. 2004; 14:410–423. [PubMed: 15028645]

Hertzog C, McGuire CL, Horhota M, Jopp D. Does believing in "use it or lose it" relate to self-rated memory control, strategy use, and recall? Int. J. Aging Hum. Dev. 2010; 70:61–87. [PubMed: 20377166]

Hertzog C, McGuire CL, Lineweaver TT. Aging, attributions, perceived control, and strategy use in a free recall task. Aging Neuropsychol. Cogn. 1998; 5:85–106.

Hildebrandt H, Brand A, Sachsenheimer W. Profiles of patients with left prefrontal and left temporal lobe lesions after cerebrovascular infarcations on California Verbal Learning Test-like indices. J. Clin. Exp. Neuropsychol. 1998; 20:673–683. [PubMed: 10079043]

Hirst W, Volpe BT. Memory strategies with brain damage. Brain Cogn. 1988; 8:379–408. [PubMed: 3214591]

Hultsch DF, Hertzog C, Dixon RA. Ability correlates of memory performance in adulthood and aging. Psychol. Aging. 1990; 5:356–368. [PubMed: 2242240]

Jacobs DM, Rakitin BC, Zubin NR, Ventura PR, Stern Y. Cognitive correlates of mnemonics usage and verbal recall memory in old age. Neuropsychiatry Neuropsychol. Behav. Neurol. 2001; 14:15–22. [PubMed: 11234905]

Jernigan TL, Archibald SL, Fennema-Notestine C, Gamst AC, Stout JC, Bonner J, Hesselink JR. Effects of age on tissues and regions of the cerebrum and cerebellum. Neurobiol. Aging. 2001; 22:581–594. [PubMed: 11445259]

Kennedy KM, Raz N. Aging white matter and cognition: differential effects of regional variations in diffusion properties on memory, executive functions, and speed. Neuropsychologia. 2009; 47:916–927. [PubMed: 19166865]

Kirchhoff BA, Buckner RL. Functional-anatomic correlates of individual differences in memory. Neuron. 2006; 51:263–274. [PubMed: 16846860]

Kirchhoff BA, Anderson BA, Barch DM, Jacoby LL. Cognitive and neural effects of semantic encoding strategy training in older adults. Cereb. Cortex. 2012a; 22:788–799. [PubMed: 21709173]

Kirchhoff, BA.; Smith, SE.; Luntz, JD. Prefrontal cortex and self-initiated encoding strategy use in healthy younger and older adults.. In: Stuss, DT.; Knight, RT., editors. Principles of frontal lobe function. Oxford University Press; New York: 2012b. p. 567-581.

Kondo Y, Suzuki M, Mugikura S, Abe N, Takahashi S, Iijima T, Fujii T. Changes in brain activation associated with use of a memory strategy: a functional MRI study. Neuroimage. 2005; 24:1154–1163. [PubMed: 15670693]

Lattin JM, Carroll JD, Green PE. Analyzing multivariate data. Brooks Cole, Pacific Grove. 2003

Lindenberger U, von Oertzen T, Ghisletta P, Hertzog C. Cross-sectional age variance extraction: what's change got to do with it? Psychol. Aging. 2011; 26:34–47. [PubMed: 21417539]

Mathalon DH, Sullivan EV, Rawles JM, Pfefferbaum A. Correction for head size in brain-imaging measurements. Psychiatry Res. 1993; 50:121–139. [PubMed: 8378488]

Matsui M, Suzuki M, Zhou S, Takahashi T, Kawasaki Y, Yuuki H, Kato K, Kurachi M. The relationship between prefrontal brain volume and characteristics of memory strategy in schizophrenia spectrum disorders. Prog. Neuropsychopharmacol. Biol. Psychiatry. 2008; 32:1854–1862. [PubMed: 18796324]

Meinzer M, Antonenko D, Lindenberg R, Hetzer S, Ulm L, Avirame K, Flaisch T, Flöel A. Electrical brain stimulation improves cognitive performance by modulating functional connectivity and task-specific activation. J. Neurosci. 2012; 32:1859–1866. [PubMed: 22302824]

Michielse S, Coupland N, Camicioli R, Carter R, Seres P, Sabino J, Malykhin N. Selective effects of aging on brain white matter microstructure: a diffusion tensor imaging tractography study. Neuroimage. 2010; 52:1190–1201. [PubMed: 20483378]

Miotto EC, Savage CR, Evans JJ, Wilson BA, Martins MGM, Iaki S, Amaro E. Bilateral activation of the prefrontal cortex after strategic semantic cognitive training. Hum. Brain Mapp. 2006; 27:288–295. [PubMed: 16082657]

Murphy C, Nordin S, Acosta L. Odor learning, recall, and recognition memory in young and elderly adults. Neuropsychology. 1997; 11:126–137. [PubMed: 9055276]

Naveh-Benjamin M, Brav TK, Levy O. The associative memory deficit of older adults: the role of strategy utilization. Psychol. Aging. 2007; 22:202–208. [PubMed: 17385995]

Nohara S, Suzuki M, Kurachi M, Yamashita I, Matsui M, Seto H, Saitoh O. Neural correlates of memory organization deficits in schizophrenia: a single photon emission computed tomography study with ^{99m}Tc-ethyl-cysteinate dimer during a verbal learning task. Schizophr. Res. 2000; 42:209–222. [PubMed: 10785579]

Nyberg L, Sandblom J, Jones S, Neely AS, Petersson KM, Ingvar M, Bäckman L. Neural correlates of training-related memory improvement in adulthood and aging. Proc. Natl. Acad. Sci. USA. 2003; 100:13728–13733. [PubMed: 14597711]

Pellegrino JW, Battig WF. Relationships among higher order organizational measures and free recall. J. Exp. Psychol. 1974; 102:463–472.

Perfect TJ, Dasgupta ZRR. What underlies the deficit in reported recollective experience in old age? Mem. Cognit. 1997; 25:849–858.

Pfefferbaum A, Adalsteinsson E, Sullivan EV. Frontal circuitry degradation marks healthy adult aging: evidence from diffusion tensor imaging. Neuroimage. 2005; 26:891–899. [PubMed: 15955499]

Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav. Res. Methods. 2008; 40:879–891. [PubMed: 18697684]

Rannikko I, Paavola L, Haapea M, Huhtaniska S, Miettunen J, Veijola J, Murray GK, Barnes A, Wahlberg KE, Isohanni M, Jääskeläinen E. Verbal learning and memory and their associations with brain morphology and illness course in schizophrenia spectrum psychoses. J. Clin. Exp. Neuropsychol. 2012; 34:698–713. [PubMed: 22512417]

Raz N, Gunning FM, Head D, Dupuis JH, McQuain J, Briggs SD, Loken WJ, Thornton AE, Acker JD. Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. Cereb. Cortex. 1997; 7:268–282. [PubMed: 9143446]

Raz N, Rodrigue KM. Differential aging of the brain: patterns, cognitive correlates and modifiers. Neurosci. Biobehav. Rev. 2006; 30:730–748. [PubMed: 16919333]

Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, Dahle C, Gerstorf D, Acker JD. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cereb. Cortex. 2005; 15:1676–1689. [PubMed: 15703252]

Resnick SM, Pham DL, Kraut MA, Zonderman AB, Davatzikos C. Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. J. Neurosci. 2003; 23:3295–3301. [PubMed: 12716936]

Rowe EJ, Schnore MM. Item concreteness and reported strategies in paired-associate learning as a function of age. J. Gerontol. 1971; 26:470–475. [PubMed: 5107121]

Rundus D. Analysis of rehearsal processes in free recall. J. Exp. Psychol. 1971; 89:63–77.

Sachdev P, Wen W, Chen X, Brodaty H. Progression of white matter hyperintensities in elderly individuals over 3 years. Neurology. 2007; 68:214–222. [PubMed: 17224576]

Salat DH, Tuch DS, Greve DN, van der Kouwe AJW, Hevelone ND, Zaleta AK, Rosen BR, Fischl B, Corkin S, Rosas HD, Dale AM. Age-related alterations in white matter microstructure measured by diffusion tensor imaging. Neurobiol. Aging. 2005; 26:1215–1227. [PubMed: 15917106]

Sanders RE, Murphy MD, Schmitt FA, Walsh KK. Age differences in free recall rehearsal strategies. J. Gerontol. 1980; 35:550–558. [PubMed: 7400548]

Savage CR, Deckersbach T, Heckers S, Wagner AD, Schacter DL, Alpert NM, Fischman AJ, Rauch SL. Prefrontal regions supporting spontaneous and directed application of verbal learning strategies: evidence from PET. Brain. 2001; 124:219–231. [PubMed: 11133799]

Schmitt FA, Murphy MD, Sanders RE. Training older adult free recall rehearsal strategies. J. Gerontol. 1981; 36:329–337. [PubMed: 7229280]

Shipley WC. A self-administering scale for measuring intellectual impairment and deterioration. J. Psychol. 1940; 9:371–377.

Stricker JL, Brown GG, Wixted J, Baldo JV, Delis DC. New semantic and serial clustering indices for the California Verbal Learning Test - Second Edition: background, rationale, and formulae. J. Int. Neuropsychol. Soc. 2002; 8:425–435. [PubMed: 11939700]

Stuss DT, Alexander MP, Palumbo CL, Buckle L, Sayer L, Pogue J. Organizational strategies of patients with unilateral or bilateral frontal lobe injury in word list learning tasks. Neuropsychol. 1994; 8:355–373.

Verhaeghen P, Marcoen A. Production deficiency hypothesis revisited: adult age differences in strategy use as a function of processing resources. Aging Cognition. 1994; 1:323–338.

Weist RM. The role of rehearsal: recopy or reconstruct. J. Verb. Learn. Verb. Behav. 1972; 11:440–450.

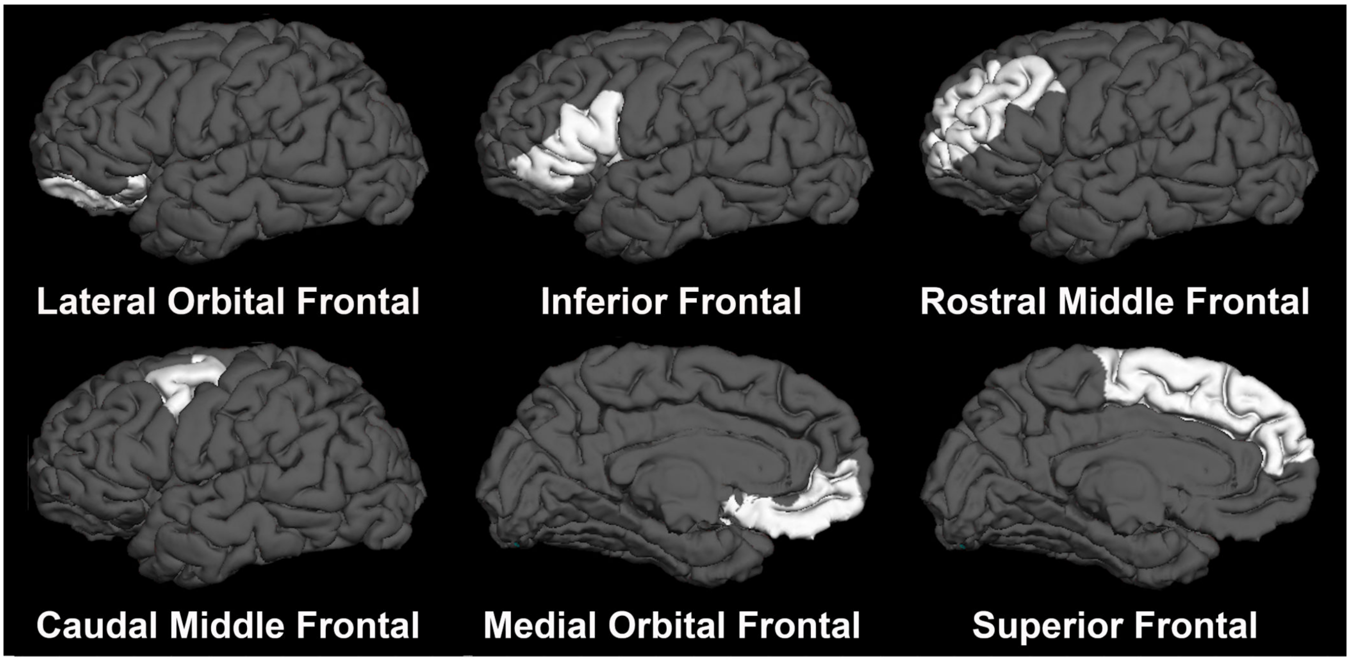

Figure 1.
Left hemisphere regions of interest (ROIs) displayed on the Freesurfer template brain.

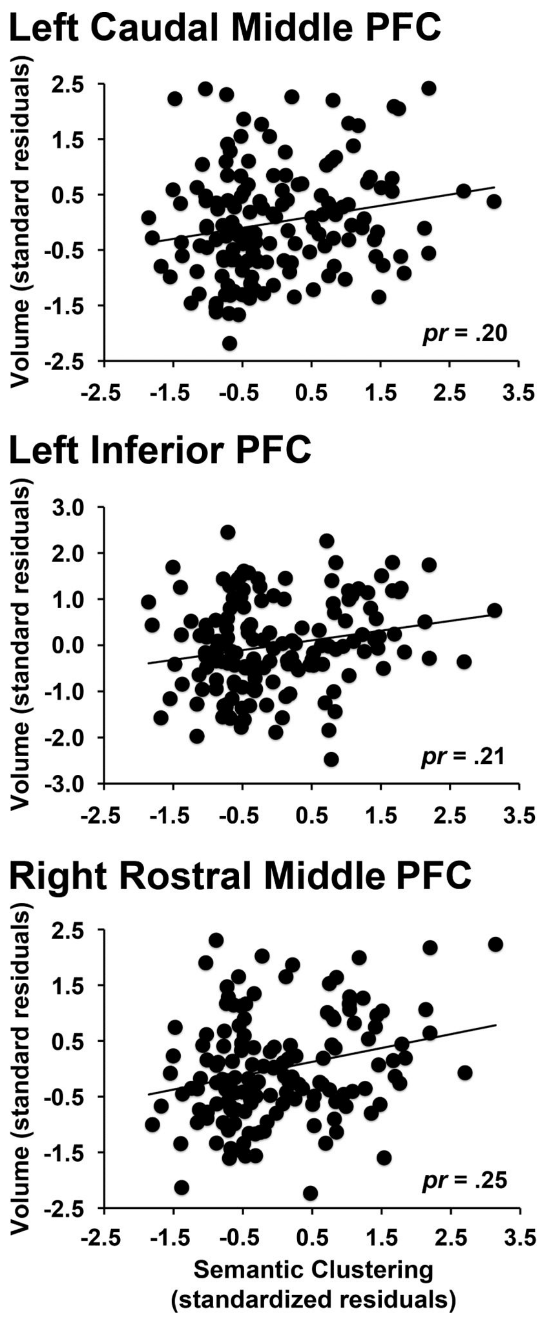

Figure 2.

Prefrontal cortex supports self-initiated semantic strategy use. Gray matter volume was positively correlated with semantic clustering in left caudal middle, left inferior, and right rostral middle frontal regions. Data are standardized residuals controlling for sex, gross cognitive status, and semantic processing ability. PFC = Prefrontal Cortex.

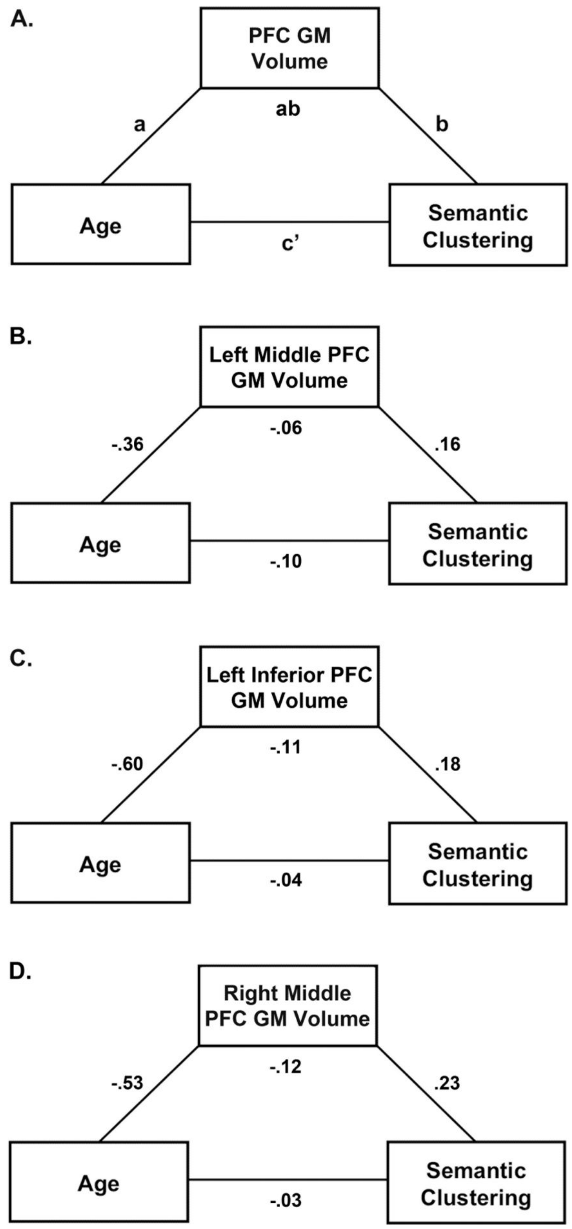

Figure 3.

Bilateral middle and left inferior frontal regions mediate age effects on semantic clustering. A) Representative, B) left caudal middle, C) left inferior, and D) right rostral middle frontal mediation models of the relationships among age, prefrontal regional gray matter volumes, and semantic clustering. The indirect effects of age on semantic clustering mediated by gray matter volume were significant in these regions while the direct effects of age on semantic clustering when controlling for gray matter volume were non-significant. a = The effect of age on prefrontal regional gray matter volume. b = The effect of prefrontal regional gray

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matter volume on semantic clustering controlling for the effect of age. ab = The indirect effect of age on semantic clustering mediated by prefrontal regional gray matter volume. c' = The direct effect of age on semantic clustering when controlling for prefrontal regional gray matter volume. PFC = Prefrontal Cortex.

Table 1

Participant characteristics.

	Mean	SD
Age	55.1	22.2
Female/Male	96/54	
Education[a]	4.1	1.5
MMSE[b]	29.1	0.9
Shipley Vocabulary[c]	34.6	3.8
CVLT-II Forward Serial Clustering	0.7	1.4
CVLT-II Semantic Clustering	2.0	2.4
CVLT-II Immediate Recall	54.1	10.8

MMSE = Mini-Mental State Exam. CVLT-II = California Verbal Learning Test - II.

[a]education code: 1 = less than high school graduate, 2 = high school graduate/GED, 3 = some college or trade, technical, or business school, 4 = Bachelor's degree, 5 = some graduate work, 6 = Master's degree, 7 = M.D., J.D., Ph.D., or other advanced degree.

[b]range = 27 - 30.

[c]n = 149.

Table 2

Partial correlations between prefrontal regional gray matter volumes and age and self-initiated strategy use.

Region	Age		Forward Serial Clustering		Semantic Clustering	
	pr [a]	***p***	***pr*** [a]	***p***	***pr*** [a]	***p***
Left Superior	−.69*	.000	.11	.091	.06	.242
Left Caudal Middle	−.36*	.000	−.10	.123	.20*	.008
Left Rostral Middle	−.54*	.000	.08	.172	.13	.062
Left Inferior	−.60*	.000	.06	.244	.21*	.005
Left Medial Orbital	−.24*	.002	−.02	.427	.09	.152
Left Lateral Orbital	−.45*	.000	.06	.225	.09	.132
Right Superior	−.58*	.000	.02	.387	.08	.162
Right Caudal Middle	−.29*	.000	.01	.470	.14	.045
Right Rostral Middle	−.53*	.000	−.02	.387	.25*	.001
Right Inferior	−.63*	.000	.09	.143	.07	.207
Right Medial Orbital	−.25*	.001	.00	.496	.11	.096
Right Lateral Orbital	−.54*	.000	−.00	.497	.17	.018

[a] Partial correlation coefficient controlling for sex, gross cognitive status, and semantic processing ability.

* indicates significant correlation after FDR multiple comparisons correction.

Table 3

Prefrontal mediation of the relationship between age and self-initiated semantic strategy use.

	Direct (c')			Indirect (ab)			
Region	**Coeff**	**SE**	***p***	**PE**	**SE**	**Lower**	**Upper**
Left Caudal Middle	−.096	.086	.270	−.059	.035	−.141	−.001*
Left Inferior	−.044	.101	.663	−.111	.058	−.231	−.001*
Right Rostral Middle	−.032	.094	.734	−.122	.058	−.247	−.018*

Direct Coeff = direct effect coefficient (unstandardized). Direct SE = standard error of direct effect coefficient. Direct p = p value for test of the significance of the direct effect ($\alpha = 0.05$). Indirect PE = mean of indirect effect point estimates (unstandardized). Indirect SE = estimate of the standard error of the indirect effect point estimates. Lower = lower bound of 95% confidence interval for indirect effect. Upper = upper bound of 95% confidence interval for indirect effect.

* significant indirect effect of age on semantic clustering mediated by gray matter volume.