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Research article

Prefrontal Lobe Gray Matter, Cognitive Control and Episodic Memory in Healthy Cognition

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Abstract: Objective: We combined neuropsychological and structural magnetic resonance imaging (MRI) measures to examine the neural and informational processes underlying episodic memory in healthy participants. **Method**: The Doors-and-People Test (DPT) provided a detailed assessment of episodic memory, including recall and recognition tasks of matched difficulty for social (e.g., people) and non-social (e.g., shape) content. The Wisconsin Card Sorting (WCS) test provided a measure of category learning that relies heavily on executive control and inhibition. A subset of participants also had available high-resolution, 3-T MRI gray matter volume studies of prefrontal cortex (PFC) parcellated into four regions: 1) frontal pole; 2) superior frontal gyrus; 3) middle frontal gyrus; and 4) inferior frontal gyrus. **Results:** Bivariate neuropsychological correlations revealed a highly statistically significant relationship of reduced WCS perseverative errors and stronger recall for people but not for shapes. By contrast, WCS perseveration did not correlate with any recognition measures. Hierarchical regression revealed that perseverative errors and people recall test scores combined to account for approximately 29.98% to 57.78% of the variance in left PFC gray matter volume. **Conclusions:** These results may point to an important role of the PFC in mnemonic process of retrieval inhibition in episodic memory for recall of social content in healthy participants.

Keywords: Neuropsychology; MRI; gray matter volume; executive attention; category learning

1. Introduction

Memory and attention have long been viewed as foundations of higher cognition and advanced learning. No less than the eminent psychologist William James (1890) wrote in his classic Principles of Psychology, "…we cannot deny that an object once attended to will remain in the memory, while one inattentively allowed to pass will leave no traces behind…"[1]. More recently, Nobel Prize recipient Eric Kandel (2008) cited the question of how attention and memory interact as one of the most important and intriguing topics for 21st century neuroscience. Contemporary neuropsychological studies have also underscored the importance of classifying memory and attention each into distinct forms that entail underlying processes and mechanisms supported by discrete neural systems [2–9]. However, much less research interest has typically been directed toward studying the interaction and interdependence of memory and attention in relation to higher order cognition [10].

Yet particular aspects of memory and attention do interact closely and may, in some specific conditions, reflect the same underlying informational processes supported by shared neural circuitry [10]. For example, empirical data and theoretical models have suggested that memory retrieval might reflect selective attention to internal representations [11,12], supported in large part by neural circuitry of the prefrontal cortex (PFC) [10,11]. Functional brain imaging studies have shown that these retrieval processes help form the PFC-mediated executive control system of working memory that governs effortful encoding, elaboration, and consolidation of new information [13,14]. These executive control processes have, in turn, been shown to be essential to working memory as well as to higher-order cognitive functions of remembering, abstraction, perception, and learning [15–19].

Still other studies have emphasized a specific role for inhibitory processes of cognitive control in episodic memory [20–22]. From this perspective, subroutines of the PFC may support retrieval inhibition processes of episodic memory [23,24]. These PFC-supported retrieval inhibition processes act to reduce interference by suppressing competing representations so that multiple elements of a past episode can be bound, accessed, selected, and ultimately recalled [25,24]. By contrast, working memory operations of the posterior parietal regions are thought to house content specific buffers that are crucial for active maintenance of information for on on-line computation [13].

Recently, we [26,27] examined neuropsychological performance on tests of intelligence and episodic memory in relation to PFC neural circuitry, as measured by magnetic resonance imaging (MRI) gray matter volumes of the medial orbital frontal cortex and rostral anterior cingulate cortex, and by Diffusion Tensor Imaging (DTI)-derived fractional anisotropy (FA) of the integrity of white matter pathways connecting these two regions. The findings of our studies pointed to distinct relationships between these basic structural parameters of PFC circuitry and cognition, with higher

memory scores strongly linked to increased left rostral anterior cingulate gray matter and higher intelligence scores to greater white matter integrity of posterior medial orbital frontal-rostral anterior cingulate cortex connections [26]. In a subsequent study, we [28] investigated whether the previously demonstrated PFC and intelligence relationship may reflect, in part, processes of cognitive control, as measured by well-known neuropsychological tests of executive function, specifically perseveration errors derived from the Wisconsin Card Sort (WCS) test [29] and Trails B [30] response time. Here the results provided support for the cognitive control hypothesis, and in fact hierarchical regression analyses showed that Trails B time and right middle orbital gyrus gray matter volume jointly accounted for approximately 32.95% to 54.82% of the variance in IQ scores.

The current study sought to extend these findings by examining the relationship of cognitive control, as measured by WCS perseverative errors, and episodic memory, as assessed by the Doors and Peoples Test (DPT) [31]. We first investigated in a large sample of healthy controls neuropsychological performance on the WCS and DPT indexes of both recall and recognition. The WCS is a widely-used measure of categorical learning that relies heavily on executive attentional processes of cognitive control and inhibition that may be assessed by perseverative errors [31–34]. The DPT, on the other hand, provides a comprehensive measure of episodic memory that includes recall and recognition tasks of matched difficulty for social (e.g., people) and non-social (e.g., shape) content [31,35,36]. Taken together, these neuropsychological measures provide a framework for the current study to explore the interaction of executive attention and episodic memory in general, and to test the specific hypothesis that cognitive control, as measured WCS perseverative errors, plays a critical role in recall but not recognition on the DPT.

The second aim of the current study is to examine how the PFC may influence the relationship of cognitive control and episodic memory. PFC neural circuitry has long been thought to play a key role in working memory, in general, and executive functions of control and inhibition, in particular, that are critical for learning and higher-order cognition [14]. For working memory, these PFC executive control functions work in concert with posterior parietal regions that house content-specific buffers that are crucial for active maintenance of information for on on-line computation [13]. More broadly, however, the PFC is considered an important hub of a wider, common brain network that is essential for healthy aging and cognitive development, and yet often very vulnerable and compromised by disease [37]. PFC neurons have distinct response properties that may be especially well suited for adaptive learning [38]. For example, single-cell recordings in monkeys have recently demonstrated that PFC neurons adapt their response properties to multiple processing demands and task parameters [39]. Such multidimensional or mixed selectivity is thought to provide the neural infrastructure for adaptive coding that supports the PFC role in higher-order cognition [38,39].

The current study thus employed 3-T magnetic resonance imaging (MRI) of the PFC, parcellated into four sub-regions: 1) frontal pole; 2) superior frontal gyrus; 3) middle frontal gyrus; and 4) inferior frontal gyrus. These MRI data allowed us to test empirically how individual

differences in PFC gray matter volume may be directly related to cognitive control and episodic memory. Indeed, to the extent that the MRI signal captures key cellular properties of the brain, individual differences in gray matter volume may reflect the density and number of neuronal bodies and dendritic expansions of PFC structures, which we now examined in relation to performance on neuropsychological tests of categorical learning and episodic memory.

2. Method

All participants (N = 146) were between the ages of 21 and 58 years, right-handed, native speakers of English, without histories of ECT, neurological illness, and without alcohol or drug abuse in the past 5 years. Recruited as healthy comparison subjects for prior neuropsychological studies of veterans with schizophrenia [40,26,27], all participants met Structured Clinical Interview for DSM-IV Axis I Disorders-Non-patient Edition (SCID-NP) criteria of no past or current Axis 1 and/or Axis II disorder [41,42]. Participants had a mean age of 40.63 years (SD = 9.09) and a mean education of 14.79 years (SD = 2.08). All participants gave informed consent. The neuropsychological tests were administered at the Boston VA Medical Center (Brockton, MA Division) and the MRI studies were conducted on a subset of participants (N = 27) at the Brigham and Women's Hospital in Boston, MA. MRI studies and neuropsychological testing were completed over the course of approximately three months. The research protocol was approved by the Institutional Review Board of the Boston VA Medical Center and Harvard Medical School.

2.1. Neuropsychological Measures

The DPT consists of four subtests: 1) verbal recall (Peoples test); 2) visual recall (Shapes test); 3) verbal recognition (Names test), and 4) visual recognition (Doors test). For the Peoples test of verbal recall, participants are asked to learn the names of four people (a doctor, a minister, a postman, and a paperboy). Participants view, one at a time, photographs of each of the four people with their name and their job printed underneath their picture. There are three learning trials. After viewing all four pictures and names, verbal recall is tested immediately after each of the three learning trails and then following a delay by asking the participants the name associated with each job (e.g., "What was the doctor's name"). For the Shapes test of visual recall, participants first copy each to-be-remembered line drawings presented singly. Participants are then asked to draw the four shapes from memory and unless performance is perfect, a second learning trial is administered in which all four drawings are again shown, singly, and then participants are asked to draw all four shapes from memory. A third learning trial is repeated if necessary, and immediate visual recall is calculated following each learning trial and delayed visual recall after a specified interval. For the Names test of verbal recognition, participants are instructed to remember a series of names, and are subsequently asked to pick the target name from a group of four names. For the Doors test of visual recognition, participants are presented pictures of doors, one at a time, and then are asked to identify target doors

from image arrays of four doors. Participants also completed a computerized version of the Wisconsin Card Sorting (WCS) test [29] a well-known test of category learning that relies heavily on executive attentional processes of inhibition and shifting set. The WCS dependent measures were the number of categories achieved (0–6), perseverative errors, and non-perseverative errors. There were 146 participants who completed the WCS, 64 of whom also completed the DPT.

2.2. MRI Processing

MRI studies were available for 27 healthy right-handed, participants who served as normal comparison subjects for prior MRI studies of veterans with schizophrenia [27]. The MRI processing is described in detailed in Ohtani et al. 2014. In brief, MR images were acquired with a 3-Tesla General Electric scanner (GE Medical Systems, Milwaukee, WI) at the Brigham and Women's Hospital in Boston, Massachusetts. A three-dimensional Fourier transformed spoiled gradient-recalled (fast SPGR) acquisition sequence yielded a coronal series of contiguous 1.0 mm images (TE = 3 msec, TR = 7.4 msec, TI = 600, 10 degree flip angle, field of view = 25.6 × 25.6 cm, acquisition matrix = 256 × 256, voxel dimension = 1 × 1 × 1 mm). Next, a XETA (extended Echo Train Acquisition) sequence yielded a series of contiguous axial T2-weighted images (TE = 80 msec, TR = 2500 msec, field of view = 25.6 × 25.6 cm, voxel dimensions = 1 × 1 × 1 mm). The T2 images from the XETA sequence were registered to the SPGR images. An expectation-maximization (EM) segmentation technique [43,44] was used to segment the images into three major tissue classes: gray matter, white matter, and CSF, using both SPGR and T2-weighted MR information as well as spatial priors. Intracranial contents (ICC) included all gray matter, white matter, and CSF volumes above the most inferior axial slice containing cerebellum, and was derived from the EM atlas segmentation. For manual tracing of the PFC ROI, images were realigned using the line between the anterior and posterior commissures and the sagittal sulcus to correct head tilt, and resampled into isotropic voxels ($1mm^3$). This realignment procedure was essential for precise and consistent ROI delineation. Using the segmented gray matter, the PFC ROIs were manually drawn on each coronal slice of the realigned SPGR according to the neuroanatomical definitions described below. To provide reliable delineation of the PFC ROI we used a software package for medical image analysis (3D slicer, http://www.slicer.org) operating on Linux workstations. This provided three-dimensional information, including parasagittal, axial, and coronal views, as well as user-selected angles for viewing.

2.3. Neuroanatomical definitions of PFC sub-regions

These PFC sub-regions are displayed in Figure 1.

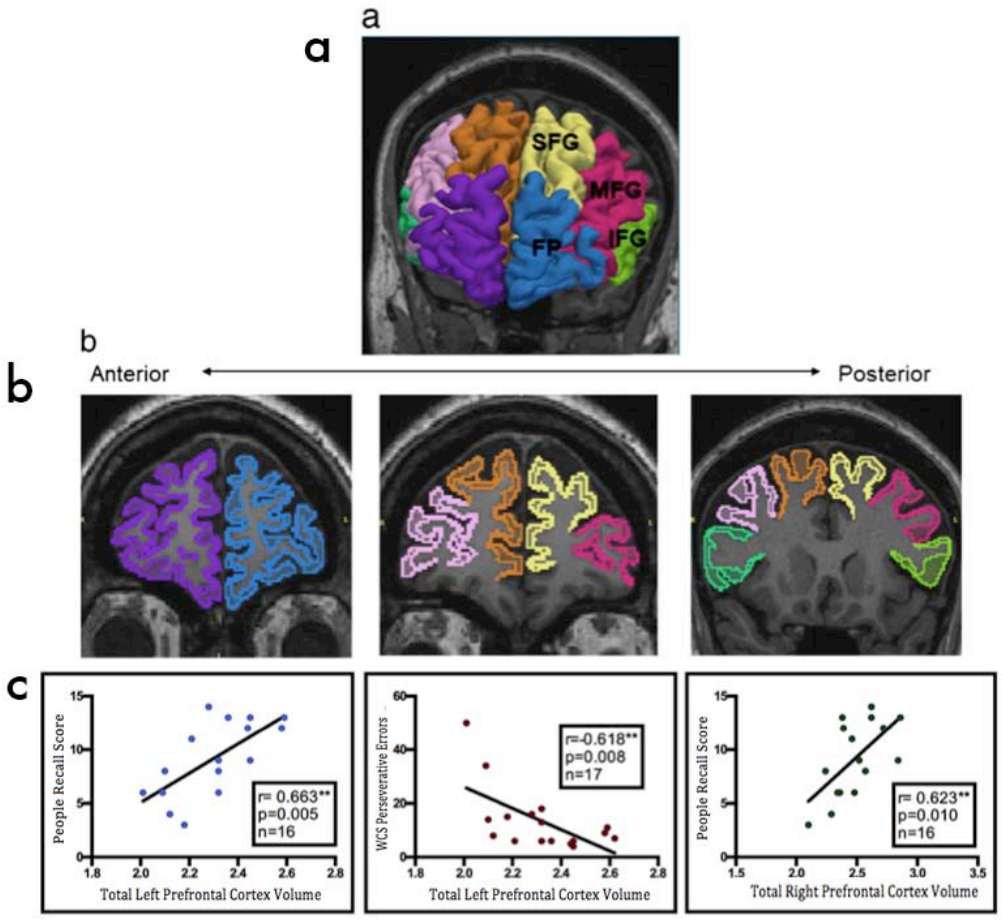

Figure 1. MR images of four prefrontal cortex (PFC) sub-regions. In each case, radiologic convention is followed with left hemisphere of participant shown on viewer's right. (a) 3-Dimensional reconstruction of four PFC sub-regions. ROIs are superimposed on coronal SPGR image: frontal pole (FP left: blue, right: purple), superior frontal gyrus (SFG left: yellow, right: brown), middle frontal gyrus (MFG left: red, right: pink), and inferior frontal gyrus (IFG left: light green, right: dark green). (b) ROIs in coronal slices of SPGR images. Color coding of (b) is the same of that of (a). Boundary definitions are described in Method. (c) Scatter plots of total left PFC gray matter volume with People recall scores and WCS perseverative errors; scatter plot of total right PFC gray matter volume and People recall scores.

2.3.1. Frontal Pole (FP)

The FP was defined as the most anterior 15 slices of brain (equivalent to 15.0 mm), because the anterior fusing of gyri made reliable gyral differentiation problematic. For example, when the lateral surfaces of the frontal lobe reach the frontal pole, the longitudinally oriented frontal gyri are interrupted by transverse folds: the transverse frontopolar gyri. The FP extends onto the lateral, orbital and medial surfaces of the cortex.

2.3.2. Superior Frontal Gyrus (SFG)

The posterior border of the SFG was determined by the most posterior slice that contained the genu of corpus callosum. The inferior boundary was the superior frontal sulcus that was observed on the lateral aspect of the cerebral hemisphere. When the sulcus was interrupted into two or three segments, the most-inferior one was chosen as a boundary on each coronal slice. The cingulate sulcus formed the posterior part of the infero-medial boundary of the SFG. When the cingulate sulcus had a double-parallel configuration, the most inferior one was selected as a boundary on each coronal slice. The superior rostral sulcus formed the anterior part of the infero-medial boundary. If the superior rostral sulcus was unconnected to the cingulate sulcus, the inferior boundary of the SFG was determined by extending the posterior aspect of the superior rostral sulcus to intersect the cingulate sulcus on coronal slice. The anterior border of the SFG was determined by the most posterior slice of the FP.

2.3.3. Middle Frontal Gyrus (MFG)

The superior boundary of the MFG was formed by the superior frontal sulcus. The inferior boundary of the MFG was formed by the inferior frontal sulcus. When the inferior frontal sulcus was interrupted into two or three segments, the most-superior one was chosen as a boundary on each coronal slice. In the more anterior part, the lateral orbital sulcus formed the inferior boundary. When the lateral orbital sulcus could not be visualized in consecutive coronal slices, the tracing in the coronal section that last contained the sulcus was extended onto the neighboring slices. The inferior frontal sulcus also formed the inferior boundary of the MFG in the anterior part when the inferior frontal sulcus joined the lateral orbital sulcus, and these sulci intersected at a coronal plane anterior to the FP. We did not adopt the frontomarginal sulcus as a landmark, since it was highly variable and could not be reliably defined. The posterior boundary of the MFG was formed by the most posterior slice that contained the genu of corpus callosum as same as that of the SFG. The anterior border of the MFG was determined by the most posterior slice of FP.

2.3.4. Inferior Frontal Gyrus (IFG)

The superior boundary of the IFG was formed by the inferior frontal sulcus. The posterior boundary of the IFG was the most posterior slice that contained the genu of corpus callosum as same as that of the SFG and the MFG. The anterior boundary of the IFG was defined by the most anterior slice that contained the inferior frontal sulcus. The inferior boundary of the IFG consisted of the lateral orbital sulcus in the anterior part and the superior circular sulcus of insula in the posterior part. When both the lateral orbital sulcus and the superior circular sulcus were visualized on each coronal slice, the superior circular sulcus was chosen as a boundary. The guidelines to be followed when the

lateral orbital sulcus could not be visualized in consecutive coronal slices are described above in the MFG ROI description.

All manual delineations were performed by T.O., who was blinded to subject diagnosis. The intra-class correlation coefficients based on five randomly-selected cases were 0.98 for the left FP, 0.97 for the right FP, 0.96 for the left SFG, 0.97 for the right SFG, 0.95 for the left MFG, 0.96 for the right MFG, 0.95 for the left IFG, and 0.95 for the right IFG.

2.4. Statistical Analyses

MRI gray matter volumes and neuropsychological test scores (WCS, DPT) were submitted to separate within-subjects analyses of variance (ANOVA). Pearson product moment correlation tested MRI-neuropsychological associations. We then conducted parametric, hierarchical regression analyses to partition the total variance of PFC gray matter volume among the independent variables of the WCS and DPT. To examine the unique contribution of the WCS and DPT to PFC gray matter volume, we computed partial (*r*p) and semi-partial (*r*sp) correlations in a series of hierarchical regression analyses, allowing us to evaluate significant univariate relationships by partitioning the total variance of the dependent variable (e.g., PFC gray matter volume) among the independent variables (WCS, DPT). The squared partial correlation (*r*p 2) represented the proportion of variance of a PFC gray matter volume explained by a specific neuropsychological measure (e.g., WCS) after the effects of the other neuropsychological measure (e.g., DPT) had been removed from both PFC gray matter volume and the other neuropsychological measure (e.g., WCS) [45]. Calculation of this statistic allowed us to answer the question, “What proportion of the remaining variance in PFC gray matter volume (i.e., that which is not estimated by the other independent variables in the equation) is uniquely estimated by this neuropsychological measure?”

In contrast, the square of the semi-partial correlation (*r*sp2) estimated the amount variance of PFC gray matter volume uniquely shared with a particular neuropsychological measure after the effects of all other neuropsychological measures on that particular measure had been removed [45]. It is labeled semi-partial because the effects of the other independent variables have been removed from the independent variable but not from the dependent variable. In conjunction with the other linear regression statistics, partial and semi-partial correlations provided a comprehensive picture of how neuropsychological measures (DPT, WCS) relate to PFC gray matter volume when collinearity is controlled. In all regression analyses, the *F*-to-enter probability was 0.05, and the *F*-to-exclude probability was .10. Significance levels were two-tailed.

3. Results

Table 1 presents the neuropsychological scores for the DPT and WCS. For the DPT, ANOVA with two within-subjects factors of memory (recall, recognition) and content (verbal, visual) revealed significant effects for memory, F (1, 67) = 14.48, $p < 0.001$, Partial Eta Squared = 0.178, content,

F (1, 67), = 9.06, $p < 0.004$, Partial Eta Squared = 0.397, and the interaction of memory x content, F (1, 67) = 44.04, $p < 0.001$, Partial Eta Squared = 0.397. Follow-up planned comparisons using paired t-tests revealed overall higher scores for recognition than recall, t (67) = −3.73, $p < 0.001$, specifically for verbal recognition of names in comparison to verbal recall of peoples' names and occupations, t (67) = −6.84 $p < 0.001$ By contrast, scores did not differ significantly for visual recognition of doors and visual recall of shapes, t (67) = 1.49, $p = 0.141$. For the WCS, participants completed on average 5.29 categories (SD = 1.51), with similar scores for perseverative (M = 12.36, SD = 11.81) and non-perseverative (M = 12.14, SD = 11.12) errors (see Table 1).

Table 1. Demographic information and neuropsychological scores for research participants.

Demographic Information	Mean (± Standard Deviation)
Age of Testing	39.49 ± 9.930
Education	14.828 ± 2.0827
SES	2.31 ± 1.022
Doors-and-People Test (DPT)	
Recall	
People	9.60 ± 3.645
Shapes	10.49 ± 3.030
Total	20.16 ± 5.611
Recognition	
Names	12.76 ± 3.168
Doors	9.87 ± 3.390
Total	22.65 ± 5.574
Wisconsin Card Sorting (WCS)	
Categories Completed	5.32 ± 1.476
Perseverative Errors	12.36 ± 11.809
Non-perseverative Errors	12.14 ± 11.115

As shown in Table 2, bivariate correlations indicated that as WCS perseverative errors decreased, DPT recall scores increased for total recall ($r = −0.299$, $p = 0.017$), verbal recall ($r = −0.316$, $p = 0.011$) and recall for people (r = −0.341, $p = 0.006$). Fewer WCS perseverative errors also correlated very strongly with lower rates of visual forgetting on the DPT ($r = −0.349$, $p = 0.005$). Hierarchical regression indicated that among the WCS measures (perseverative errors, non-perseverative errors, categories completed), only perseverative errors (standardized beta = −0.480, t = −2.19, $p = 0.032$) contributed significantly and specifically to DPT memory recall, uniquely accounting for approximately 7.08% to 7.40% of the variance in performance. In addition, for recall of people, perseverative errors (standardized beta = 0.648, t = −3.05, $p = 0.003$) also contributed significantly and specifically to performance, uniquely accounting for approximately 12.96% to 13.40% of the variance in scores for this measure of episodic memory.

Table 2. Correlations of DPT scores and WCS performance measures.

	Doors-and-People Test (DPT)					
		Recall			Recognition	
Wisconsin Card Sorting	*People*	*Shapes*	*Total*	Names	Doors	Total
Categories Completed	*0.176*	*0.122*	*0.188*	0.097	0.003	0.059
Perseverative Errors	*−0.341***	*−0.149*	*−0.299**	−0.171	−0.143	−0.186
Non-Perseverative Errors	*−0.192*	*−0.146*	*−0.206*	−0.46	−0.048	−0.057

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$

Table 3 presents PFC gray matter volumes. ANOVA with two within-subjects factors of region (frontal pole, superior frontal gyrus, middle frontal gyrus, and inferior frontal gyrus) and side (left, right) revealed highly significant effects for region, F (3, 78) = 205.29, $p < 0.001$, Partial Eta Squared = 0.888, side, F (1, 26) = 30.96, $p < 0.001$, Partial Eta Squared = 0.544, and for the region x side interaction, F (3, 78) = 9.75, $p < 0.001$, Partial Eta Squared = 0.273. Follow-up planned comparisons using paired t-tests showed significantly greater right than left gray matter volume for total PFC ($p < 0.001$), particularly for frontal pole ($p < 0.001$) and middle frontal gyrus ($p = 0.002$).

Table 3. Prefrontal Cortex Gray Matter Volumes.

PFC sub-region	**Mean (± Standard Deviation)**
Frontal Pole	
Left	0.5048 (± 0.07958)
Right	0.5974 (± 0.08295)
Superior Frontal Gyrus	
Left	0.7193 (± 0.06498)
Right	0.7100 (± 0.07874)
Middle Frontal Gyrus	
Left	0.6952 (± 0.06560)
Right	0.7485 (± 0.08108)
Inferior Frontal Gyrus	
Left	0.4015 (± 0.06893)
Right	0.4170 (± 0.06736)

Note. Values are means plus or minus standard deviations.

Table 4 presents the correlations of PFC gray matter volumes DPT measures of episodic memory for the subset of participants who had available MRI DPT (n = 16). As shown in Table 4, prefrontal gray matter volumes correlated significantly with recall but not with recognition DPT scores. For the DPT, higher recall but not recognition scores correlated very significantly with increased gray matter volumes for right PFC (r = 0.634, $p = 0.008$), particularly right MFG

(r = 0.706, p = 0.002). As also shown in Table 4, higher recall scores for people but not shapes correlated very significantly with increased gray matter volume for left PFC (r = 0.663, p = 0.005), right PFC (r = 0.623, p = 0.01), right MFG (r = 0.678, p = 0.004), and right IFG (r = 0.610, p = 0.01). Figure 1 presents the scatter plots depicting the significant correlations for people recall scores with total left (r = 0.663, p = 0.005) and right (r = 0.623, p = 0.01) PFC gray matter volume. For the WCS test, increased left PFC gray matter volume correlated very significantly with more categories completed (r = 0.628, p = 0.007) and fewer perseverative (r = −0.618, p = 0.008) and non-perseverative (r = −0.628, p = 0.007) errors. Figure 1 presents the scatter plot for the significant correlation of perseverative errors and total left PFC gray matter volume (r = −0.618, p = 0.008).

Table 4. Correlations of DPT scores and prefrontal gray matter volumes.

	Doors-and-People Test (DPT)					
	Recall			Recognition		
	People	Shapes	Total	Names	Doors	Total
Frontal Pole						
Left	0.580*	−0.15	0.313	−0.22	−0.387	−0.318
Right	0.430	0.191	0.417	−0.376	−0.107	−0.273
Superior Frontal Gyrus						
Left	0.199	0.437	0.403	−0.196	0.288	0.025
Right	−0.006	0.354	0.21	0.116	0.463	0.294
Middle Frontal Gyrus						
Left	0.482	0.184	0.449	0.223	0.304	0.279
Right	0.678**	0.383	0.706**	0.214	0.325	0.284
Inferior Fontal Gyrus						
Left	0.423	−0.34	0.091	0.235	−0.041	0.118
Right	0.610*	−0.14	0.341	0.379	0.192	0.316
Total Prefrontal Cortex						
Left	0.663**	0.057	0.498*	−0.008	0.03	0.01
Right	0.623**	0.327	0.634**	0.112	0.331	0.227

** Correlation is significant at the 0.01 level (2-tailed); * Correlation is significant at the 0.05 level (2-tailed).

Last, as a planned follow-up to these bivariate correlations, we used hierarchical regression to quantify the specific and joint contributions of these two neuropsychological measures to PFC gray matter volume. Specifically, based on bivariate neuropsychological correlations of DPT and WCS measures reported above, we entered WCS perseverative errors and people recall as predictors of left PFC gray matter volume. WCS perseverative errors produced a significant R square change of 0.367 (F = 7.54, df = 1, 13, p = 0.017) and people recall scores produced a significant R square change of 0.238 (F = 7.23, df = 1, 12 p = 0.02). Left PFC gray matter volume and WCS perseverative errors revealed a partial correlation value of -0.449 and a semi-partial correlation value of −0.316. These values indicated that WCS perseverative errors uniquely accounted for approximately 9.98% to 20.2%

of the variance in left PFC gray matter volume. Left PFC gray matter volume and people recall scores revealed a partial correlation value of 0.613 and a semi-partial correlation value of 0.448. These values indicated that people recall test scores uniquely accounted for approximately 20.01% to 37.58% of the variance in left PFC gray matter volume. Together, perseverative errors and people recall test scores combined to account for approximately 29.98% to 57.78% of the variance in left PFC gray matter volume.

4. Discussion

The neuropsychological results provided strong empirical evidence linking category learning and declarative episodic memory in healthy cognition. In particular, the data pointed to a rather specific neuropsychological relationship of reduced perseverative errors for WCS category learning with increased scores on the DPT of episodic recall. Indeed, the specificity of this relationship is evident by the absence of any significant correlation of perseverative errors and recognition, even though DPT recognition and recall measures are psychometrically matched in difficulty [31]. Moreover, this pattern is consistent with functional brain imaging studies that have shown greater dependence on left PFC-related retrieval inhibition processes for recall in comparison to recognition tasks of memory [46]. Similarly, neither WCS measures of categories completed nor non-perseverative errors correlated with any of the DPT measures of episodic recall. For example, hierarchical regression results indicated that only WCS perseverative errors contributed significantly and specifically to recall of people, uniquely accounting for approximately 12.96% to 13.40% of the variance in scores on this measure of episodic recall.

MRI-neuropsychological correlations also revealed evidence of significant brain-behavior relationships between PFC gray matter volumes and WCS indexes and DPT measures of recall. That is, for the WCS measure of category learning, increased PFC gray matter volumes correlated with the three performance indexes of more categories completed and with fewer errors of both perseveration and non-perseveration. These strong correlations are of course entirely consistent with a well-established body of evidence, spanning neuropsychological, neurophysiological, and neuroimaging studies, and all ascribing to the PFC a key role in executive functions that are central to category learning, as was measured here by the WCS test [14]. By comparison, for the DPT indexes, the PFC correlations pointed to a more selective pattern than that evident with the WCS. Here, the correlations with PFC gray matter volumes were restricted to DPT recall measures, and there were no correlations of PFC gray matter volumes and recognition measures, which previous studies have suggested may be specifically associated with medial temporal lobe structures, particularly the hippocampus [35,47].

The current study showed that healthy individuals with greater left PFC gray matter volume made significantly fewer perseverative errors on the WCS and scored higher on the DPT of recall, especially for a task that required associative learning of peoples' names and their occupations. In addition, we used hierarchical regression to quantify the specific and joint contributions of WCS

perseverative errors and recall of people to PFC gray matter volume. These results showed that perseverative errors and people recall test scores combined to account for approximately 29.98% to 57.78% of the variance in left PFC gray matter volume. As such, these data provided strong empirical support that a very sizeable percentage of variance in MRI gray matter PFC volume was specifically and directly explained by these two neuropsychological measures.

The current study aimed to test the hypothesis that cognitive control, as indexed by WCS perseverative errors, plays a critical role in the demonstrated relationship of PFC and episodic memory. From this perspective, PFC circuitry supports specific cognitive control processes related to retrieval inhibition [23]. These inhibitory processes [48] in turn act to reduce interference by suppressing competing representations so that multiple elements of a past episode can be bound, accessed, selected, and ultimately recalled [25]. Thus, for the current study, WCS perseverative errors may have indexed the efficiency of such left PFC-supported inhibitory processes that in turn facilitated effective retrieval of past episodes as measured by overall recall on the DPT.

The current results also suggested that left PFC-supported retrieval inhibitory processes may play an especially important role in verbal paired associative learning of peoples' names and their occupations. Indeed, the results indicated this relationship held only for verbal memory for peoples' names and occupations but not for visual memory for shapes. Whether PFC involvement demonstrated here was related to the social content of learning peoples' names and jobs is unclear. We previously examined in healthy participants the relationship of social cognition, which included the DPT, with MRI PFC gray matter volume, specifically comparing middle orbital and lateral orbital gyri [40]. Results from this prior study pointed to PFC involvement in episodic memory for both people and shapes [40]. Both the current and previous studies were correlational in design and did not provide sufficient experimental control to test the role of the hypothesized PFC-supported retrieval inhibition in social memory. An experimental approach with fMRI is needed to provide a stronger and more direct test of the role of PFC in social memory. In a similar vein, the current findings are somewhat ambiguous regarding the role of right PFC structures in retrieval inhibition processes of episodic memory. Here the data pointed to a strong relationship between overall DPT recall with not only total left but also total right PFC gray matter ($r = 0.634$, $p < 0.01$). By contrast, WCS perseverative errors correlated only with total left but not total right PFC gray matter. It is not clear why right PFC gray matter failed to correlate with executive cognitive control processes that are presumed to be indexed by WCS perseverative errors and are theorized to play a key role in general retrieval inhibition process of episodic memory.

Nevertheless, the findings of the current study helped to quantify and characterize the specific contribution of PFC to episodic memory in healthy cognition. However, the cognitive control processes of the PFC do not operate in isolation but rather work in concert with medial temporal lobe structures and together these interactions allow for successful remembering [49]. The PFC is functionally and anatomically diverse with extensive reciprocal connections with sensory association cortices, including temporal and parietal regions and many subcortical structures [49]. Most

prominent among these are the large cortico-cortical direct reciprocal connections between the PFC and medial temporal lobe structures, traveling through the uncinate fasciculus, anterior temporal stem, and anterior corpus callosum, and providing the structural pathways for encoding-retrieval interactions that largely underlie the dynamics of declarative episodic memory [50]. These connections may help to form a distributed functional network of regions involved in episodic memory of which PFC and medial temporal lobe are key hubs [49]. In this neural model, medial temporal lobe centers are thought to play a critical role in binding stimuli into specific episodes that are stored, later retrieved through processes supported by PFC, and ultimately consciously recollected [51,49]. In fact, we [50] previously showed that medial temporal lobe structures, specifically hippocampal gray matter volume and fornix white matter integrity correlated with higher DPT recall but not recognition scores in healthy participants. Taken together, the current findings along with our previous study [50] linked individual differences in recall memory to normal structural variation in both medial temporal lobe and PFC regions. As such, these data provide evidence of how the PFC and the medial temporal lobe structures help to form a distributed functional network of brain regions involved in declarative episodic memory.

In summary, the results of the current study showed how normal variation in brain structure may influence neuropsychological functioning in healthy cognition. These results add to a growing body of evidence generated from studies of individual differences in structural brain imaging and healthy cognition that have helped to elucidate some of the critical neurodevelopmental [52], neuroanatomical [53] and information processing [54] mechanisms underlying normal variation in performance on neuropsychological tests. However, the current study is limited by the correlational nature of the research design, the relatively small number of participants with available brain magnetic resonance studies, and the reliance on one neuroimaging technique. Future studies are needed combining structural and functional brain imaging with neuropsychology to test further the hypothesized relationship demonstrated here linking increased prefrontal lobe gray matter volume with both stronger cognitive control and better episodic recall.

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Conflict of Interest

The authors have no conflict of interest.

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