

Individual differences in regional prefrontal gray matter morphometry and fractional anisotropy are associated with different constructs of executive function

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Abstract Although the relationship between structural differences within the prefrontal cortex (PFC) and executive function (EF) has been widely explored in cognitively impaired populations, little is known about this relationship in healthy young adults. Using optimized voxel-based morphometry (VBM), surface-based morphometry (SBM), and fractional anisotropy (FA) we determined the association between regional PFC grey matter (GM) morphometry and white matter tract diffusivity with performance on tasks that tap different aspects of EF as drawn from Miyake et al.'s three-factor model of EF. Reductions in both GM volume (VBM) and cortical folding (SBM) in the ventromedial PFC (vmPFC), ventrolateral PFC (vlPFC), and dorsolateral PFC (dlPFC) predicted better common EF, shifting-specific, and updating-specific performance, respectively. Despite capturing different components of GM morphometry, voxel- and surface-based findings were highly related, exhibiting regionally overlapping relationships with EF. Increased white matter FA in fiber tracts that connect the vmPFC and vlPFC with posterior regions of the brain also predicted better common EF and shifting-specific performance, respectively. These results suggest that the neural mechanisms supporting

distinct aspects of EF may differentially rely on distinct regions of the PFC, and at least in healthy young adults, are influenced by regional morphometry of the PFC and the FA of major white matter tracts that connect the PFC with posterior cortical and subcortical regions.

Keywords MRI · Anatomy · PFC · Executive function · Grey matter · White matter

Introduction

Executive function (EF) is widely characterized as higher-order cognitive processes enabling one to flexibly control goal-oriented behavior. Despite the vital role of EF and its ubiquity in behavioral control, there exists an incomplete understanding of the psychological constructs and neural mechanisms supporting EF. An abundance of lesion studies and those employing functional MRI implicates the prefrontal cortex (PFC) as the main neuroanatomical region involved in EF (Alvarez and Emory 2006; Jurado and Rosselli 2007; Miller and Cohen 2001; Stuss and Alexander 2000), though the relationship between individual differences in regional PFC morphometry and executive function remains underspecified.

Studies examining the associations between grey matter (GM) morphometry and EF have yielded variable results, suggesting highly complex, dynamic relationships between multiple morphometric measures and EF, which are modulated by age and clinical status. Of these studies, the vast majority has interrogated GM morphometry/EF relationships in cognitively impaired, clinical and aging populations, leaving the nature of these relationships in healthy young adults widely unexplored. The general trend observed across studies indicates that adults with a variety

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of psychopathologies, neurological disorders, and typical age-related deficits exhibit abnormal PFC GM morphometry including volume, surface area, cortical thickness and folding, as well as fractional anisotropy (FA) measured via diffusion tensor imaging (DTI), which has been related to white matter integrity, compared to healthy controls (Antonova et al. 2005; Bonilha et al. 2008; Dineen et al. 2009; Duarte et al. 2006; Fornito et al. 2009; Hartberg et al. 2010; Koutsouleris et al. 2010; Kuperberg et al. 2003; Li et al. 2010; Makris et al. 2008; McAlonan et al. 2009; Medina et al. 2006; Nakamura et al. 2008; Radua and Mataix-Cols 2009; Rüsçh et al. 2007; Vasic et al. 2008; Zhang et al. 2013). Importantly, the degree of neuroanatomical abnormalities has been shown to relate to EF performance, with less volume/density, cortical thickness, cortical folding, and FA predicting worse performance on a range of EF-tapping paradigms, across a number of disorders (Bonilha et al. 2008; Depue et al. 2010; Duarte et al. 2006; Dufour et al. 2008; Hartberg et al. 2010; Huey et al. 2009; Keller et al. 2009; Koutsouleris et al. 2010; Matsui et al. 2007; Nagano-Saito et al. 2005; Pa et al. 2010; Schmitz et al. 2008; Vasic et al. 2008; Voineskos et al. 2012). Similarly, in non-clinical aging populations, when compared to younger controls, there is a general reduction in cortical volume/density, surface area, thickness, and folding (Hogstrom et al. 2013), with the degree of these reductions having been shown to predict EF performance (Burzynska et al. 2012; Duarte et al. 2006; Kochunov et al. 2009; Newman et al. 2007; Ruscheweyh et al. 2012).

Though the aforementioned clinical and aging work is highly informative, very few, if any, studies have examined how individual differences in multiple measures of PFC GM morphometry and FA relate to individual differences in discrete EF abilities in a healthy, young adult population. The current investigation sets out to explore these relationships in healthy young adults to enhance our basic understanding of the neural mechanisms supporting cognition and EF. Moreover, this line of research has the potential to contribute to the identification of biomarkers for psychiatric or neurological disruptions observed in early adulthood by providing normative information on the relationship between brain anatomy and EF, an ability affected across a large number of neurological and psychiatric disorders.

In the few studies linking GM morphometry or FA to EF in healthy adult populations, researchers have used both general (e.g., composite task and questionnaire variables) and single-task measures of EF, employing commonly used paradigms putatively tapping a number of EF constructs. These studies report relationships of PFC GM morphometry and FA with performance on EF tasks, but generally yield inconsistent results beyond the basic observation that correlations exist. There is little consensus with regard to

the specific regions of PFC associated with individual differences in discrete EFs and, even more basically, with regard to the direction of the relationship between neuroanatomical variables and performance on EF tasks (i.e., in some cases increases in GM morphometry or FA is predictive of better EF performance and in other cases the relationship is reversed). For example, some results regarding GM volume/density in relation to EF in healthy adults (often healthy control samples) have shown that increased GM volume/density is associated with better EF performance (Elderkin-Thompson et al. 2008, 2009; Etinger et al. 2005; Gunning-Dixon and Raz 2003; Head et al. 2009; Kaller et al. 2012; Nakamura et al. 2008; Newman et al. 2007; Ruscheweyh et al. 2012; Zimmerman et al. 2006), while others show that decreased GM volume/density is associated with better EF performance (Duarte et al. 2006; Elderkin-Thompson et al. 2008, 2009; Gautam et al. 2011; Kaller et al. 2012; Koutsouleris et al. 2010; Raz et al. 1998; Salat et al. 2002; Takeuchi et al. 2012a, b). Though very few exist, studies examining the relationships of neuroanatomical features other than volume/density with EF in healthy adults similarly do not implicate common, overlapping regions across studies, but do converge on the general direction of neuroanatomy/EF relationships. Such studies suggest that increased cortical thickness (Burzynska et al. 2012; Hartberg et al. 2010; Kochunov et al. 2009) and greater FA values (Deary et al. 2006; Grieve et al. 2007; Murphy et al. 2007; Nagy et al. 2004) are both associated with better EF performance, though the relationship of other morphometric features, such as cortical surface area and cortical folding, with EF remains unaddressed.

To date, no single study has evaluated the relative contributions of multiple neuroanatomical measures, including voxel, surface, and tensor-based measures, to performance on discrete EF constructs in healthy young adults. Previous studies have generally evaluated relationships between voxel-based measures of GM volume/density and EF, often ignoring more precise, surface-based measures of cortical morphometry, like cortical surface area, cortical thickness, and cortical folding, which may contribute to and/or better account for associations between morphometry and EF than voxel-based measures alone. Additionally, previous studies demonstrate considerable variability in the tasks employed to measure EF, yet they often fail to differentiate distinct EF constructs from each other, as well as from more general cognitive processes, such as attention, perception, and motor speed (for a discussion of the differentiation amongst EF constructs and their relationship to other more general cognitive processes, see Miyake et al. 2000). To address these issues, the current study employs the unity and diversity model of EF of Miyake et al. (2000) to help guide the investigation of the relationship between specific EF constructs, and

multiple measures of prefrontal neuroanatomy, including voxel and surface-based morphometry, as well as a tensor-based measure of white matter tract diffusivity, FA.

The unity and diversity model, which was derived from identifying correlations in performance across a wide variety of EF tasks across individuals (Miyake et al. 2000, Miyake and Friedman 2012), posits that EF is differentiated into at least three distinct constructs; a common EF factor (unity), which most likely represents the ability to maintain a task set, and two specific factors that capture construct-specific EF performance over and above what is accounted for by common EF (diversity), namely the ability to shift sets (shifting-specific), and the ability to update working memory (updating-specific) (Miyake and Friedman 2012).

Using both whole brain and region of interest (ROI) VBM, SBM, and DTI analysis techniques, we aimed to test the hypothesis that individual differences in performance on the three EF constructs are related to variations in GM morphometry and FA. Though we predict that neuroanatomical features of the PFC will relate to EF performance, it is difficult to draw specific hypotheses regarding the exact association that we expect to observe between individual differences in performance on EF tasks and GM morphometry or FA. One possibility is that individual differences in behavioral performance will correlate with variation of GM morphometry in brain regions similar to those identified by prior meta-analyses of brain activation as measured by fMRI. Therefore, we predict that individual differences in common EF, updating and shifting will be associated with GM morphometry in the lateral PFC (IPFC) (Banich 2009; Collette et al. 2005; Duncan and Owen 2000; Petrides 2005; Wager and Smith 2003), although indications also suggest that shifting may be associated with medial regions as well (Wager et al. 2004; Derrfuss et al. 2005). Conversely, brain regions sensitive to the individual differences in GM–EF relationships may be different than brain regions associated with general group-level activations as measured by fMRI, in which case EF performance may relate to more disparate regions of GM outside of the PFC.

With regard to FA, the degree to which prefrontal regions underlying EF can exert control on posterior and/or subcortical regions may depend on the anatomical connections between such regions. Therefore, we would expect that FA in a variety of tracts connecting frontal to posterior and/or subcortical regions may influence individual differences in EF. These include the superior longitudinal fasciculus (SFL), inferior longitudinal fasciculus (IFL), superior fronto-occipital fasciculus, (sFOF), inferior fronto-occipital fasciculus, (iFOF), genu of corpus callosum (genu), cingulum bundle (CCg) and the anterior limb of the internal capsule (ALIC). We additionally set out to

determine whether individual differences in the relationship of GM morphometry and FA of specific fiber tracts co-occur with variation in EF performance.

Methods

Participants

A total of 68 healthy, right-handed individuals (35 females) were included in the study (mean age 21.5, SD 2.3 years). Data from all individuals were included in the optimized VBM analyses, although five participants were excluded from the DTI analyses due to incorrect scanning parameters and five participants that had outlying values for surface-based measurements [$N(\text{VBM})$ 68, $N(\text{DTI})$ 63, $N(\text{SBM})$ 63]. Data collection for each participant involved two sessions. During the first, participants completed a behavioral battery of EF tasks, and in the second, which on average occurred a month later, high-resolution structural and resting state MR scans were obtained (the latter of which is discussed in another report; Reineberg et al., in revision). All participants were either undergraduate or graduate students at the University of Colorado (CU), Boulder. Participants were recruited through an online, CU-Boulder-based recruitment website, and were paid for their participation. Written informed consent was obtained prior to both experimental sessions and all experimental protocols were approved by CU-Boulder's Institutional Review Board prior to data collection.

Executive function battery

In order to best capture discrete EF constructs, we employed tasks previously shown to load highly on the three constructs posited in the unity and diversity model of EF: common EF, shifting-specific, and updating-specific processes (Miyake et al. 2000, Miyake and Friedman 2012; Friedman et al. 2006). The tasks are as follows.

Anti-saccade task (AS) (adapted from Roberts et al. 1994)

This task measures a person's ability to actively maintain a task set in the face of distraction, in this case by suppressing, or inhibiting, a prepotent, motoric response (eye movement) (Miyake et al. 2000). Participants first focus on a centrally located fixation cross for 1–4 s. When the fixation cross disappears, a cue flashes either to the left or the right of the fixation. The cue then disappears and a target appears for 150 ms before being obscured by a gray box. The target consists of a single digit, 1 through 9, and participants are instructed to report the target digit out loud for each trial as the experimenter types in the response. The

task is divided into two conditions: pro-saccade and anti-saccade trials. Under the pro-saccade condition, the target always appears on the same side as the cue, and participants are explicitly told that this will be the case. Under the anti-saccade condition, the target appears on the opposite side of the cue, and participants are told that, in order to accurately report the target during this condition, they must look to the side opposite the cue for the target. Participants first perform a block of pro-saccade trials, reinforcing a prepotent tendency to look towards the cue, and then perform three anti-saccade blocks, measuring how well they are able to inhibit the prepotent response to look towards the cue location, under three distinct cue–target intervals. Participants are measured on the number of correctly identified target, with more identified targets equating to better inhibitory control.

Category-switch task (CS)

(adapted from Mayr and Kliegl 2000)

This task measures a person's ability to effectively switch between task sets. Participants are presented with words one at a time and instructed to classify each word on either animacy (living or non-living) or size (smaller or larger than a soccer ball) judgment criteria. For each trial, participants are first cued as to what judgment to make (animacy or size) prior to a word appearing, superimposed over the cue. Participants record their judgments by pressing one of two buttons, with non-living and small responses mapped to one button, and living and large responses mapped to the other button. Participants perform one practice block of 12 trials, followed by the experimental blocks of 64 trials. The judgment criteria switches on some but not all trials, allowing researchers to measure differences in reaction times between switching and repeating judgment criteria on successive trials. Changes in reaction times between switch and repeat trials (i.e., switch cost), as well as the number of correct responses are both measures of task performance, with smaller switch costs and less errors both indicating better set-shifting ability.

Keep track task (KT) (adapted from Yntema 1963)

This task measures a person's ability to update working memory. Participants are presented with a string of words, with each word belonging to one of six categories and each category containing six words. Participants are instructed to keep track of the most recent word presented from each of 2–5 categories and verbally report their responses at the end of each trial. There are 16 trials, with each trial consisting of a stream of 15–25 words. Participants perform two practice trials with two categories to keep track of, and then perform four, randomly ordered instances of two-,

three-, four-, and five-category trials. Each trial begins with a list of categories, and this list remains on the bottom of the screen until the recall portion of the trial. Each word appears for 2,000 ms and is immediately followed by the next word. Performance is measured through the number of correctly remembered target items as a function of the number of target items presented in each trial.

Computing common EF and the executive function-specific residuals

Following the procedures of Miyake and Friedman, we calculated a z value for each participant's performance, across the entire group for each of the three tasks individually: anti-saccade (inhibition/common EF), category-switch (set-shifting), and keep track (working memory updating) tasks. These three resulting z values were averaged for each subject to create a composite score reflecting common EF (unity). We then regressed category-switch performance against keep track and anti-saccade performance, yielding a shifting-specific residual. Similarly, we regressed keep track performance against category-switch and anti-saccade performance, yielding an updating-specific residual. Higher scores on all three measures indicate better performance on that construct.

Imaging data acquisition

All structural MRI images were acquired using a Siemens 3-Tesla MAGNETOM Trio MR scanner located at the University of Colorado, Boulder. A 12-channel headcoil was used for radiofrequency transmission and reception. Foam padding was placed around the head, within the head coil, to limit head motion during the scan. Structural images were obtained via a T1-weighted Magnetization Prepared Rapid Gradient Echo sequence (MPRAGE) in 192 sagittal slices. Imaging parameters were as follows: echo time (TE) 1.64 ms, repetition time (TR) 2,530 ms, flip angle 7.0°, field of view (FOV) 256 mm, and voxel size 1 mm³. Scan parameters were consistent for all imaging sessions associated with this study.

Structural connectivity was assessed with a diffusion-weighted scan [71 gradient directions; TR 9,600 ms; TE 86 mm; GRAPPA parallel imaging factor 2; β value 1,000 s/mm²; FOV 256 mm; 72 slices; 2 mm³ isomorphic voxels; 7 β 0 images].

Voxel-based morphometry (VBM)

All VBM analyses were performed using the FSL-VBM toolbox and follow the processing pipeline put forth by Ashburner and Friston (2000) and Good et al. (2001). This pipeline is specific in regard to optimized VBM using

modulation. Modulation refers to the incorporation of volumetric changes during normalization into the analysis. This involves multiplying (or modulating) voxel values in the segmented images by the Jacobian determinants derived from the spatial normalization step. First, the raw T1-weighted images were brain-extracted using the FSL default BET brain extraction process, which strips the skull and removes any non-brain tissue from the image using the FAST4 tool. The resulting GM images were then aligned to MNI152 standard space using the affine registration tool FLIRT, followed by nonlinear registration using FNIRT. The resulting images were averaged to create a study-specific template, to which the native GM images were then non-linearly re-registered using FNIRT. The registered partial volume images were then modulated (to correct for local expansion and contraction) by dividing the Jacobian of the warp field. The modulated segmented images were then smoothed with an isotropic Gaussian kernel with a sigma of 2, yielding full-width half-maximum (FWHM) $2 \times 2.3 \text{ mm} = 4.6 \text{ mm}$ FWHM. The resulting subject-specific GM probability maps were input into a general linear model (GLM) evaluating correlations between all voxels of GM and z -transformed performance on the common EF, shifting-specific, and updating-specific constructs, respectively, using both age and whole-brain GM volume as nuisance covariates.

Surface-based morphometry (SBM)

Cortical reconstruction and volumetric segmentation was performed with the Freesurfer image analysis suite (free-surfer-Linux-centos4_x86_64-stable-pub-v5.0.0), which is documented and freely available for download online (<http://surfer.nmr.mgh.harvard.edu/>). The technical details of these procedures are described in prior publications (Dale et al. 1999). Briefly, this processing includes motion correction and averaging (Reuter et al. 2010) of volumetric T1-weighted images, removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne et al. 2004), automated Talairach transformation, intensity normalization (Sled et al. 1998), tessellation of the gray matter white matter boundary, automated topology correction (Fischl et al. 2001; Segonne et al. 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale et al. 1999; Dale and Sereno 1993; Fischl and Dale 2000). Once the cortical models are complete, a number of deformable procedures were performed for further data processing and analysis including surface inflation (Fischl et al. 1999a), registration to a spherical atlas which utilized individual cortical folding patterns to match cortical geometry across subjects

(Fischl et al. 1999b), parcellation of the cerebral cortex into units based on gyral and sulcal structure (Desikan et al. 2006; Fischl et al. 2004a), and creation of a variety of surface-based data including maps of cortical volume, surface area, thickness, curvature, sulcal depth, and local gyrification index.

Diffusion tensor analyses

Diffusion-weighted images were processed using FSL's (ver. 5.0) FDT toolbox (<http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT>; Behrens et al. 2003a, b), and tract-based spatial statistics (TBSS; <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS>; Smith et al. 2006). Images were corrected for motion and eddy current distortions. A diffusion tensor model was fitted at each voxel, resulting in fractional anisotropy (FA) images. FA images for each participant were non-linearly aligned to a $1 \times 1 \times 1 \text{ mm}$ standard space FA template (Andersson et al. 2007a, b). Aligned FA images were then skeletonized, and an average FA skeleton mask was created. White matter (WM) tract ROIs were extracted from the JHU white matter atlases available in FSL (Hua et al. 2008). White matter ROIs were masked with the average FA skeleton, and the mean FA values were extracted for each participant from these ROIs. WM-ROIs were based on a priori determination of the most probable white matter tracts connecting the PFC to posterior and subcortical regions. These included bilateral: superior and inferior longitudinal fasciculus (SLF/ILF), superior and inferior fronto-occipital fasciculus (sFOF/iFOF), the cingulum bundle (CB) which included the averaged FA values from the cingulum cingulate gyrus (CCg), the genu of the corpus callosum (genu) and the anterior limb of the internal capsule (ALIC).

ROI and whole-brain analyses

Because of the breadth of previous work implicating the PFC as the hub of executive functioning, we used a PFC mask in order to maximize power while investigating relationships between regional GM morphometry as measured by VBM and SBM, and EF (common EF, shifting-specific, and updating-specific performance). VBM measures included volume, while SBM measures included volume, cortical thickness, cortical surface area, sulcal depth, and local gyrification index (LGI). The PFC mask conformed to Montreal Neurological Institute (MNI) space, and consisted of frontal regions anterior to the supplementary motor area (SMA), as delineated by the Harvard-Oxford Cortical Atlas. Whole-brain and ROI-based VBM analyses used voxel-wise thresholding applied using permutation-based non-parametric testing with Monte Carlo simulations, correcting for multiple voxel comparisons. A

total of 5,000 simulations were run for each permutation test. Cluster-wise extent correction was applied using FSL's built-in cluster-based thresholding technique, with a threshold of $t > 2.3$. For SBM analyses, this PFC mask was warped into FreeSurfer space, thus allowing for a common mask to be used in both VBM and SBM analyses. Regions within the PFC were considered significant at the vertex level of $z > 3.3$, $p = 0.001$, correcting for multiple voxel comparisons within the GLM. Subsequently, the average parameter estimates for VBM and SBM clusters in the PFC that significantly predicted EF performance were extracted. These average parameter estimates were then used as variables in the additional multiple regression and mediation analyses described in the next section.

Regression and mediation analyses

Regional VBM and SBM estimates, FA values, EF performance z scores, age, and total GM volume were included into regression models using robust regression (Huber's method) with permutation testing (3,000 Monte Carlo simulations; NCSS 9.0) to adjust for any potential outliers and multiple comparisons. Robust multiple regression models were used to examine the relative variance explained by VBM and SBM estimates and FA on EF construct performance, while controlling for age and total GM volume. Cross validation (leave one out) was performed to validate feature selection. Mediation analyses were carried out using SPSS Amos (Arbuckle 2006) to examine the indirect effect of any potential mediators (VBM, SBM, FA) influencing the relationship of independent variables (VBM, SBM, FA) on the dependent variable (EF construct performance). Bootstrapping was applied to resample the data and estimate confidence intervals (3,000 permutations).

Results

Behavioral performance

To assess whether the performance of our sample was consistent with the relationship between these EF tasks found with larger groups of participants (e.g., Miyake et al. 2000, Miyake and Friedman 2012), we examined the correlations across tasks. Performance on the anti-saccade task (inhibition/common EF measure) was significantly correlated with performance on both the category-switch task (shifting) ($r = 0.39$, $p = 0.001$) and performance on the keep track task (updating) ($r = 0.29$, $p = 0.017$). In contrast, the correlation between performance on the shifting and updating tasks was not significant ($r = 0.04$, $p > 0.05$). The fact that anti-saccade performance correlated with both

shifting and updating performance is consistent with a common EF construct, and supports our use of the average z score across tasks as a measure of common EF (unity). Furthermore, because shifting and updating performance were not significantly correlated with each other, we also find support for the notion of discrete EF constructs (diversity), which justifies our use of the residual of performance (after accounting for common EF) on the category-switch and keep track tasks as measures of shifting-specific and updating-specific abilities, respectively.

Grey matter morphometry and fractional anisotropy regression with executive function

Significant results from the analyses examining VBM, SBM and FA with behavioral measures of each of the three EF constructs are shown in Table 1; Figs. 1, 2 and 3, respectively. We first examined the association of VBM (volume; panel a of Figs. 1, 2, 3), SBM measures [including cortical: volume, surface area, thickness, curvature, sulcal depth and local gyrification index (LGI) panel b of Figs. 1, 2, 3], and FA with EF performance for each of the three EF constructs. We then carried out robust multiple regression and mediation analyses to determine the relationships between these variables, as well as their respective contributions to EF performance for each of the three EF constructs.

Common EF

Results indicated that greater common EF was associated with reduced voxel-based GM volume (GMV) in the vmPFC, specifically BA25/11 ($r^2 = 0.12$, $p < 0.005$; Fig. 1a, c), reduced LGI in the vmPFC ($r^2 = 0.23$, $p < 0.003$; Fig. 1b, d), and increased FA of the right SLF ($r^2 = 0.09$, $p < 0.05$; Fig. 1a, c). Additionally, reduced vmPFC GMV was associated with reduced vmPFC LGI ($r^2 = 0.36$, $p < 0.0001$; Fig. 1d) and increased FA of the right SLF ($r^2 = 0.09$, $p < 0.05$; Fig. 1c), while reduced vmPFC LGI was associated with increased FA of the right SLF ($r^2 = 0.14$, $p < 0.03$; Fig. 1d). Multiple regression VBM results indicated that common EF performance was predicted by vmPFC GMV and FA of the right SLF better than either variable alone. Together they accounted for 22 % of the variance ($r^2 = 0.22$, $F(61) = 8.62$, $p < 0.001$) in common EF, GMV accounted for 18.5 % of the variance, while FA value accounted for 1.6 %. Multiple regression SBM results indicated that common EF performance was predicted by vmPFC LGI and FA of the right SLF better than either variable alone. Together these two variables accounted for 27 % of the common EF performance variance ($r^2 = 0.27$, $F(61) = 11.12$, $p < 0.0003$), with vmPFC LGI accounting for 21.2 % and right SLF FA

Table 1 Measure (GMV = VBM volume, LGI = SBM local gyri-fication index, FA = fractional anisotropy), coordinates (MNI), region of correlation or white matter tract label, laterality, Brodmann area (BA) and significance-level of all significant correlations

| Construct | Measure | Coordinate | Region/tract | Laterality | BA | Sig. |
|-------------------|---------|-------------|--------------|------------|---------|-------------|
| Common | GMV | 4, 32, -16 | vmPFC | Medial | 25/11 | $p < 0.005$ |
| EF | LGI | -6, 16, -10 | vmPFC | Medial | 25/11 | $p < 0.003$ |
| | FA | X | SLF | Right | X | $p < 0.05$ |
| Shifting-specific | GMV | 28, 56, -10 | vIPFC | Left | 10/47 | $p < 0.05$ |
| | LGI | 28, 49, -10 | vIPFC | Left | 10/47 | $p < 0.05$ |
| | FA | X | iFOF | Left/right | X | $p < 0.05$ |
| Updating-specific | GMV | -44, 36, 12 | dIPFC | Right | 9/45/46 | $p < 0.05$ |
| | LGI | -43, 41, 10 | dIPFC | Right | 9/45/46 | $p < 0.03$ |

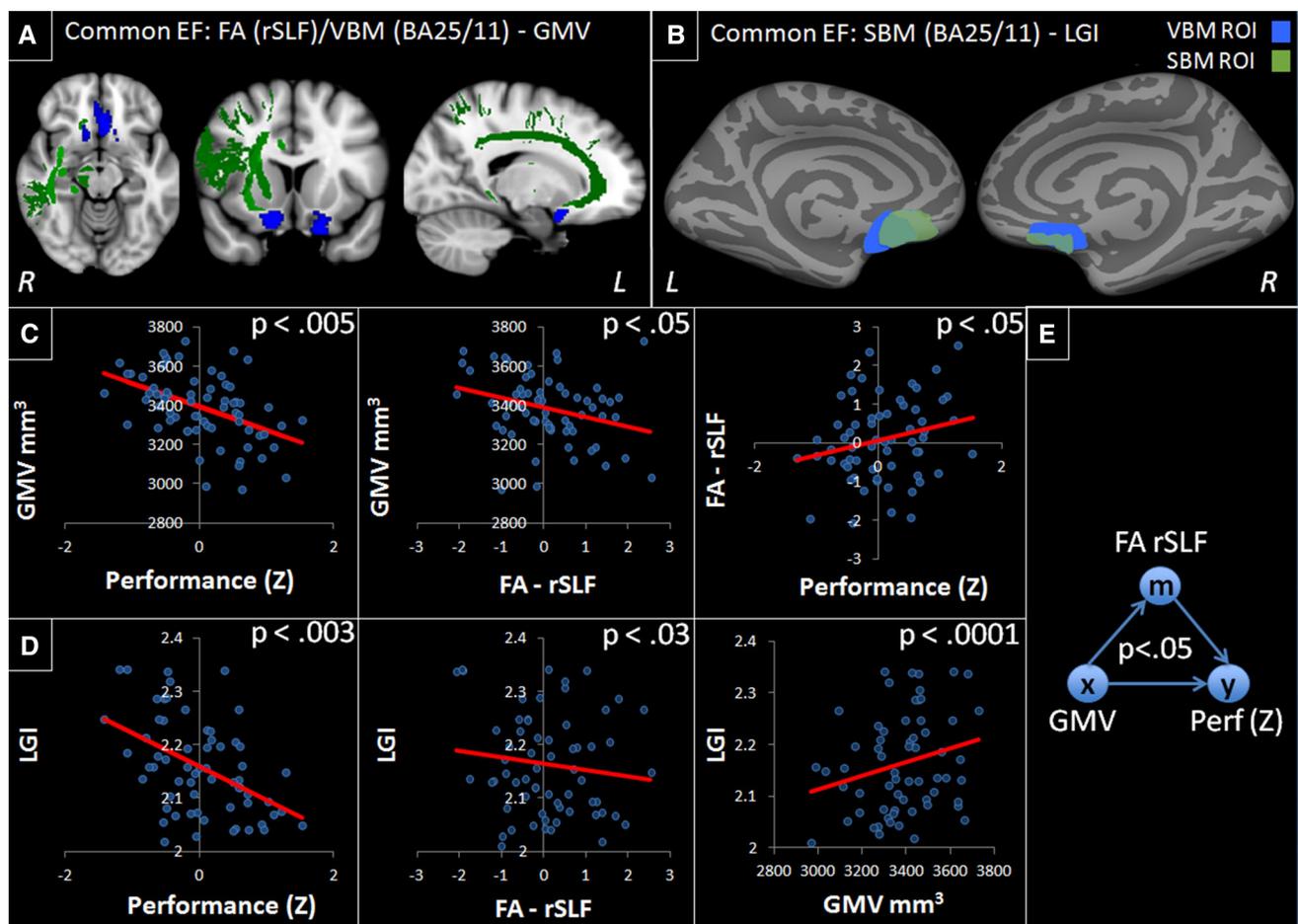


Fig. 1 **a** Correlations of common EF performance (slice $z = -16$, $y = 32$, $x = 4$, MNI), regional GMV (blue) and FA values (green). **b** Correlations of common EF performance and regional LGI. Blue VBM - GMV ROI warped onto the FreeSurfer inflated brain, translucent green = SBM - LGI ROI to illustrate the overlap between VBM and SBM findings. **c** Scatter plots for GMV (mm³) with common EF performance (z score), with FA value, and common

between PFC GMV, LGI, FA and performance on EF constructs, including common EF (z score composite), shifting-specific (residuals), and updating-specific (residuals)

EF performance (z score) with FA value. **d** Scatter plots for LGI with common EF performance (z score), with FA value, and with GMV (mm³). **e** Mediation analysis examining indirect effects. Statistics between common EF performance and GMV/LGI represent independent PFC mask analyses and not ROI-extracted parameter estimate non-independent analyses. Scatter plots are presented as a visual reference

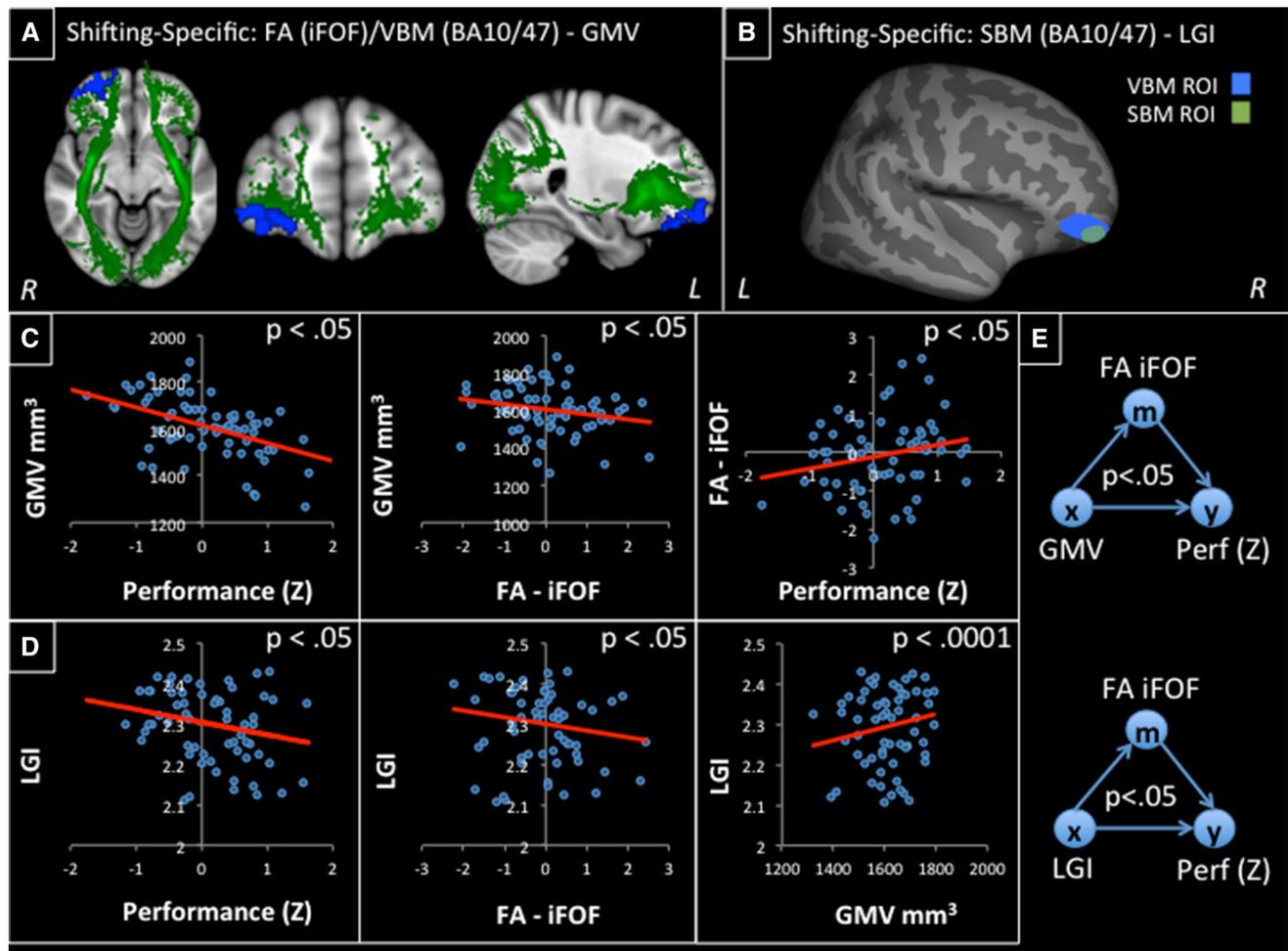


Fig. 2 **a** Correlations of shifting-specific performance (slice $z = -10$, $y = 56$, $x = 28$, MNI), regional GMV (blue) and FA values (green). **b** Correlations of shifting-specific performance and regional LGI. Blue = VBM – GMV ROI warped onto the FreeSurfer inflated brain, translucent green = SBM – LGI ROI to illustrate the overlap between VBM and SBM findings. **c** Scatter plots for GMV (mm³) with shifting-specific performance (z score), with FA value, and

shifting-specific performance (z score) with FA value. **d** Scatter plots for LGI with shifting-specific performance (z score), with FA value, and with GMV (mm³). **e** Mediation analysis examining indirect effects. Statistics between shifting-specific performance and GMV/LGI represent independent PFC mask analyses and not ROI-extracted parameter estimate non-independent analyses. Scatter plots are presented as a visual reference

accounting for 4.8 % of the variance. Indirect mediation analyses indicated that the relationship of vmPFC GMV with common EF performance was partially mediated by FA of the right SLF ($r^2 = 0.06$, $p = 0.05$; $\beta = 0.078$ LCI = 0.002, UCI = 0.18; Fig. 1e).

Shifting-specific

Better shifting-specific performance was associated with reduced GMV in right lateralized vlPFC, specifically BA10/47 ($r^2 = 0.07$, $p < 0.05$; Fig. 2a, c), reduced LGI in the vlPFC ($r^2 = 0.09$, $p < 0.05$; Fig. 2b, d), and increased average FA of the left and right iFOF ($r^2 = 0.08$, $p < 0.05$; Fig. 2a, c). Additionally, within the vlPFC, reduced GMV was strongly associated with reduced LGI ($r^2 = 0.29$,

$p < 0.0001$; Fig. 2d) and increased average FA of the left and right iFOF ($r^2 = 0.07$, $p < 0.05$; Fig. 2c), while reduced vlPFC LGI was also associated with increased average FA of the left and right iFOF ($r^2 = 0.09$, $p < 0.05$; Fig. 2d). Multiple regression results indicated that shifting-specific performance was predicted by vlPFC GMV and average FA of the left and right iFOF better than either variable alone, accounting for 26 % of the variance ($r^2 = 0.26$, $F(61) = 10.25$, $p < 0.0002$). GM volume accounted for 21.5 % of the variance, while FA value accounted for 1.6 %, suggesting that GM volume and FA value share a large portion of explanatory variance. Similarly, shifting-specific performance was predicted by vlPFC LGI and average FA of the left and right iFOF better than either variable alone. Together these two variables accounted for 11 % of the shifting-specific performance variance ($r^2 = 0.11$,

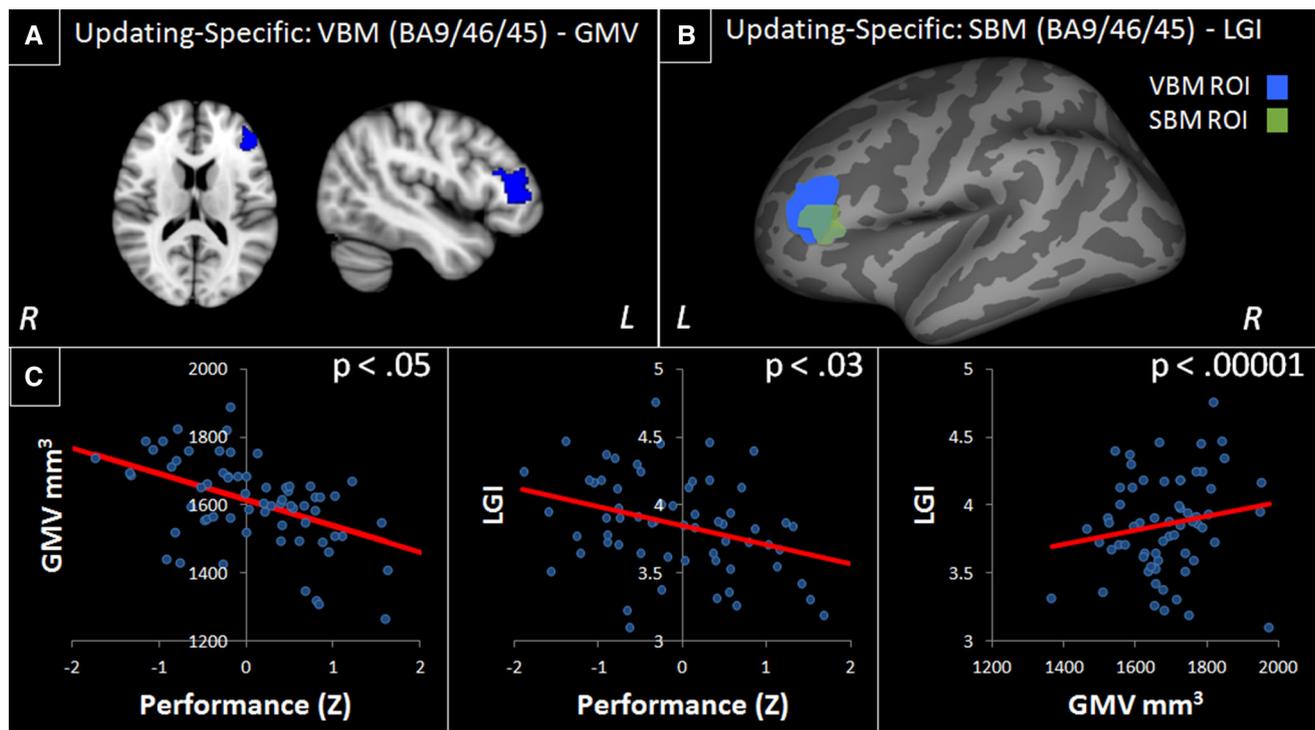


Fig. 3 **a** Correlations of updating-specific performance (slice $z = 12$, $x = -44$, MNI) and regional GMV (blue). **b** Correlations of updating-specific performance and regional LGI. Blue = VBM – GMV ROI warped onto the FreeSurfer inflated brain, translucent green = SBM – LGI ROI to illustrate the overlap between VBM and SBM findings. **c** Scatter plots for GMV (mm^3)

with updating-specific performance (z score), LGI with updating-specific performance (z score), and LGI with GMV (mm^3). Statistics between updating-specific performance and GMV/LGI represent independent PFC mask analyses and not ROI-extracted parameter estimate non-independent analyses. Scatter plots are presented as a visual reference

$F(61) = 3.82$, $p < 0.03$), with vlPFC LGI accounting for 5.8 % and average FA of the left and right iFOF accounting for 3.6 %. Indirect mediation analyses indicated that the relationships of vlPFC GMV with shifting-specific performance and vlPFC LGI with shifting-specific performance were partially mediated by average FA of the left and right iFOF (GMV— $r^2 = 0.10$, $p < 0.05$; $\beta = 0.085$, LCI = 0.016, UCI = 0.17; see Fig. 2e; LGI— $r^2 = 0.09$, $p < 0.05$; $\beta = 0.325$, LCI = -0.97 , UCI = 0.021; see Fig. 2e).

Finally, better updating-specific performance was associated with reduced GMV in dlPFC, specifically BA9/45/46 ($r^2 = 0.06$, $p < 0.036$; Fig. 3a, c) and LGI in the dlPFC ($r^2 = 0.13$, $p < 0.02$; Fig. 3b, c) though no significant relationship with FA was observed. Additionally, within the dlPFC, reduced GMV was strongly associated with reduced LGI ($r^2 = 0.34$, $p < 0.00001$; Fig. 3c). Because updating-specific performance was not significantly related to FA of any white matter tracts, further regression and mediation analyses were not carried out.

We also carried out exploratory whole-brain VBM and SBM analyses to determine whether regional variations in GM morphometry across the entire brain predicted performance. No whole-brain results were significant after accounting for multiple comparisons.

Overall, these results are consistent with views that suggest individual differences in EF constructs are inter-related to features of regional GM morphometry within the prefrontal cortex and the diffusivity of the white matter tracts that connect these regions to posterior and subcortical areas of the brain. These effects also appear to be separable for a general EF construct (common EF; unity) and discrete EF constructs (shifting, updating; diversity), as different prefrontal regions and the FA of different fibers tracts were predictive for the different EF constructs. Voxel-based measures of GMV and surface-based measures of LGI were strongly related for all EF constructs, indicating that VBM, though measuring volume, is highly sensitive to individual differences in cortical folding patterns, as indicated by SBM analyses and as suggested elsewhere (Palaniyappan and Liddle 2012; Winkler et al. 2010).

Discussion

Our results provide evidence that, in a homogeneous, young adult sample, individual differences in performance on three EF constructs are related to variations in GM

morphometry in distinct regions of the PFC and the diffusivity of white matter tracts that connects those regions with posterior and subcortical aspects of the brain. Specifically, our results indicated that reduced GMV (VBM) and LGI (SBM) in the vmPFC, dlPFC, and vlPFC is associated with better performance on common EF, updating-specific, and shifting-specific constructs, respectively, while our DTI results indicated that increased FA in the SLF and iFOF are associated with better common EF and shifting-specific performance. Additionally, we not only found evidence for a strong positive relationship between GMV and LGI in regions of the PFC, but also evidence suggesting that FA of select white matter tracts is associated with GM morphometry and partially mediates the relationships of GMV/LGI with EF performance. These results suggest that, at least in younger adults, less GMV/LGI may possibly be related to characteristics of brain connectivity between brain regions, resulting in better EF performance. In addition, not only are our results consistent with theories regarding EF as having both common and specific components, but also indicate that individual differences in these EF constructs may differentially rely on separate neural circuits connecting distinct regions of the PFC to other, more posterior and/or subcortical brain regions.

The current study is to our knowledge, the only one to utilize a multi-factor model of EF in conjunction with VBM, SBM, and DTI methodologies in a homogenous sample of healthy young adults. By using a multi-factor model of EF consisting of a composite measure and construct-specific residuals, we were able to identify the relative contributions of discrete EF processes to complex EF task performance with a degree of construct specificity that has not been utilized in previous structural MR studies.

Of particular methodological and theoretical importance is the observed relationship between voxel-based measures of GMV and the surface-based measure, LGI. Of note, researchers have taken issue with VBM, claiming that it is susceptible to systematic errors in registration stemming from inter-individual differences in cortical folding and in extent and location of cortical regions, and should thus not be used with imperfectly registered images as the results may misrepresent GMV (Amunts et al. 1999; Bookstein 2001). The notion that MRI analyses should not be conducted with imperfectly registered images is not unique to VBM, but is instead a tenet of all MRI analyses involving brain registration to a common template. Though registration methods that employ greater degrees of freedom than VBM may better capture sub-voxel nuances in brain morphometry, it is unclear whether higher-resolution registration techniques yield more accurate results when warping individual subject brains to a common template (Ashburner and Friston 2001). In fact, recent work

evaluating the relationship between voxel- and surface-based measures of brain morphometry has suggested that VBM may be sensitive to morphometric differences that emerge from the interaction of multiple surface-based measures, differences that are not captured by the individual surface-based measures alone (Palaniyappan and Liddle 2012). For example, in a study evaluating partial meditation effects of various SBM measures on the relationship between regional GMV (VBM) and diagnostic status in schizophrenia, it was shown that LGI, surface area, and cortical thickness differentially mediated GMV/clinical status relationships in various regions throughout the brain (Palaniyappan and Liddle 2012). Additionally, the specific SBM measure that mediated GMV/diagnostic status relationships varied by region, and no single SBM measure accounted for more than 20 % of the variance of these relationships in any region of the brain (Palaniyappan and Liddle 2012).

In line with previous findings, our results demonstrate very strong relationships between GMV and LGI in common regions of the PFC, with both measures being predictive of EF performance. While some may interpret these relationships between VBM and SBM measures as reason to discontinue VBM analyses and to instead employ more specific measures of GM morphometry that are provided through SBM, we see this as reason to employ both VBM and SBM analyses simultaneously. We suggest that GMV, as assessed by optimized VBM, can be viewed as a gross anatomical index of GM morphometry, while using more specialized SBM measures (e.g., cortical thickness, surface area, folding indices), may fail to detect morphometric differences that emerge from the interaction of multiple surface-based features. Thus, it maybe that individual SBM measures in isolation do not show significant relationships with behavioral performance on their own, but when the interaction of multiple surface-based features in a given region is taken into account, an effect of GM morphometry on performance is found. Therefore, it may be advantageous to employ VBM and SBM methodologies in a complimentary fashion, first using VBM to identify gross differences in morphometry and then using the more precise SBM to interrogate the specific morphometric features responsible for any differences observed through VBM.

Despite general inconsistencies in the relatively scant literature on GM morphometry–EF relationships in healthy young adults, our results are consistent, to varying degrees, with a number of previous findings. Negative relationships between vmPFC GM volume/density and EF performance have been observed before in healthy young adults through both questionnaire (Takeuchi et al. 2012a) and single-task measures of EF, such as the Trail Making Task (TMT) (Koutsouleris et al. 2010), suggesting the vmPFC is important to individual differences in EF processes in

general, not specific to certain differential EF sub-processes. Because our common EF measure taps processes common across a variety of EF paradigms, it is not surprising that this finding is consistent with a number of prior studies, in which the tasks employed may also load on a common EF factor.

The regional specificity of our shifting- and updating-specific findings is consistent with another prior study investigating EF performance, in which vIPFC and dlPFC GM volume/density were shown to predict TMT (set-shifting analog) and Backwards Digit Span (updating analog) (Ruscheweyh et al. 2012), respectively, though these studies report that increased GM volume/density is associated with better EF performance, contrary to what we observe. However, their sample involved older adults, for whom greater GM typically is associated with higher EF, whereas our study examined younger adults, where the directionality of such GM–EF relationships is underspecified. Though a few preexisting studies have evaluated the relationship of EF with inter-hemispheric LGI asymmetries in healthy control samples (Fornito et al. 2008), no preexisting study we are aware of has demonstrated relationships between absolute measures of LGI and EF in healthy young adults.

The mechanism that leads to our observation of decreased GMV and LGI, as well as increased FA, being associated with higher EF cannot be fully addressed by our study. However, we list a number of potential candidate mechanisms that could speculatively be involved and provide intrigue for further studies. It may be that neurodevelopmental processes account for these brain–behavior relationships. Throughout early adolescence and into young adulthood, distinct regions of the brain undergo reductions in GM volume/density attributed to neuronal pruning, a process by which redundant and superfluous neurons are eliminated, resulting in increased neural efficiency (Blakemore and Choudhury 2006; Gogtay et al. 2004; Petanjek et al. 2011; Sowell et al. 2001, 2003). Similarly, after a rapid increase in gyrification during fetal development and early childhood, gyrification has been shown to continually decrease as people age from their early 20s onwards (Hogstrom et al. 2013). Concomitantly during this same developmental timeframe, the myelination of WM tracts is ongoing, resulting in improved connectivity throughout the brain, as measured through FA (Courchesne et al. 2000; Sowell et al. 2004). Developmentally, pruning and myelination processes begin in posterior regions of the brain and move anteriorly as people mature towards young adulthood, with the PFC being the final area to undergo these neurodevelopmental processes, which generally concludes during the mid- to late-20s (Gogtay et al. 2004; Petanjek et al. 2011; Andersen 2003).

With a mean age of 21.5 (SD 2.3), our sample is in an age range that is likely to be affected by individual differences in the PFC pruning and myelination processes. Two of our results support this view: (1) our regression analyses suggested a negative relationship of GMV/LGI with FA value and (2) our meditation results indicated an indirect effect of FA on the relationships between GMV/LGI with EF performance. These results also suggest that, perhaps reduced GMV/LGI and increased FA within discrete neural circuits are crucial to optimal EF performance. Thus, regional GM morphometry and white matter tract diffusivity may potentially index individual differences in neurodevelopmental maturation, with young adults who have undergone greater prefrontal pruning and myelination, consequently exhibiting better EF performance. Of note, two limitations must be noted within the current analyses. First, while our results are based on a sample of over 60 individuals, which may appear to be large for a neuroimaging study, this can be considered under-powered for individual difference analyses. Therefore, we caution that these results need replication and likely include false negatives. Second, an alternative explanation regarding our FA results should be considered. Our findings indicating increased FA may have resulted from decreases in white matter connectivity, represented by decreases in white matter fiber crossing, and therefore, an increase in FA values. These limitations of FA as a method should be noted and results need to be replicated with the advent of diffusion techniques as alternatives to FA.

Although some of our hypotheses regarding specific localization of neuroanatomical variation differed from fMRI studies, there still existed considerable overlap. Therefore, it is beneficial to consider the functionality of the PFC regions identified in the current study in comparison with fMRI studies. This research suggests that a common EF construct could be instantiated by either: (1) most of the PFC (Duncan and Owen 2000), or (2) more specific PFC regions, including the anterior PFC (Burgess et al. 2003; Koshino et al. 2011) dlPFC (Narayanan et al. 2005; Wager and Smith 2003) and/or dmPFC (Dosenbach et al. 2006). In the current study, we find that a specific region of the PFC is correlated with the level of common EF, specifically the vmPFC. Notably this region is not one traditionally considered to support EF (however, see work regarding cognitive flexibility, Kehagia et al. 2010), but rather is a region implicated in emotion, motivation, and reward processing (Glascher et al. 2009; Plassmann et al. 2007; Sescousse et al. 2010; Tanaka et al. 2004; Wunderlich et al. 2010). If one considered reduced GMV and LGI to reflect a higher degree of pruning, then our observed correlations may be indexing individual differences in the development of motivation and reward processing areas, modulating the degree of reward value assigned to

performance. Because participants did not receive any explicit reward for performance, this reward value is likely internally generated and highly variable across subjects. Indeed, single cell recording work in monkeys has demonstrated that neurons in vmPFC differentially relate to internally generated motivation, whereas vlPFC regions are sensitive to motivation arising from external cues (Bouret and Richmond 2010). Moreover, the fiber tract (rSLF) we found to be correlated with reduced GMV and LGI in this region and common EF performance courses medially and contains bidirectional projections to and from the frontal lobes through each of the other major lobes (occipital, parietal and temporal) and striatum (Wakana et al. 2004). Therefore, as common EF represents an overarching EF construct that may require the interaction of many different brain regions, it is not surprising that increased FA of the rSLF was correlated with common EF performance, as the rSLF is vital to the integration of disparate brain regions. It may be that of the number of neuropsychological processes that comprise common EF, it is internal motivation supported by the vmPFC and white matter tracts providing its structural connectivity that most strongly drives individual differences in EF performance.

The shifting-specific GM morphometry results implicating BA10/47 are also consistent with fMRI studies. Although meta-analyses of fMRI data implicate dorsal portions of both the lateral and medial regions of the PFC in this process (Wager et al. 2004; Derrfuss et al. 2005), more focused single-study fMRI investigation have implicated anterior portions of vlPFC in set-shifting (Goel and Vartanian 2005; Hampshire and Owen 2006; Konishi et al. 1998; Monchi et al. 2001; Provost et al. 2012), spatially consistent with our results. BA10's importance in set-shifting may stem from this area's general involvement in the hierarchical control of abstract goal representations held in working memory (WM) (Braver and Bongiolatti 2002; Koechlin et al. 1999). In the case of our current study, participants must control the abstract goal of switching between two task-set representations (judgments based on size or living/non-living) and organization of semantic/object-based knowledge on which the judgments are made. Moreover, the fiber tract (left and right iFOF), which was found to be correlated with reduced GMV and LGI in this region and shifting-specific performance, courses laterally and contains bidirectional projections to and from the inferior frontal lobes through the inferior temporal and occipital lobes (Wakana et al. 2004). Therefore, as shifting-specific performance may require the interaction of frontal regions involved in WM and anterior/inferior temporal regions involved in the storage of semantic/object knowledge (Patterson et al. 2007), it is not surprising that increased FA of the left/right iFOF was correlated with shifting-specific performance.

Similarly, our updating-specific GM morphometry results implicating the dlPFC are consistent with fMRI studies. Many fMRI studies relate BA9/46 with the manipulation of recent sensory experiences and goal representations in WM (e.g., Barbey et al. 2013; Curtis and D'Esposito 2003; D'Ardenne et al. 2012; Narayanan et al. 2005; Wager and Smith 2003). Specifically, we found that GMV in the left dlPFC as being related to the updating of items based on semantic category, as has been observed in similar studies evaluating the manipulation of linguistic or semantic representations in WM (Narayanan et al. 2005; Snyder et al. 2011). Dominant theories on the updating of WM suggest that the dlPFC receives and maintains information held in posterior multimodal association cortex (e.g., semantic information) via connections and gating mechanisms in the basal ganglia when updating occurs (O'Reilly and Frank 2006; Miller and Cohen 2001). Therefore, the dlPFC is in a position to continually update and manipulate the contents of WM during updating tasks.

In conclusion, our study is novel in our approach of using a multi-factorial design to investigate the relationship between GMV, LGI, FA, and EF in a homogeneous sample of young adults. Employing the "unity and diversity" model of EF, as posited by Miyake and Friedman (2012), we found that performance on discrete EF constructs differentially relate to neuroanatomical structure in distinct regions of the PFC. The results indicated that less regional GMV and LGI in the vmPFC, vlPFC, and dlPFC correlates with better common EF, shifting-specific, and updating-specific performance, respectively. Conversely, increased FA in major white matter tracts connecting the vmPFC and vlPFC to posterior and/or subcortical brain regions correlates with better common EF and shifting-specific performance, respectively. Both shifting-specific and updating-specific performance was related to differences in GM morphometry in regions consistent with fMRI studies (vlPFC and dlPFC, respectively), while common EF was associated with regions not frequently implicated by fMRI studies (vmPFC). These findings suggest the possibility that regions associated with reward evaluation and motivation may influence individual differences in common EF. The negative associations between GMV and LGI with EF, in conjunction with the opposing positive association between FA and EF, as well as the observed relationships between GM morphometry and FA, point to a potential relationship between GM morphometry and white matter tract diffusivity in determining EF abilities. Additionally, by showing distinct relationships between regionally specific prefrontal GM morphometry, white matter tracts and each of the EF constructs investigated, our results provide confirmatory evidence of the unity and diversity model's utility in describing the neuropsychological sub-processes of which EF is comprised.

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