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Neuroanatomical Substrates of Executive Functions: Beyond Prefrontal Structures

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Abstract

Executive functions are often considered lynchpin "frontal lobe tasks", despite accumulating evidence that a broad network of anterior and posterior brain structures supports them. Using a latent variable modeling approach, we assessed whether prefrontal grey matter volumes independently predict executive function performance when statistically differentiated from global atrophy and individual non-frontal lobar volume contributions. We further examined whether fronto-parietal white matter microstructure underlies and independently contributes to executive functions. We developed a latent variable model to decompose lobar grey matter volumes into a global grey matter factor and specific lobar volumes (i.e. prefrontal, parietal, temporal, occipital) that were independent of global grey matter. We then added mean fractional anisotropy (FA) for the superior longitudinal fasciculus (dorsal portion), corpus callosum, and cingulum bundle (dorsal portion) to models that included grey matter volumes related to cognitive variables in previous analyses. Results suggested that the 2-factor model (shifting/inhibition, updating/working memory) plus an information processing speed factor best explained our executive function data in a sample of 202 community dwelling older adults, and was selected as the base measurement model for further analyses. Global grey matter was related to the executive function and speed variables in all four lobar models, but independent contributions of the frontal lobes were not significant. In contrast, when assessing the effect of white matter microstructure, cingulum FA made significant independent contributions to all three executive function and speed variables and corpus callosum FA was independently related to shifting/inhibition and speed. Findings from the current study indicate that while prefrontal grey matter volumes are significantly associated with cognitive neuroscience measures of shifting/inhibition and working memory in healthy older adults, they do not *independently* predict executive function when statistically isolated from global atrophy and individual non-frontal lobar volume contributions. In contrast, better microstructure of

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fronto-parietal white matter, namely the corpus callosum and cingulum, continued to predict executive functions after accounting for global grey matter atrophy. These findings contribute to a growing literature suggesting that prefrontal contributions to executive functions cannot be viewed in isolation from more distributed grey and white matter effects in a healthy older adult cohort.

Keywords

Aging; Executive Control; Neuroimaging; diffusion tensor imaging; cognitive; neuropsychology

1. Introduction

Executive functions (EF) reflect a constellation of higher order cognitive processes that are markedly vulnerable to the aging process (Albinet, Boucard, Bouquet, & Audiffren, 2012; Bugg, Zook, DeLosh, Davalos, & Davis, 2006; Fisk & Sharp, 2004). Although considerable evidence suggests that these diverse cognitive processes are supported by anterior and posterior, as well as cortical and subcortical structures (Kennedy & Raz, 2009; Kramer et al., 2007; Sasson, Doniger, Pasternak, Tarrasch, & Assaf, 2013), executive functions are often characterized as lynchpin "frontal lobe tasks". Moreover, as Stuss (2011) noted in a recent review paper, the terms 'executive functions' and 'frontal lobes functions' are often reciprocally used when describing this construct, setting up a potentially problematic idea that they are synonymous. In order to better understand the relationship between prefrontal volumes and executive functions, non-lesion studies are needed that carefully disentangle the independent effect of prefrontal volumes on this construct from not only global atrophy, but also individual lobar contributions (e.g. parietal and temporal cortices).

Specifically, the classic frontal lobe hypothesis and the frontal hypothesis of aging (Dempster, 1992; West, 1996) posit that aging is characterized by decrements in executive functions and speed of processing, and this negative trajectory stems from structural changes in the prefrontal cortex. Consistent with this hypothesis, one of the more widely reported findings in cognitive aging research is the relationship between poor executive functions and both smaller prefrontal grey matter volume and worse white matter integrity (Gunning-Dixon & Raz, 2003; Kerchner et al., 2012; Miyake et al., 2000), suggesting that the selective vulnerability of this cognitive domain is driven at least in part by frontal lobe changes.

Importantly, however, a rich literature with healthy adults also point to the role of more distributed networks, highlighting integral roles of posterior parietal cortices and fronto-parietal connections in bolstering executive functions (Brass, Ullsperger, Knoesche, von Cramon, & Phillips, 2005; Burgess, 1997; Cole et al., 2013; Rabbitt et al., 2007). Extending this research into patient populations has given rise to numerous cases and patient groups in which 'frontal symptoms' and executive dysfunction are induced by parietal tumors (Teixidor et al., 2007) and posterior lesions (Vilkki, Levanen, & Servo, 2002). Notably, these findings are not limited to working memory functions, a subcomponent of executive functions with well-established frontoparietal underpinnings, as deficits in abstraction and cognitive flexibility are evident in patients with non-frontal brain injuries (Godefroy, 2003). In addition to both healthy and brain injured patient samples, electrostimulation mapping

studies have noted that striking executive dysfunction can be *generated* by electrostimulation of non-frontal cortical and subcortical structures (Duffau, 2012). Collectively, these elegantly conducted studies raise the question of whether prefrontal cortices can explain executive dysfunction when viewed outside the lens of a larger system of supportive grey and white matter brain regions.

The purpose of the current study is to assess whether prefrontal grey matter volumes independently predict executive function performance when *statistically differentiated* from global atrophy and individual non-frontal lobar volume contributions. Using a latent variable modeling approach, we tested two competing hypotheses: 1) prefrontal volumes independently predict executive functions, even after accounting for global atrophy and temporal/parietal contributions; and 2) global brain atrophy, as indexed by total volume, is a more robust predictor of executive functions than individual lobar volume contributions. In addition, considering the extensive literature on the role of white matter microstructure in bolstering executive functions, we also examined a third hypothesis: 3) fronto-parietal white matter microstructure, as indexed by diffusion tensor imaging fractional anisotropy, independently predicts executive functions, even after accounting for global grey matter atrophy. Given the multifaceted nature of executive functions, we developed latent measures of executive functions based on a set of tasks designed to assess working memory, set-shifting, and inhibitory control. Furthermore, in order to garner a more specific analysis of executive functions, we examined the role of processing speed (Salthouse, 1992, 2005) in supporting the executive function and grey matter associations.

2. Materials and Methods

2.1 Participants

A sample of 202 neurologically healthy, community dwelling older adult participants was selected from the University of California, San Francisco Memory and Aging Center database based on the availability of cognitive testing with the extensive executive functioning protocol. In addition, a large subset of these individuals underwent structural neuroimaging with FreeSurfer 5.1 analysis and diffusion tensor imaging ROI analysis. MRI and cognitive testing occurred within a 90-day period. Participants were recruited from a larger umbrella study on healthy aging and cognition (i.e., NIH Aging and Cognition study; Larry J. Hillblom foundation study), and were between the ages of 63 and 99 years. Participants were reviewed in a screening visit, which entailed an informant interview, neurological examination, and cognitive testing. Inclusion as a "neurologically healthy" participant was based on several criteria, including a Mini-Mental State Exam score of ≥ 26, Clinical Dementia Rating score of 0, and no subject or informant report of significant cognitive decline during the previous year. Participants were excluded if they had a major psychiatric disorder, neurological condition affecting cognition (e.g., Parkinson's disease, epilepsy; large vessel infarct), dementia or mild cognitive impairment, substance abuse, significant systemic medical illness (e.g., cancer; renal failure), current medications likely to affect CNS functions (e.g., long-active benzodiazepines), significant sensory or motor deficits that would interfere with cognitive testing, current depression (Geriatric Depression Scale Score greater than 15 of 30) (Yesavage et al., 1982), or insulin-dependent diabetes.

Primary demographic and cognitive variables are reported in Table 1. The study was approved by the UCSF committee on human research, and all subjects provided written, IRB-approved informed consent before participating.

2.2 Measures

2.2.1 Cognitive Assessment: Executive Functions—Participants were administered tests of executive function from the NIH Aging and Cognition Study. Development and selection of these tests were predicated on Miyake's conceptual framework for executive functions (Miyake et al., 2000) and include measures of mental set shifting, information updating [working memory], and inhibition of pre-potent responses.

Set-Shifting (Mental Set Shifting): The set-shifting paradigm was modeled after experiments studying general and specific shift costs (Kray & Lindenberger, 2000; Monsell, 2003), and involves homogenous color, homogeneous shape, and heterogeneous shape and color blocks. We utilized a version designed for the NIH EXAMINER battery (Kramer, 2014). Target shapes are presented in the middle of the screen (i.e. blue triangle or red rectangle) with equal frequency and are picked randomly. Matching is based on the cue at the bottom of the screen ("Shape" or "Color") and is set up with a red triangle on the bottom left and a blue rectangle on the bottom right. The matching cue ("Shape" or "Color") appears in the lower middle part of the screen for 800 ms, followed by a central fixation cross for 200 ms. The target shape is presented over the fixation cross in the middle of the screen for 5000 ms or until the subject responds. In task-homogeneous blocks, participants match to either color or shape. In task-heterogeneous blocks, participants alternate between the two tasks pseudo-randomly. Our primary measure was the heterogeneous block (median time). This was subsequently residualized for homogeneous blocks (median time) in the measurement model (see statistical analyses section).

Number-Letter (Mental Set Shifting): The number-letter task was previously described by Miyake and colleagues (2000) and adapted from Rogers and Monsell (Rogers & Monsell, 1995). In this task, a number–letter pair (e.g., 7G) is presented in one of four quadrants on the computer screen. The participants are instructed to indicate whether the number is odd or even when the number–letter pair was presented in either of the top two quadrants and to indicate whether the letter is a consonant or a vowel (G, K, M, and R for consonant; A, E, I, and U for vowel) when the number–letter pair is presented in either of the bottom two quadrants. The trials within the first two blocks require no task switching, whereas half of the trials in the third block require participants to shift between these two types of categorization operations. Our primary measure was obtained from the shifting trials (median time). This was subsequently residualized for non-shifting trials (median time) in the measurement model.

Design Fluency (Mental Set-Shifting): Design Fluency from the D-KEFS has been described in many prior publications (Houston et al., 2005; Kramer et al., 2007; Suchy, Kraybill, & Gidley Larson, 2010), and requires the participant to quickly draw designs using four straight lines that connect dots, with every design being different. Our primary measure

was the shifting condition (total correct), which was subsequently residualized for the empty dot condition (total correct) in the measurement model.

Enclosed Flanker Test (Inhibition): The flanker test (Eriksen & Eriksen, 1974) is a commonly used measure of inhibition, in which the target stimulus is a centrally presented arrow facing either to the left or right. Participants are instructed to identify the direction of this central arrow by pressing one key for the left direction and a different key for the right direction. The targets are flanked on either side by two arrows that were either facing the same direction (congruent condition) or the opposite direction (incongruent condition). Accuracy rates and median reaction times were calculated for the congruent and incongruent trials. Our primary measure was the incongruent condition (median time), which was subsequently residualized for the congruent condition (median time) in the measurement model.

Antisaccade Task (Inhibition): The antisaccade task (Hellmuth et al., 2012) is a measure of inhibition that begins with a fixation point presented in the middle of the computer screen for a variable amount of time (ranging between 1500 and 3500 ms). A visual cue (0.4°) consisting of a black square is presented on one side of the screen for 225 ms, followed by the presentation of a target stimulus (2.0°) on the opposite side for 150 ms before being masked by grey cross-hatching. The target stimulus consisted of an arrow inside an open square. Subjects are instructed to indicate the direction of the arrow (left, up, or right) with a button press response. The proportion of target trials answered correctly served as the primary measure of interest.

Stroop Inhibition (Inhibition): The Stroop Interference test contained two conditions: Color Naming and Interference. In the first condition, Color Naming, participants were shown a stimulus with 126 (18 rows of 7) word-length strings of 'X's (e.g., XXX XXXXX XXXX) printed in blue, red, or green ink, and asked to name the ink color of each. In the second condition, Interference, participants were shown a stimulus with 77 (11 rows of 7) color words (blue, red, and green) written in incongruent colors and asked to name the ink color in which the words are written. Our primary measure was the incongruent condition (total correct), which was subsequently residualized for the color naming condition (total correct) in the measurement model.

Dot Counting (Updating/Working Memory): Dot counting is a working memory task developed for the NINDS sponsored NIH-EXAMINER (Kramer, 2014; Kramer et al., 2014). The dot counting task is a variation of the counting span paradigm used extensively in studies of auditory working memory (Conway et al., 2005; Hitch & McAuley, 1991). Participants are presented with a series of computer screens on which there was an array of blue and green circles and squares. Subjects were instructed to count the number of blue circles and remember their tally for later recall. The screens were presented in series that ranged in length from two to six circles. At the end of each series of screens, participants were required to state the total number of blue circles on each screen in that series. A partial-credit scoring system was used, based on how many totals the examinee recalled correctly from each trial. Our primary measure was the total score.

Running Letter Memory (Updating/Working Memory): The letter memory task (Miyake et al., 2000) involves visual presentation of letters presented serially for 2 seconds per letter, of increasing length (up to 12). Participants are required to recall the last 4 letters presented in the list. Our primary measure was the proportion of letters recalled correctly.

N-back 1 and 2 (Updating/Working Memory): We employed the NIH-EXAMINER version of the classic n-back test during which examinees were shown a series of white squares that appeared in 15 different locations on a black screen. Each square is presented for 1000 milliseconds, and all of the locations are equidistant from the center of the screen. During the 1-back, the examinee is instructed to press the left arrow key whenever the square was presented in the same location as the previous one [2-back: same location as square two squares prior] and the right arrow key if the square is presented in a different location than the previous one [2-back: different location than square two squares prior]. A d-prime was calculated for both 1- and 2-back and served as our primary variables.

Digit Span Backwards (Updating/Working Memory): Digit span backwards is a task that has been described in detail in previous publications (Kramer et al., 2003). Total span backwards (maximum points: 9) was used as our primary variable.

2.2.2 Cognitive Assessment: Processing Speed—Considering the strong association between executive functions and processing speed (Salthouse, 1992; Salthouse, 2005), we utilized the low processing conditions for several aforementioned tasks as indices of speed. Tasks included: non-shift trials for the set-shifting and number-letter tasks (median time); empty condition for design fluency (total correct); congruent condition for enclosed flanker (median time); and color naming condition for Stroop (total correct).

2.2.3 Structural and Diffusion Neuroimaging—MRI scans were obtained on a 3.0 Tesla Siemens (Siemens, Iselin, NJ) TIM Trio scanner equipped with a 12-channel head coil located at the UCSF Neuroscience Imaging Center. Whole brain images were acquired using volumetric magnetization prepared rapid gradient-echo sequence (MPRAGE; TR/TE/TI = 2300/2.98/900 ms, $\alpha = 9°$). The field of view was 240×256 mm, with 1×1 mm in-plane resolution and 1 mm slice thickness. Diffusion imaging data were acquired via a spin-echo, echo planar imaging sequence with 55 slices 2 mm thick (TR/TE = 8000/109 ms, FOV= 220 mm, matrix = 100×100) in two series. One series contained diffusion gradients and 64 diffusion directions (b= 0 and b= 2000 s/mm^2, 1 average) while the other had no diffusion gradients and 6 diffusion directions (b= 0, 10 averages).

FreeSurfer: The T1 MPRAGE structural MR images were analyzed using the FreeSurfer 5.1 image analysis suite, which is documented and freely available for download online at: http://surfer.nmr.mgh.harvard.edu. Previous publications have provided detailed descriptions and validation of the software (Dale, Fischl, & Sereno, 1999; Fischl, Liu, & Dale, 2001; Segonne et al., 2004). Freesurfer is a surface-based structural MRI analysis tool that segments white matter and tessellates both grey and white matter surfaces (Segonne, Pacheco, & Fischl, 2007). The procedure, in brief, involves the removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne et al., 2004) and intensity normalization (Sled, Zijdenbos, & Evans, 1998), followed by automated Talairach

transformation and volumetric segmentation of cortical and subcortical grey and white matter, subcortical limbic structures, basal ganglia and ventricles (Fischl et al., 2002; Fischl et al., 2004). Estimated total intracranial volume (ICV) is calculated via an atlas normalization procedure. The surfacing algorithm uses intensity and continuity data, and corrects topological defects to generate a continuous cortical ribbon used to calculate grey matter volume and thickness (Fischl & Dale, 2000; Fischl et al., 2001), a procedure validated against histological analysis (Rosas et al., 2002) and manual measurements (Kuperberg et al., 2003). This cortical surface is then inflated and registered to a spherical atlas and parcellated into regions of interest (ROI) based on gyral and sulcal structure (Desikan et al., 2006).

For the purposes of this study, the T1 image for each subject was processed through FreeSurfer version 5.1, and then individually quality checked for anatomical accuracy of white/grey matter segmentation. Common geometric inaccuracies in white matter and pial surfaces were manually corrected using the built in editing packages of FreeSurfer.

We calculated total grey matter volumes for frontal, parietal, temporal, and occipital grey matter, based on the Desikan atlas (Desikan et al., 2006). Left and right parietal total volume was defined as posterior cingulate, inferior parietal, precuneus, superior parietal, and supramarginal grey matter volumes. Left and right occipital lobe was defined as lingual, pericalcarine, cuneus, and lateral occipital grey matter volumes. Frontal lobe volumes were defined by rostral and caudal middle frontal, pars opercularis, pars triangularis, pars orbitalis, inferior frontal, anterior cingulate, orbitofrontal, frontal pole, and superior frontal gyri. Finally, temporal lobe volumes were defined by the banks of the superior temporal gyrus, superior, inferior, middle, and transverse temporal gyri. We also calculated grey matter volumes for multiple, more granular ROIs for each lobe. These were as follows: 1) frontal: medial orbital, dorsal middle, and lateral frontal gyri; 2) temporal: middle inferior, superior, and medial temporal gyri; 3) parietal: inferior, medial, and superior parietal gyri; and 4) occipital: medial and lateral occipital gyri. Left and right hemisphere volumes for each ROI were averaged and these averaged values were entered into analyses.

White Matter FA: We also examined white matter fractional anisotropy (FA) in several specific white matter tracts relevant to executive function. We elected to employ the most commonly used measure of white matter microstructure in our white matter analyses (FA) to limit the number of analyses conducted. Specifically, considering the association between fronto-parietal structure and executive functions, we chose to examine the contribution of the superior longitudinal fasciculus (SLF), corpus callosum, and cingulum ROI's on executive function in our model. ROI's were extracted using the JHU ICBM-DTI-81 white matter labels. Mean FA values for each white matter region was calculated using the FSL utility fslstats. Left and right hemisphere white matter regions were averaged to form a unitary measure. Separate corpus callosum values for the genu, body, and splenium were averaged to form an overall FA measure for the corpus callosum.

2.3 Statistical analyses

We used the Blom transformation to normalize test scores and to equate variables on the same scale. The Blom transformation replaces raw scores with the normal equivalent deviate of the raw score percentile rank.

Latent variable modeling methods were used to ascertain latent variables that a) characterize the associations among executive function variables, independent of indicator variables of processing speed (measurement model), b) evaluate the relationships between these latent variables and measures of grey matter volume (individual lobar and global atrophy) and age (structural model), and c) evaluate the relationships between these latent variables and diffusion tensor imaging measures of fronto-parietal white matter microstructure. A secondary analysis evaluated the cognitive measurement model using executive and speed measures that were residualized for age.

2.3.1 Measurement model

Executive Function Measurement Model: The initial step in model building identified a measurement model that explained the associations among measures of executive functions. We residualized five of the executive function scores for their speed-based, low processing load counterparts by regressing: design fluency switching condition on empty dots condition; number-letter shifting on number-letter non-shifting; set-shifting condition on non-shifting condition; incongruent flanker on congruent flanker; and stroop incongruent on congruent condition. Latent variables were used to capture the residuals from these regressions as speed independent measures of executive function. We then used these five residuals, their speed-based low processing load counterparts, and the other six executive function measures as indicators for confirmatory factor analyses (CFA) to identify an optimal measurement model.

We tested alternative CFA models to explain covariance among the executive function measures. Models that were tested included the following: 1) speed plus three executive factors - mental set-shifting, updating/working memory, and inhibition; 2) speed plus two factors - updating/working memory and shifting/inhibition; and 3) speed plus a single-factor global executive function factor defined by all 11 executive function variables. Due to overlapping methodologies, n-back 1 and n-back 2 were allowed to have a residual correlation in all models. We evaluated model fit to identify the optimal cognitive measurement model. Figure 1 shows a diagram of the speed + 2-factor model.

We also evaluated this model using cognitive indicators that were residualized for the effects of age. Each observed executive and processing speed measure was regressed on age and the residual variance not explained by age was captured by a latent variable. These latent variables were then used as indicators for factors in the alternate CFA models. Latent variables defining residuals and factors were simultaneously estimated for each model.

Grey Matter Structure Measurement Model: We developed a latent variable model to decompose grey matter volumes into a global grey matter factor and specific lobar volumes that were independent of global grey matter. This model is presented in Figure 2. Grey

matter volumes from lobar sub-regions were used as multiple indicators for lobe-specific and global grey matter factors. Specific ROI volumes were regressed on total intracranial volume (ICV) to remove effects of overall head size and a bi-factor structure was used to define latent variables that represented global grey matter and lobe specific grey matter volumes. Global and specific factors were constrained to be uncorrelated and the global factor was uncorrelated with specific factors to identify the model. The global factor captures common variance in brain grey matter volumes not explained by ICV, and the specific factors capture lobe-specific differences from what is expected on the basis of ICV and global grey matter.

2.3.2 Structural Model: Grey Matter Analyses—We merged executive function and lobar grey matter volume measures in the next step of model development and used grey matter volumes as independent variables to explain executive function factors. For Analysis 1, we first examined whether prefrontal lobe grey matter was related to the executive function factors. This allowed us to replicate an extensive prior literature relating executive functions to frontal lobe structure. As noted, we regressed frontal lobe volume on ICV and captured the residual with a latent variable. We then tested the association between cognition and brain structure by regressing the executive function factors and speed factor on residual prefrontal grey matter volume. We then repeated this analysis in separate models for the other three lobar volumes entered as lone independent variables to explain executive and speed factors.

For Analysis 2, we evaluated effects of global grey matter volume and lobe specific residual volumes on executive function and speed factors, thereby disentangling global and lobe-specific effects. We merged the measurement model for executive function (Figure 1) with the measurement model for grey matter volumes (Figure 2). First we included global grey matter as the lone independent variable to explain executive and speed factors. Then in a separate analysis for each lobe, we regressed the executive function factors on global grey matter and the lobe specific residual grey matter not explained by ICV or global grey matter. Finally, we examined the role of age in modifying the relationship between executive function and grey matter brain volume latent variables.

2.3.4 Structural Model: White Matter Microstructure Analyses—In order to evaluate whether fronto-parietal white matter microstructure underlies and independently contributes to executive functions, we added mean FA for the superior longitudinal fasciculus (dorsal portion), corpus callosum, and cingulum bundle (dorsal portion) to models that included grey matter volumes related to cognitive variables in previous analyses.

Model estimation was performed with Mplus version 7.2 (Muthén & Muthén, 1998–2012). All model parameters were simultaneously estimated in each step. That is, for example, in the model testing effects of global grey matter and frontal-specific grey matter on executive function, executive factors, brain factors, and regression of executive factors on brain factors were simultaneously estimated. Model fit was evaluated using an overall χ^2 test supplemented by fit indices: the comparative fit index (CFI) (Bentler, 1990), the Tucker-Lewis index (TLI) (Tucker & Lewis, 1973) and the root mean square error of approximation

(RMSEA) (Cudek & Browne, 1983). CFI and TLI values of 0.95 and higher indicate good fit; RMSEA value of 0.08 and lower indicate acceptable fit.

3. Results

3.1 Executive Function Measurement Model

The 2-factor plus speed and 3-factor plus speed models both showed good model fit. There were technical problems with the 3-factor plus speed model due to high intercorrelations of factors; the intercorrelation of set-shifting with inhibition was 0.97. This indicates that these factors are not differentiable, and consequently, the 2-factor plus speed model was selected as the base measurement model for further analyses (see Table 2 for fit indices; model displayed in Figure 1). Speed was highly correlated with shifting/inhibition (r=0.88) even though processing speed variance was removed from the time dependent indicators for individual shifting/inhibition measures. The correlation of updating/working memory with shifting/inhibition was 0.53 and with Speed was 0.58.

Results were essentially unchanged when executive and speed variables were residualized for the effects of age. The 2-factor plus speed and 3-factor plus speed models fit well, but set-shifting and inhibition were not differentiable in the 3-factor plus speed model (correlation=0.95). Correlations of factors in the 2-factor plus speed model were quite similar to those in the primary model: shifting/inhibition with speed= 0.85, working memory with shifting/inhibition= 0.46, working memory with speed = 0.54.

3.2 Analysis 1: Executive Function and Lobar Grey Matter Volumes

Executive function and speed factors were regressed on lobar grey matter volumes adjusted for ICV in a separate analysis for each lobe. Table 3 shows these simple effects of lobar volumes adjusted for ICV on updating/working memory, shifting/inhibition, and speed factors. All lobar volumes were associated with all three factors, and there was not a clear difference in strength of effects associated with different lobes. While frontal lobe grey matter was related to all three executive and speed variables, this was not the strongest effect for any variable.

3.3 Analysis 2: Executive Function and Lobar Grey Matter Independent of Global Atrophy

We next examined independent contribution to executive function and speed of global grey matter and specific lobar volumes. The executive function and speed factors were first regressed on the global grey matter factor. Global grey matter was related to updating/working memory (standardized $\beta = 0.332$, SE =0.086, $p < 0.001$), shifting/inhibition ($\beta = 0.403$, SE =0.077, $p < 0.001$), and speed ($\beta = 0.327$, SE =0.078, $p < 0.001$). Then, lobe specific grey matter volumes and global grey matter were added as independent variables in separate models. Global grey matter continued to be related to all the executive function variables and speed in all models (see Table 4). Relatively weak but statistically significant specific temporal lobe effects were found for speed, and specific occipital lobe effects were found for shifting/inhibition and speed. Neither frontal[1] nor parietal lobe grey matter contributed to executive and speed variables independent of global grey matter. A subsequent model included specific temporal and occipital volume factors along with global

grey matter volume. Global grey matter was related to all three variables (updating/working memory standardized β= 0.318 (0.088), shifting/inhibition standardized β =0.360 (0.080), speed standardized β = 0.285 (0.081)). Temporal grey matter was independently related to updating/working memory (β = 0.185 (0.091) and occipital grey matter was independently related to shifting/inhibition (β = 0.264 (0.121)).

Age was then added as a covariate to the model that included global grey matter and specific temporal and occipital lobe volumes as independent variables. Age effects were significant for shifting/inhibition and speed factors, and approached significance for working memory (p=.080). Global grey matter effects in this model were significant though attenuated for updating/working memory and shifting/inhibition (updating/working memory - β = 0.255, SE =0.100, p = 0.011; shifting/inhibition- β = 0.210, SE =0.093, p = 0.023) and approached significance for speed (β = 0.172, SE =0.091, p = 0.058). Temporal lobe effects on updating/working memory and occipital effects on shifting/inhibition approached significance (p's >0.10).

3.4 Analysis 3: Executive Function and Fronto-parietal White Matter Microstructure

We also examined whether white matter microstructure in the cingulum, corpus callosum, and SLF added explanatory power for speed and executive factors. We estimated separate models for each FA ROI that also included global grey matter, temporal and occipital grey matter volumes as independent variables. Cingulum FA made significant independent contributions to all three variables (updating/working memory: β =0.199, SE=0.085, p=0.019; shifting/inhibition: β =0.200, SE=0.078, p=0.011; Speed: β =0.290, SE=0.075, p<0.001) and corpus callosum FA was independently related to shifting/inhibition (β =0.283, SE= 0.083, p=0.001) and speed (β =0.377, SE=0.077, p=0.000) but not updating/working memory (β =0.095, SE=0.092, p=0.306). No independent effects of the SLF FA were observed on cognitive measures (p>0.100 for all). We estimated separate models for the genu, body, and splenium of the corpus callosum. Similar results were found in the three models but associations with corpus callosum FA were slightly stronger when the average of the three sub-regions was used.

A final model included global grey matter, temporal grey matter, occipital grey matter, cingulum FA, and corpus callosum FA as joint independent variables. Results are shown in Table 5. Global grey matter volume was independently related to updating/working memory and shifting/inhibition, cingulum FA was independently related to updating/working memory, and corpus callosum FA was independently related to shifting/inhibition and speed. To rephrase, global grey matter made a strong contribution to updating/working memory, global grey matter and corpus callosum FA both had notable effects on shifting/inhibition, and corpus callosum FA was strongly related to speed.

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[1]We also examined specific frontal lobe regions associated with executive functions to determine whether 'specific' regions (e.g. dorsal and inferior frontal gyri, anterior cingulate) were more strongly predictive than total prefrontal grey mater. Results using this approach were comparable, with no independent effects of any specific frontal ROI.

4. Discussion

This study examined the structural relationship between indices of executive functions (i.e. shifting/inhibition and updating/working memory), prefrontal and non-frontal lobar volumes, and global grey matter in a cohort of healthy, community dwelling older adults. Our findings suggest that while prefrontal grey matter volumes are significantly associated with executive functions, they do not *independently* predict executive function when *statistically isolated* from global atrophy. Thus, global atrophy was the major, independent predictor of executive functions when considering the simultaneous role of individual lobar and global grey matter volumes. Including age as a covariate in our models did not substantively affect results, although it did attenuate the effect size. In an evaluation of fronto-parietal white matter microstructure, study results further suggest that higher corpus callosum and cingulate (dorsal) FA predicted better executive functions, independent of global grey matter atrophy. To our knowledge, this is the first study to employ latent variable modeling techniques to elucidate the sensitivity and specificity of prefrontal lobe volume contributions and fronto-parietal white matter microstructure to executive functions in healthy older adults; results moreover support a large body of literature suggesting that a broad range of grey and white matter structures subserve executive functions.

The rich literature on executive functions suggests that a dorsal fronto-parietal network of grey and white matter regions are important, if not keystone structures for these higher order processes (Brass et al., 2005; Burzynska et al., 2012). Despite increasing evidence that executive dysfunction can originate or be elicited from disruption in non-frontal regions, executive function tasks are still often conceptualized as 'frontal' neuropsychological measures. Results from our study highlight that while prefrontal lobe volumes are unsurprisingly associated with executive functions, they cannot be viewed in isolation from more distributed volume effects in a healthy older adult cohort. By disentangling the contribution of prefrontal lobe volumes from temporal, parietal and occipital effects as well as global atrophy, the independent role of prefrontal lobe volumes on executive functions is markedly diminished. In fact, our analyses showed significant, albeit weak independent effects of temporal and occipital lobe on executive function and speed measures. This is not to suggest that executive functions are driven by generalized, non-specific brain morphology, but more to highlight that prefrontal lobe contributions are part of a rich network of grey (and white) matter structures that support this complex cognitive construct. Although we did not directly test the role of network connectivity in this study, our findings suggest that sequestering prefrontal contribution to executive functions from other brain regions may obscure and oversimplify important brain-behavior relationships.

Moreover, secondary analyses of fronto-parietal white matter microstructure provided additional support for both grey and white matter contributions to executive functions. Results suggested that cortical grey matter makes a strong contribution to updating/working memory (although cingulum FA independently contributes as well), cortical grey matter and corpus callosum FA both contribute to shifting/inhibition, and corpus callosum FA displays strong associations with speed. No independent effects were noted for the SLF. Although the latter was somewhat surprising given the SLF's extensive role in fronto-parietal connectivity, the robust, independent associations between the corpus callosum and both shifting/

inhibition and speed variables are consistent with prior studies (Kennedy & Raz, 2009). Notably, in contrast to the lack of *independent* effects of prefrontal grey matter on executive functions, the corpus callosum [shifting/inhibition, speed] and cingulate [updating/working memory] fibers evidenced a strong association with individual executive function variables after accounting for global grey matter atrophy. This may be due in part to the fronto-parietal nature of these structures. Nonetheless, study results provide evidence for a critical, albeit distributed role of both grey and white matter structures in supporting the broad construct of executive functions. Future work using white matter tractography methodologies may be beneficial to further explicate these complex associations, and to elucidate the interaction between grey and white matter structures.

Considering that the study sample consisted of healthy older adults, it is also important to consider the role of age in modifying the relationship between executive functions and grey matter volume. Study results indicate that age did not have a substantive effect on the observed relationships between shifting/inhibition, updating/working memory, speed and global grey matter volume, but did attenuate the effect size of the associations. The inclusion of age as a covariate is often a reflexive decision in modeling any cognitive constructs in late life populations; however, it is important to consider whether by controlling for age we are in fact dampening meaningful, and potentially explainable variance in these models. We elected to include both models, with and without age as a covariate, but it remains unclear whether the former is a better or more robust characterization of these structural relationships.

This study had several strengths, including the detailed, hypothesis-based characterization of executive functions. Eleven measures of executive functions were included in the model, and were selected based on prior theoretical models of this construct (Miyake et al, 2000) to measure mental set-shifting, updating/working memory, and inhibition. Interestingly, confirmatory factor analysis of a priori alternate measurement models indicated that while this 3-factor model fit the data well, it did not produce differentiable inhibition and set-shifting factors. As such, we combined inhibition and set-shifting measures to form a 'shifting/inhibition' factor along with the updating/working memory factor. Differences between our factor analytic results (i.e. 2-factor rather than 3-factor) and previous studies may stem from subtle differences in specific tasks used. The high correlations observed between these factors are commonly reported in the literature and not necessarily surprising given the overlapping nature of this heterogeneous construct; thus, creating discrete sub-categories is often a challenging task. The careful delineation of executive functions in this study also included a focused examination of processing speed, which was related to both factors as well as global grey matter volume. By controlling for the baseline conditions for all time-based executive function tasks (e.g. controlled for congruent/non-switching conditions when evaluating incongruent/switching task conditions), we also disentangled some aspects of information processing speed from executive control, allowing for a more 'pure' executive construct.

An additional strength of the study was the use of latent variable modeling to differentiate the independent effects of prefrontal and individual lobar contributions from the effects of global atrophy on executive functions. This facilitated a focused examination of our

competing hypotheses on the role of prefrontal lobe volumes in supporting executive functions. Although numerous prior studies have associated prefrontal volumes (as well as parietal volumes) with executive functions in health aging, these investigations did not disentangle relationships with global atrophy or non-frontal volumes. By extracting and controlling for shared variance between frontal, non-frontal and global volumes, we were able to more thoroughly assess the association between prefrontal volumes and executive functions in a community dwelling older adult cohort.

It is also prudent to highlight several limitations to interpretation. First, it may be that our use of a healthy cohort (rather than a neurodegenerative group) obscured or dampened our ability to find independent effects of prefrontal or non-frontal lobar volumes on executive functions, particularly considering the well documented lack of association between other aspects of cognition (e.g. memory) and brain structure (e.g. hippocampal volume) in normal aging (Van Petten, 2004). That said, ample variability was noted in volumes and an association between prefrontal volumes and executive functions was clearly observed, but did not hold up when controlling for global atrophy. A related consideration is that we primarily examined the role of grey matter volume, which is only one metric by which we can measure frontal lobe contributions. Further investigations of cortical thickness, diffusion metrics (including mean diffusivity and radial diffusivity), and resting state networks will likely add to our understanding of the dynamic and complex roles of prefrontal volumes. In line with this limitation, given our interest in examining frontoparietal white matter contributions, we did not conduct a fine grain analysis of lobar specific white matter diffusion metrics; thus broad conclusions regarding grey vs white matter contribution should not be drawn from the results. Due to the number of analyses, we did not conduct permutation tests wherein the relative contributions of each independent variable could be contrasted in reference to an empirically generated null-distribution. Thus, strong *comparative* statements about individual lobar contributions to executive functions are limited. Finally, although our sample was comprised of 'healthy', community dwelling older adult research participants, it is possible and likely that a portion of these individuals had underlying Alzheimer's disease pathology without overt clinical manifestations.

In summary, findings from the current study indicate that while prefrontal grey matter volumes are significantly associated with cognitive neuroscience measures of shifting/ inhibition and working memory in healthy older adults, they do not *independently* predict executive function when statistically isolated from global atrophy and individual non-frontal lobar volume contributions. In contrast, better microstructure of fronto-parietal white matter, particularly the corpus callosum, continued to predict executive functions after accounting for global grey matter atrophy. These findings contribute to a growing literature suggesting that executive functions are a heterogeneous and complex construct that requires on-line integration and manipulation of multiple cognitive processes from several input modalities. As such, prefrontal contributions to executive functions cannot be viewed in isolation from more distributed grey and white matter effects in a healthy older adult cohort.

Acknowledgments

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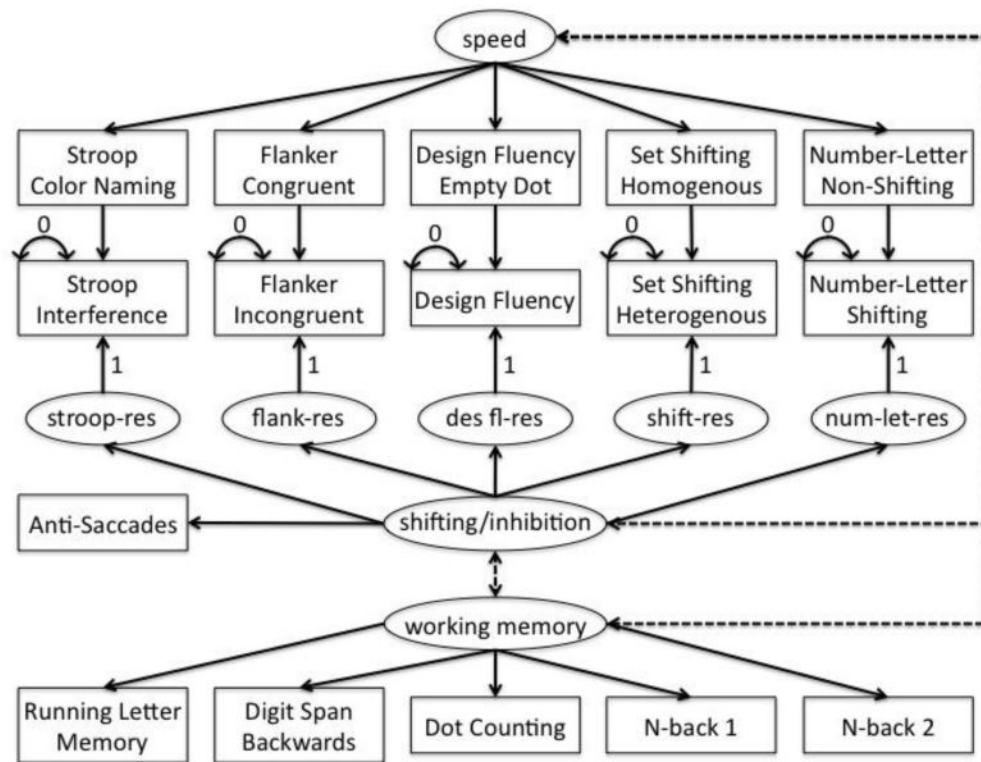
Figure 1. Executive Function Two Factor Measurement Model

Figure 1 displays the two factor measurement model, resulting in a shifting/inhibition factor and an updating/working memory factor. Key: Res=residual.
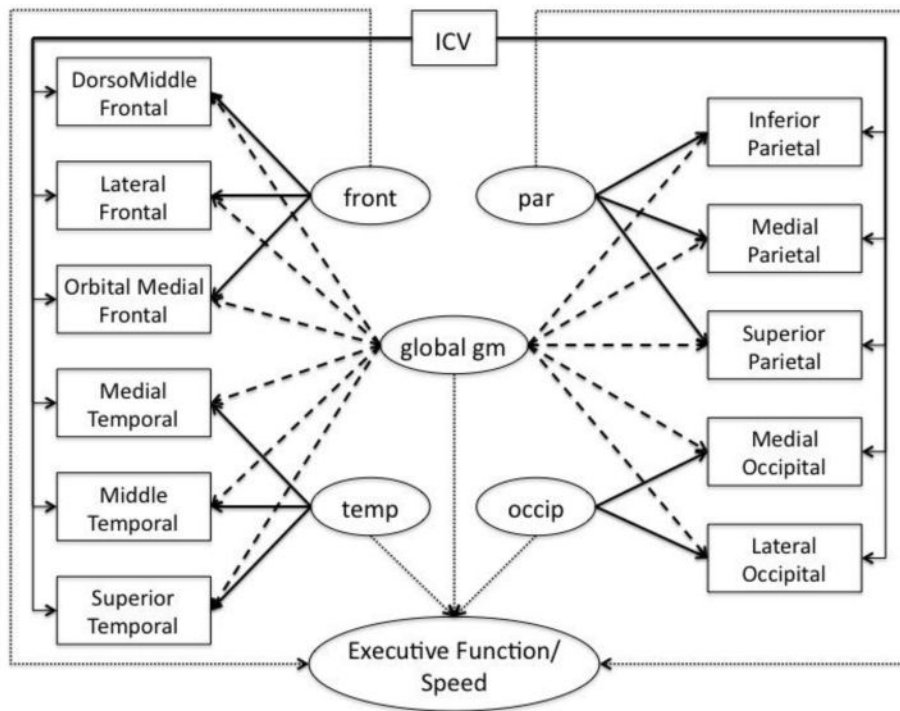
Figure 2. Grey Matter Measurement Model

Figure 2 displays the grey matter measurement model. Key: gm=grey matter; front=frontal; par=parietal; temp=temporal; occip=occipital

Table 1

Demographic, Cognitive and Neuroimaging Characteristics of Participants

	N	Mean (Standard Deviation)	Range
Demographics			
Age (Years)	202	73.68(6.60)	63–99
Education (Years)	202	17.67(2.19)	12–22
Female Sex (%)	202	50.50	
Executive Functions Measures:			
Set-Shifting, Shift Trials (ms)	195	865.61(243.15)	478.00–1595.50
Number-Letter, Shift Trials (ms)	198	1460.76(351.08)	855.00–2879.50
Design Fluency, Shift Condition (Total Correct)	198	7.54(2.46)	0.00–14.00
Enclosed Flanker, Incongruent Condition (ms)	197	567.61 (73.15)	412.00–802.5
Antisaccade (Proportion Correct)	138	64.21(25.09)	0.00–100.00
Stroop, Inhibition Condition (Total Correct)	182	47.93(11.36)	27.99–77.00
Dot Counting (Total Correct)	199	35.77 (7.54)	16.00–53.00
Running Letter Memory (Proportion Correct)	180	40.36(12.94)	6.00–67.00
N-Back 1 (D-Prime)	199	2.46(0.67)	0.47–3.67
N-Back 2(D-Prime)	148	1.36(0.66)	−0.79–3.24
Digit Span Backwards (Total Span)	180	5.47(1.33)	3.00–8.00
Speed Measures			
Set-Shifting, Non-Shift Trials (ms)	195	724.20(185.12)	428.00–1801.50
Number-Letter, Non-Shift Trials (ms)	198	779.84(127.71)	534.50–1386.50
Design Fluency, Empty Condition (Total Correct)	199	11.54(3.08)	4.00–19.00
Enclosed Flanker, Congruent Condition (ms)	197	472.63 (78.15)	335.00–762.00
Stroop, Color Naming Condition (Total Correct)	182	84.14(14.96)	43.00–126.00
Neuroimaging Measures:			
Intracranial Volume (mm^3)	184	1455437.75 (167491.23)	1015197.97–1923332.17
Frontal Lobe Volume (mm^3) [*];	184	157767.89 (15996.06)	121536.00–202132.00
Parietal Lobe Volume (mm^3) [**];	184	98699.58 (9776.96)	76319.00–131674.00
Temporal Lobe Volume (mm^3)	184	84623.11(9003.58)	64346.00–108144.00
Occipital Lobe Volume (mm^3)	184	46141.08 (6096.25)	32988.00–71915.00
Superior Longitudinal Fasciculus Fractional Anisotropy	193	0.39 (0.02)	0.29–0.45
Corpus Callosum Fractional Anisotropy	193	0.51 (0.03)	0.43–0.57
Cingulate (Dorsal) Fractioanl Anisotropy	193	0.33 (0.02)	0.26–0.37

[*] Excluding primary motor cortex

[**] Excluding primary sensory cortex ms=milliseconds mm=millimeters

Table 2

Fit Indices for Measurement Models of Executive Functioning Constructs

Model	Overall χ^2[df]	CFI	TLI	RMSEA (90% CI)
1 Factor Plus Speed				
Global executive function	190.087 [97]	0.929	0.913	0.069 [0.054–0.083]
2 Factor Plus Speed				
Shifting/inhibition, updating/working memory	144.120 [95]	0.963	0.953	0.051 [0.033–0.067]
3 Factor Plus Speed				
Set-shifting, updating/working memory, and inhibition	134.865 [92]	0.968	0.958	0.048 (0.029–0.065)

Table 3

Effects of Individual Lobar Grey Matter Volumes on Executive and Speed Factors.

Independent Variable	Dependent Variable	Estimate	Standard error	*p-value*
Frontal Grey Matter	Updating/Working Memory	0.307	0.083	0.000
	Shifting/Inhibition	0.328	0.077	0.000
	Speed	0.274	0.077	0.000
Temporal Grey Matter	Updating/Working Memory	0.318	0.083	0.000
	Shifting/Inhibition	0.339	0.077	0.000
	Speed	0.283	0.077	0.000
Parietal Grey Matter	Updating/Working Memory	0.274	0.085	0.001
	Shifting/Inhibition	0.336	0.077	0.000
	Speed	0.258	0.078	0.001
Occipital Grey Matter	Updating/Working Memory	0.217	0.087	0.013
	Shifting/Inhibition	0.413	0.074	0.000
	Speed	0.339	0.074	0.000

Estimates are standardized regression coefficients from models where a single grey matter volume is entered as an independent variable.

Table 4

Effects of Global Grey Matter Volumes and Individual Lobar Grey Matter Volumes on Executive and Speed Factors.

Dependent Variable	Independent Variable	Estimate	Standard error	*p-value*
Updating/Working Memory				
	A. Frontal Grey Volume	−0.042	0.103	0.683
	Global Grey Volume	0.337	0.087	0.000
	B. Temporal Grey Volume	0.165	0.087	0.058
	Global Grey Volume	0.317	0.087	0.000
	C. Parietal Grey Volume	−0.066	0.093	0.477
	Global Grey Volume	0.344	0.086	0.000
	D. Occipital Grey Volume	−0.059	0.126	0.642
	Global Grey Volume	0.337	0.087	0.000
Shifting/Inhibition				
	A. Frontal Grey Volume	−0.131	0.097	0.176
	Global Grey Volume	0.426	0.077	0.000
	B. Temporal Grey Volume	0.142	0.081	0.078
	Global Grey Volume	0.390	0.078	0.000
	C. Parietal Grey Volume	−0.047	0.085	0.583
	Global Grey Volume	0.415	0.077	0.000
	D. Occipital Grey Volume	0.256	0.124	0.039
	Global Grey Volume	0.379	0.079	0.000
Speed				
	A. Frontal Grey Volume	−0.140	0.092	0.129
	Global Grey Volume	0.349	0.078	0.000
	B. Temporal Grey Volume	0.171	0.079	0.030
	Global Grey Volume	0.312	0.079	0.000
	C. Parietal Grey Volume	−0.009	0.084	0.918
	Global Grey Volume	0.332	0.079	0.000
	D. Occipital Grey Volume	0.231	0.113	0.040
	Global Grey Volume	0.306	0.079	0.000

Estimates are standardized regression coefficients from models where global grey matter and a single lobar grey matter volume are entered as independent variables. All individual lobar volumes reflect lobe specific residual grey matter not explained by ICV or global grey matter.

Table 5

Effects of Global Grey Matter Volumes, Individual Lobar Grey Matter Volumes and White Matter FA on Executive and Speed Factors.

Dependent Variable	Independent Variable	Estimate	Standard error	*p-value*
Updating/Working Memory	Global Grey Volume	0.310	0.091	0.001
	Temporal Grey Volume	0.167	0.091	0.066
	Occipital Grey Volume	−0.055	0.127	0.666
	Cinguium FA average	0.241	0.112	0.031
	Corpus Callosum FA average	−0.077	0.121	0.524
Shifting/Inhibition	Global Grey Volume	0.287	0.089	0.001
	Temporal Grey Volume	0.089	0.087	0.304
	Occipital Grey Volume	0.226	0.123	0.065
	Cinguium FA average	0.038	0.107	0.722
	Corpus Callosum FA average	0.256	0.113	0.024
Speed	Global Grey Volume	0.171	0.087	0.051
	Temporal Grey Volume	0.109	0.083	0.192
	Occipital Grey Volume	0.178	0.119	0.134
	Cinguium FA average	0.092	0.104	0.377
	Corpus Callosum FA average	0.311	0.108	0.004