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Longitudinal Alterations to Brain Function, Structure, and Cognitive Performance in Healthy Older Adults: a fMRI-DTI study

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Abstract

Cross-sectional research has shown that older adults tend to have different frontal cortex activation patterns, poorer brain structure, and lower task performance than younger adults. However, relationships between longitudinal changes in brain function, brain structure, and cognitive performance in older adults are less well understood. Here we present the results of a longitudinal, combined fMRI-DTI study in cognitive normal (CN) older adults. A two time-point study was conducted in which participants completed a task switching paradigm while fMRI data was collected and underwent the identical scanning protocol an average of 3.3 years later (SD = 2 months). We observed longitudinal fMRI activation increases in bilateral regions of lateral frontal cortex at time point 2. These fMRI activation increases were associated with longitudinal declines in WM microstructure in a portion of the corpus callosum connecting the increasingly recruited frontal regions. In addition, the fMRI activation increase in the left VLPFC was associated with longitudinal increases in response latencies. Taken together, our results suggest that local frontal activation increases in CN older adults may in part reflect a response to reduced inter-hemispheric signaling mechanisms.

Keywords

aging; longitudinal; diffusion tensor imaging; fMRI

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1 INTRODUCTION

Human aging is associated with declines in cognition and alterations to brain structure and function (Cabeza & Dennis, 2012; Drag & Bieliauskas, 2010; Grady, 2008; Reuter-Lorenz & Cappell, 2008; Salthouse, 2010). Cross-sectional functional neuroimaging studies have consistently found differences in brain activation patterns of older adults compared to younger adults (Eyler, Sherzai, Kaup, & Jeste, 2011; Spreng, Wojtowicz, & Grady, 2010). While a variety of age-related alterations in brain activation have been reported, among the most common is a pattern of increased activation in frontal brain regions (Dennis & Cabeza, 2008; Drag & Bieliauskas, 2010; Reuter-Lorenz & Park, 2010). Increased frontal recruitment in older adults has been reported across a variety of task domains (Cabeza, 2002; Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008; Grady, et al., 2010; Hakun, Zhu, Johnson, & Gold, 2015; Langenecker, Nielson, & Rao, 2004; Madden, et al., 2007; Milham, et al., 2002; Nielson, Langenecker, & Garavan, 2002) and appears to be especially pronounced on difficult cognitive tasks that place high demands on executive functions (Turner & Spreng, 2012).

Findings of increased frontal recruitment in older adults have garnered considerable interest in the field of neurocognitive aging and have been interpreted in several ways (Grady, 2012). For example, compensation theories hold that frontal increases in older adults represent a positive form of cognitive plasticity which may reflect upregulation of cognitive control processes intended to offset other processing deficiencies (Cabeza, 2002; Cabeza, Anderson, Locantore, & McIntosh, 2002; Cabeza, et al., 1997; Davis, et al., 2008; Grady, 2008; Grady, et al., 1994; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008). In contrast, dysfunction accounts suggest that higher frontal response in older compared to younger adults may reflect age-related declines in regional functional specificity (i.e. dedifferentiation; Goh, 2011; Li, Lindenberger, & Sikstrom, 2001) or age-related reductions in efficiency (Park, Polk, Mikels, Taylor, & Marshuetz, 2001; Rypma & D'Esposito, 2000; Stern, 2009; Zarahn, Rakitin, Abela, Flynn, & Stern, 2007).

Currently, evidence for age-related over-recruitment has come entirely from cross-sectional comparisons between older and younger adults. While an important first step, cross-sectional studies can be influenced by cohort effects and baseline individual differences, leading to calls for longitudinal studies of neurocognitive aging (Grady, 2012; Lindenberger, 2014; Raz & Lindenberger, 2011; Salthouse, 2011). To date, however, only a limited number of studies have acquired functional brain activation data at two time points in cognitively normal (CN) older adults (Nyberg, et al., 2010; O'Brien, et al., 2010; Persson, et al., 2012). Of these studies, two focused specifically on change in medial temporal lobe activation during memory tasks, reporting fMRI increases at follow-up (O'Brien, et al., 2010; Persson, et al., 2012).

Of particular relevance to the goals of the present study, one previous longitudinal study with CN older adults observed reduced frontal activation at a six year follow-up (Nyberg, et al., 2010). This finding contrasts with cross-sectional reports of age-related frontal activation increases and with neurocognitive theories of aging developed from cross-sectional findings, such as compensation and dysfunction accounts. It should be noted, however, that this study

used a semantic judgment task in a participant sample enriched for genetic risk of Alzheimer's disease (AD). Given that age-related frontal activation increases are frequently observed in cross-sectional studies, particularly those using executive function tasks (Turner & Spreng, 2012), it is of interest to assess longitudinal functional alterations on executive tasks in CN older adults who are not enriched for AD.

While such a design could result in several different possible activation patterns in frontal cortex, the key issue explored here was how functional alterations in CN older adults over time may be associated with changes in white matter (WM) microstructure. Age-related reductions in the WM microstructure, as estimated via diffusion tensor imaging (DTI), represent a plausible contributing mechanism to functional brain activation changes in older adults because WM provides the structural means for electrochemical signaling between neurons, declines significantly with aging (Barrick, Charlton, Clark, & Markus, 2010; Madden, et al., 2012; Sullivan & Pfefferbaum, 2006), and has been correlated with fMRI activation levels in several cross-sectional studies (Bennett & Rypma, 2013; Burzynska, et al., 2013; Daselaar, et al., 2013; Madden, et al., 2007; Persson, et al., 2006; Zhu, Johnson, Kim, & Gold, 2015). However, it remains unknown whether longitudinal alterations in fMRI and DTI are associated within individuals over time.

Finally, there is also increasing interest in understanding how longitudinal functional alterations in frontal cortex may relate to in-scanner task performance change, as this issue is of relevance to neurocognitive theories of age-related compensation and dysfunction. The task switching paradigm represents an ideal framework for examining longitudinal changes in executive control and frontal cortex activation for several reasons. First, the task switching paradigm probes a number of executive control functions including selective attention, control over response conflict, inhibitory control, and working memory updating (Brown, Reynolds, & Braver, 2007; Kramer, Hahn, & Gopher, 1999; Meiran, Kessler, & Adi-Japha, 2008; Miyake & Friedman, 2012; Monsell, 2003). In addition, task switching tends to result in strong frontal cortex activation in older adults (DiGirolamo, et al., 2001; Gazes, Rakitin, Habeck, Steffener, & Stern, 2012; Hakun, et al., 2015; Madden, et al., 2010; Zhu, et al., 2015). Finally, the possibility of a relationship between longitudinal changes in task switching performance and frontal cortex activation is motivated by previous findings of correlations between performance on this task and frontal response in cross-sectional studies (DiGirolamo, et al., 2001; Gazes, et al., 2012; Hakun, et al., 2015; Madden, et al., 2010; Zhu, et al., 2015).

Here we report longitudinal results from a combined fMRI-DTI study conducted with CN older adults using a task switching paradigm. Participants completed the task switching paradigm at time point 1 and the identical scanning protocol was repeated at time point 2, an average of 3.3 years later. Longitudinal changes in fMRI activation in frontal cortex, WM microstructure in frontal tracts, and task performance were explored. In addition, inter-relationships between changes on imaging and performance measures were assessed to evaluate the cognitive and structural correlates of age-related alterations in frontal cortex activation.

2 METHODS

2.1 Participants

A total of 18 right-handed, cognitively normal older adults participated in the present study. Participants were recruited from a group of 50 monolingual older adults involved our previous cross-sectional studies comparing bilinguals and monolinguals on brain function (Gold, Kim, Johnson, Kryscio, & Smith, 2013) and WM microstructure (Gold, Johnson, & Powell, 2013). Participants in the present study were monolinguals who agreed to return for a second scan and underwent an identical scanning protocol an average of 3.3 years ($SD = 2$ months) following their baseline scan. Participation in our previous cross-sectional studies did not stipulate participation in the present follow-up scan. Instead, the present longitudinal study was based on a sample of convenience of those individuals who still resided in Lexington, KY a period of 3 years following initial participation and were willing and able to return for a second scan. Of the 50 participants initially recruited, 23 participants could no longer be contacted based on their previous contact information or had relocated to another area of the country. Of the remaining 27 participants, 9 participants failed screening due to changes in MRI-eligibility or cognitive status, or were not interested in returning for a follow-up scan. The baseline demographics (age, education, gender) and IQ scores of participants who returned for the follow-up scan and those who did not return were not significantly different (all p 's > 0.1).

Exclusionary criteria for both studies were color blindness, major head injury, stroke, neurological or psychiatric disorder, high blood pressure, diabetes, heart disease, the use of psychotropic drugs, and or the presence of metal fragments and/or metallic implants contraindicated for MRI. Written informed consent was obtained from each participant under an approved University of Kentucky Institutional Review Board protocol.

2.2 Demographic and Cognitive Measures

The Hollingshead Two-Factor Index of Social Position (ISP) was used as a measure of socioeconomic status (SES; Hollingshead & Redlich, 1958). The ISP is based on an individual's occupation and highest level of formal education. It is calculated by assigning numeric values, from 1–7, to an individual's occupation and education. Scores are then weighted by multiplying by 7 (occupation) and 4 (education). Values are then summed to produce a social index. Lower values represent higher earning occupations and more years of education.

The Cattell Culture Fair (CCF) Intelligence Test (Cattell & Cattell, 1960) was used as a measure of intelligence. The CCF was used because it assesses non-verbal intelligence associated with perceiving inductive relationships in shapes and figures, skills relevant to the present fMRI task involving switching between non-verbal perceptual judgments.

The Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) was administered at TP2 to determine if any returning participants had developed cognitive impairment. The MMSE is a 30-point questionnaire that evaluates orientation to time and location, ability to follow sequential directions and basic verbal, short-term memory, and spatial abilities.

2.3 Materials and Procedure

Participants completed a color-shape task switching paradigm described in detail in our previous work (Gold, Kim, et al., 2013). Briefly, in the color task block, participants were required to judge if each stimulus was red or blue. In the shape task block, participants were required to judge if each stimulus was a circle or a square. In the switching task block, participants alternated between shape and color judgments. Responses were made using MRI compatible response boxes (one in each hand). Participants were asked to press the left or right button to indicate whether the stimulus was blue or red, or circle or square, depending upon the cue word. Participants were asked to respond as quickly and accurately as possible.

Participants were given an instructional cue at the beginning of each trial (the word “color” or “shape”) which was displayed for 150ms center-screen. The instructional cue was replaced by the target stimulus which was displayed for 2650ms. Each trial ended with 200ms of central fixation (plus-sign) prior to the start of the next trial. During shape or color task blocks (i.e. “single task”) participants made the same judgment on every trial (e.g. the instructional cue was also repeated on every trial). During switching task blocks the task alternated pseudorandomly across trials, with a 50% chance of repeating/switching in consecutive trials.

Task blocks were 60 seconds in duration (20 trials per block), and fixation periods were 30 seconds in duration. There were three runs. Each run contained 4 task blocks and 5 fixation periods. One run consisted of two blocks of each of the color task and shape task. The other two runs contained one block each of the color task and shape task and two switching blocks. The order of runs, task blocks within runs, and stimulus-response mappings were counterbalanced across participants. Task stimuli were generated by E-prime software (Psychology Software Tools, Inc, Pittsburgh, PA) and projected to a mirror mounted on the MRI head coil using an MRI compatible projector. Response time and accuracy for subject responses on each trial were recorded by the stimulus presentation program.

Prior to scanning, participants received task instructions along with a maximum of 60 trials of practice for each task condition (i.e. each single task and the switching task) to reach 75% accuracy criterion before proceeding to the scanner. All participants reached this accuracy criterion within the allotted 60 trial maximum. After the scan session participants were given a brief break followed by administration of the neuropsychological measures.

2.4 Imaging Data Acquisition

Imaging data for both baseline and follow-up sessions were collected on the same 3T Siemens TIM scanner, using the same head coil, and pulse sequences, at the Magnetic Resonance Imaging and Spectroscopy Center of University of Kentucky. Four types of images were collected: 1) high-resolution T1-weighted image for functional image registration; 2) T2*-weighted images sensitive to the BOLD signal; 3) diffusion tensor images; and 4) B0 field map sequence for geometric unwarping of fMR and DT images.

High-resolution T1-weighted images were collected using an MPRAGE sequence (TR = 2100, ms, TE = 2.93 ms, TI = 1100 ms, 1 mm isotropic voxels). Functional images were

collected using a T2*-weighted gradient echo-planar sequence (33 interleaved slices, TR = 2000 ms, TE = 30 ms, FA = 77°, FOV = 224 mm², matrix = 64 × 64, resolution = 3.5 mm isotropic, voxels). Diffusion tensor imaging used a double spin echo EPI sequence (TR = 6900 ms, TE = 105 ms, flip angle = 90°, FOV = 224 mm, in-plane resolution = 1.75 × 1.75 mm voxels, 40 contiguous 3-mm thick axial slices). The DT images were acquired with 36 non-collinear encoding directions (b = 1000 s/mm²) and five images without diffusion weighting (b = 0 s/mm², b0). B0 field map images were collected using a double-echo planar imaging sequence (TE1 = 5.19ms; TE2 = 7.65ms).

2.5 Functional Imaging Data Preprocessing

Imaging data were preprocessed and analyzed using FMRIB's Software Library (FSL v5.0.6) and fMRI Expert Analysis Tool (FEAT; Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012; Smith, et al., 2004). Functional data were brain-extracted (i.e. skull-stripped) and motion-corrected to the median functional image using b-spline interpolation (4 df). The resulting functional images were unwarped via B0 field maps to reduce magnetic field distortions, high-pass filtered (60 s/cycle), and spatially smoothed [9 mm full width at half maximum (FWHM), isotropic]. The anatomical volume was brain-extracted and registered to standard space T1 MNI 2 × 2 × 2mm template with FMRIB's Non-linear Image Registration Tool (FNIRT; Andersson, Jenkinson, & Smith, 2010). Each participant's median functional image was co-registered to their anatomical volume and warped to standard space using the non-linear warping matrix generated by the transformation of anatomical volume to standard space. All resulting functional images were interpolated to 2 × 2 × 2mm resolution for group analysis in MNI standard space.

2.6 fMRI Single-Subject Analysis

Functional data was first modeled at the individual subject level by fitting a voxel-wise General Linear Model (GLM) to the BOLD data acquired for each run. Each run was modeled separately and included task regressors for the color, shape, and switching task blocks. Task regressors were modeled as a box-car function and convolved with a canonical double-gamma hemodynamic response function. Lower-level contrast maps for single (average of color and shape task) and switching task conditions were passed to a 2nd level fixed effects model. In the 2nd level model, maps for each condition were averaged across the three runs.

2.7 fMRI Group Analysis

Contrast maps from the 2nd level fixed effects model were entered into a 2 (time point; TP) × 2 (task condition) repeated measures ANOVA where the main-effects of TP (TP 1 vs. TP2) and task condition (switching vs. single), as well as the interaction of TP × task condition were estimated. Follow-up paired t-tests were conducted to characterize the direction of significant main-effects. A paired t-test between single and switching task conditions was conducted comparing average activation during each task condition across TPs. In addition, a paired t-test between TP1 and TP2 was conducted comparing average activation during each TP across single and switching task conditions. Only regions showing a 'task-positive' effect at either TP were considered for further analysis. Task-positive

effects were defined in the standard manner as those showing a mean positive percent signal-change increase from resting fixation and were determined using FSL's Featquery.

2.8 fMRI Thresholding and ROI Definition

Monte Carlo simulations using the AlphaSim program were used to empirically derive an appropriate combination of voxel-significance and cluster extent required to reach a whole-brain corrected significance threshold of $p < 0.05$, taking into account both native space voxel dimensions and the effective smoothness estimated directly from our preprocessed data (<http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf>). The Monte Carlo simulations used 1000 iterations and indicated a voxel-significance level of $p < 0.001$ and a minimum cluster extent of 22 contiguously significant voxels (176 mm^3) in order to reach a whole-brain corrected significance level of $p < 0.05$. This whole-brain corrected threshold was applied to all voxel-wise fMRI analyses and represents a conservative approach given that only effects within frontal cortex are explored here. For the purpose of ROI generation, clusters were separated by applying a more stringent voxel-based threshold of $p < 0.0001$. A key purpose of the ROI analyses was to correlate longitudinal alterations in BOLD magnitude with longitudinal alterations in WM microstructure. Thus, ROIs masks included all contiguous suprathreshold voxels showing longitudinal fMRI change (and DTI change; described below). Mean percent signal-change estimates were then computed within each ROI mask for each condition and participant.

2.9 Diffusion Tensor Imaging Data Preprocessing

Participants' diffusion tensor imaging (DTI) data sets were normalized to MNI152 ($1 \times 1 \times 1 \text{ mm}$) space using FSL v5.0.6 (Smith, et al., 2006). Registration of FA images into MNI space followed a series of procedures known as Tract-Based Spatial Statistics [TBSS v1.2; <http://www.fmrib.ox.ac.uk/fsl/tbss/>], as described in detail in our previous work (Gold, Powell, Andersen, & Smith, 2010). Briefly, prior to normalization, raw images were corrected for motion and residual eddy current distortion, and corrected for magnetic field distortions using B0 field maps. The FMRIB Diffusion Toolbox (FDT v3.0) was then used to fit the diffusion tensor and calculate FA eigenvalues.

Participants' FA images were then aligned to a common target (FMRIB's $1 \times 1 \times 1 \text{ mm}$ group average DTI template) using a nonlinear registration approach based on free-form deformations and B-Splines. FA datasets were then affine registered and resampled to 1 mm isotropic MNI coordinate space. All MNI-transformed FA images were then averaged to generate a mean FA image that was used to create a common white matter (WM) tract skeleton. This skeleton was then thresholded at an FA value of 0.2 in order to minimize partial volume effects after warping across subjects. Each participant's aligned FA image was subsequently projected onto the FA skeleton in order to account for residual misalignments between participants after the initial nonlinear registration.

2.10 DTI Group Analysis

A repeated measures contrast between skeletonized FA images at TP1 and TP2 was conducted using FSL's randomise. Correction for multiple comparisons was performed using FSL's threshold-free cluster enhancement (TFCE) tool. Resulting diffusion contrast

maps were thresholded at TFCE $p < 0.05$, corrected for multiple comparisons. This whole-skeleton corrected threshold represents a conservative approach given that only effects within frontal WM are explored here.

2.11 DTI ROI Definition

To limit the number of comparisons, two WM ROIs were selected for correlation with BOLD magnitudes. These WM ROIs were selected on the basis of (1) showing prominent longitudinal alterations from TP1 to TP2 (see Figure 3) and (2) containing connections between the cortical structures showing longitudinal fMRI alterations from TP1 to TP2. Longitudinal fMRI increases were observed bilaterally, with several in homologous frontal structures (see Figure 2). The CC-genu and CC-body were thus selected as WM ROIs because these portions of the CC contain cross-hemispheric connections between homologous frontal regions (Park, et al., 2008). The WM ROIs were defined using the Johns Hopkins University (JHU) WM labels atlas. ROI masks were skeletonized by aligning them with the study-specific WM tract skeleton to minimize partial voluming. Mean FA values were then computed for each participant across all voxels within each skeletonized mask showing a significant longitudinal reduction across TPs.

2.12 Probabilistic Tractography

Probabilistic tractography was performed to determine if regions showing longitudinal structure-function correlations (the CC-body and the three fMRI ROIs: bilateral pVLPFC and left aVLPFC regions) were anatomically connected in our participant group. Tractography was performed using FSL's Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques (BEDPOSTX) and probabilistic tracking (PROBTRACKX) tools (Behrens, Johansen-Berg, et al., 2003), as described in detail in our previous work (Johnson, Kim, Clasey, Bailey, & Gold, 2012). Briefly, BEDPOSTX was first used to generate local diffusion parameters in each voxel using Markov Chain Monte Carlo sampling. Two fibers were modeled in each voxel and default parameters were used for weighting and burn-in options (Behrens, Berg, Jbabdi, Rushworth, & Woolrich, 2007).

Way-point probabilistic tractography was performed with PROBTRACKX in native space with the CC-body as the seed and the three fMRI ROIs as targets. The three fMRI ROI target masks (bilateral pVLPFC and left aVLPFC) were those used in the BOLD-FA regression analyses. The CC-body seed mask included all study-specific skeletonized voxels lying within the JHU atlas CC-body ROI mask and was non-linearly registered to each participant's diffusion (i.e. native) space using inverse transformation matrices derived using FNIRT. A second analysis, classification probabilistic tractography, was run to quantify the likelihood that connections between bilateral pVLPFC regions passed through the CC-body. The classification probabilistic tractography used the bilateral pVLPFC fMRI ROI clusters as seeds and the full CC-body ROI mask from the JHU atlas as the classification target. Similarly to the way-point analysis, the CC-body ROI mask from the JHU atlas and bilateral pVLPFC clusters were non-linearly registered to each participant's diffusion space using inverse transformation matrices derived using FNIRT.

PROBTRACKX repetitively samples from the distributions on voxelwise principle diffusion directions and assigns a probability distribution to each fiber direction. Uncertainty in the data, and the existence of multiple fiber directions in each voxel, are accounted for in the form of probability density functions (Behrens, et al., 2007; Behrens, Johansen-Berg, et al., 2003). For each subject, the number of individual samples (i.e. streamlines) that were drawn through the probability distributions on the principle fiber direction was 5000 (Behrens, et al., 2007). The curvature threshold (0.2) was kept at a value that minimizes the chances of back tracking streamlines (Behrens, Johansen-Berg, et al., 2003; Behrens, Woolrich, et al., 2003), and the maximum number of steps was 2000.

The way-point tracking analysis generated a whole-brain connectivity distribution between voxels within the seed mask and the rest of the brain, with only those streamlines reaching one of the three functional ROIs being preserved (using the way-point logical “OR” option in PROBTRACKX). Classification tracking analysis generated a connectivity distribution between voxels within each seed functional ROI and their contralateral counterpart (i.e. from left to right pVLPFC, and vice versa) with only those streamlines successfully terminating at the other functional ROI being preserved. The proportion of successful streamlines passing through the classification target (the CC-body) was calculated by dividing the number of successful streamlines passing through the classification target by the total number of successful streamlines. For visualization of each analysis, each participant's connectivity distribution map was then non-linearly warped back to MNI space using FNIRT. Individual participant's native-space seed masks contained different numbers of voxels due to differences in brain size. Thus, participants' connectivity distribution maps in MNI space were normalized by their respective ‘waytotal’ (the total number of streamlines sent out from their CC-body mask that successfully terminated at a way-point) and total streamlines tested yielding a proportional connectivity map.

3 RESULTS

3.1 Demographic and Neuropsychological Characteristics

Demographic and neuropsychological characteristics of the sample were consistent with a well-educated group of cognitively normal older adults (Table 1). The mean MMSE score was 29.1 and none of the participants had a MMSE score below 27. No significant change was observed from time point 1 (TP1) to time point 2 (TP2) on age-scaled IQ scores ($p = 0.75$).

3.2 Behavioral Performance

Results of a $2 \text{ (TP)} \times 2 \text{ (task condition)}$ repeated measures ANOVA on accuracy revealed a significant main-effect of task condition ($F(1,17) = 9.05$, $MSE = 0.02$, $p = 0.008$) where overall accuracy across TPs was higher for the single task condition ($M = 97.2$, $SD = 0.03$) than for the switching task condition ($M = 94.1$, $SD = 0.05$). However, there was no main-effect of TP ($F(1,17) = 0.95$, $MSE = 0.001$, $p = 0.34$), or $\text{TP} \times \text{task condition}$ interaction ($F(1,17) = 0.0$, $MSE = 0.0$, $p = 1.00$). Follow-up t-tests revealed that overall accuracy was higher for the single task than switching task condition at both TPs (TP1 = $t(17) = 3.41$, $p = 0.003$; TP2 = $t(17) = 2.22$, $p = 0.04$; Figure 1a).

Results of a 2 (TP) $\times$ 2 (task condition) repeated measures ANOVA on response time (RT) revealed a significant main-effect of TP ($F(1,17) = 10.46$, $MSE = 134130$, $p = 0.005$) where overall RT at TP1 across task conditions ($M = 871$, $SD = 158$) was faster than at TP2 ($M = 957$, $SD = 137$), and a significant main-effect of task condition ($F(1,17) = 122.71$, $MSE = 1062554$, $p < 0.001$) where overall single task RT across TPs ($M = 793$, $SD = 107$) was faster than switching task RT ($M = 1036$, $SD = 174$). However, no TP $\times$ task condition interaction was observed ($F(1,17) = 1.97$, $MSE = 4216$, $p = 0.179$). Follow-up t-tests revealed significantly longer RT for the switching task compared to the single task condition at both TP1 ($t(17) = 9.36$, $p < 0.001$) and TP2 ($t(17) = 10.47$, $p < 0.001$). In addition, there was a significant longitudinal increase in RT between TP1 and TP2 for both the single ($t(17) = 2.70$, $p = 0.02$) and switching task conditions ($t(17) = 3.26$, $p = 0.005$; Figure 1b).

3.3 fMRI Activation

Results of a 2 (TP) $\times$ 2 (task condition) repeated measures ANOVA indicated a significant main-effect of task condition in several frontal regions including bilateral portions of the dorsolateral PFC (DLPFC), ventrolateral PFC (VLPFC) and the anterior cingulate. Follow-up paired t-tests showed that the main-effect of task condition resulted from greater activation during the switching task condition than the single task condition at each TP within each of these regions (see Figure S1). No region showed greater activation during the single task than the switching task condition.

A significant main-effect of TP was observed in multiple frontal regions (Figure 2). Follow-up paired t-tests indicated significantly higher task-positive activations at TP2 than TP1 in bilateral portions of the premotor cortex (PMC) and VLPFC (Figure 2 and Table 2). In contrast, there were no regions showing higher task-positive activations at TP1 than TP2. One region showed a significant difference in task-negative response (deactivation; i.e. higher activation during resting fixation periods compared to the active task) between TP1 and TP2 in the ventromedial PFC portion of the default mode network, which is not considered further here.

Peak task-positive activation increases from TP1 to TP2 within the PMC were located in bilateral portions of the middle frontal gyrus (~BA 6). There were three distinct clusters of activation increase within the VLPFC: bilateral activations were located in a posterior portion of the VLPFC (pVLPFC) within the pars opercularis (~BA 44; Figure 2a), and a second distinct cluster was observed in a more anterior aspect of the left VLPFC (aVLPFC) within the pars triangularis (~BA 45; Figure 2b). No TP $\times$ task condition interaction was observed. Therefore, all subsequent region of interest (ROI) analyses focused on clusters showing a main-effect of TP using mean percent signal-change across single and switching task conditions compared to baseline fixation (see Figure S2).

3.4 Diffusion Tensor Imaging

Results of a paired t-test revealed significantly lower FA at TP2 than TP1 in multiple frontal lobe WM regions (Figure 3). Significant FA reductions were most prominent within frontal commissural tracts [the genu of the corpus callosum (CC-genu) and anterior portions of the body of the corpus callosum (CC-body)]. Additional FA reductions were observed in

association tracts (bilateral portions of the superior longitudinal fasciculus, inferior fronto-occipital fasciculus, cingulum and uncinate fasciculus) and projection tracts (bilateral portions of the corticospinal tracts, anterior limb of internal capsule/corona radiata). In contrast, no FA increases in frontal lobe WM tracts were observed at TP2 compared to TP1.

3.5 Associations Between fMRI Increases and White Matter Microstructural Reductions

Correlated change analysis was performed on BOLD percent signal-change from TP1 to TP2 in frontal ROIs and FA change values from TP1 to TP2 in the corpus callosum WM ROIs. Separate partial correlations were run for the five fMRI ROIs and FA change in the CC-genu or CC-body. Each partial correlation was controlled for the effect of age, sex, IQ, and error-rate (to control for the possible effects of errors/guessing on functional activation). Additional reserve variables were tested as control variables including index of social position (ISP) and education, but were not found to change the significance of the results.

Longitudinal FA decrease in the CC-body (TP1-TP2) was significantly associated with longitudinal BOLD increases in the left pVLPFC ($r = 0.68$, $p = 0.008$), right pVLPFC ($r = 0.60$, $p = 0.025$), and left aVLPFC ($r = 0.66$, $p = 0.01$; Figure 4a-c). In contrast, longitudinal FA reduction in the CC-genu was not associated with longitudinal BOLD increases in any of the five frontal fMRI ROIs.

3.6 Associations Between fMRI Increases and Task Performance Declines

In order to assess the functional significance of the longitudinal coupling between WM microstructure decreases and BOLD increases reported above, correlated change analyses were performed on longitudinal change in overall task RT, controlling for longitudinal reduction of FA in CC-body, age, sex, IQ and error rate. Separate partial correlations were run on longitudinal change in each of the three frontal fMRI ROIs showing correlated structure-function change (bilateral pVLPFC and left aVLPFC). Longitudinal activation increase in the left pVLPFC was significantly associated with longitudinal increase in RT ($r = 0.72$, $p = 0.006$; Figure 4d). No significant relationship was observed between longitudinal increase in RT and longitudinal activation increase in left aVLPFC ($r = -0.05$, $p = 0.87$) or right pVLPFC ($r = 0.39$, $p = 0.18$).

3.7 Probabilistic Tractography

Longitudinal correlation results indicated that FA reductions in an anterior portion of the body of corpus callosum (the CC-body) were associated with fMRI increases in three portions of the VLPFC (bilateral pVLPFC and left aVLPFC). One possible reason for the specificity of this relationship to VLPFC regions is that the portion of the CC-body showing FA reductions may contain direct anatomical connections between VLPFC regions. A way-point probabilistic tractography analysis was conducted to assess this possibility. The probabilistic tractography analysis was seeded from the portion of the CC-body within the sample-specific white matter tract skeleton. Way-point targets were specified as the three fMRI ROIs: left pVLPFC, right pVLPFC and left aVLPFC clusters. Results revealed a single common portion of the CC-body within the frontal lobe connecting all three fMRI clusters, with the largest proportion of the tract connecting bilateral pVLPFC regions (Figure 5b). To quantify the likelihood that connections between bilateral pVLPFC regions passed

through the CC-body a classification tractography analysis was conducted seeded from the bilateral pVLPFC fMRI ROI clusters, with the CC-body as a classification mask. Results revealed that 76.3% of successful streamlines passed through the CC-body, and were limited to the frontal portion of the CC-body where longitudinal reductions in FA were observed (see Figure 5c).

4 DISCUSSION

The present study used a longitudinal design to explore relationships between age-related alterations in frontal cortex activation, white matter (WM) microstructure and cognitive performance. The main findings were: (1) longitudinal increases in frontal recruitment with aging; (2) longitudinal reduction in WM structures containing anatomical connections between the increasingly recruited frontal regions; and (3) an association between longitudinal frontal increases in the left pVLPFC and longitudinal increases in response latencies. Our results provide preliminary evidence suggesting that age-related frontal activation increases during executive control processing may in part reflect attempted compensation for reduced structural connectivity between those regions.

We observed longitudinal fMRI activation increases in bilateral VLPFC and bilateral PMC in CN older adults. Our longitudinal results are consistent with findings from a large number of cross-sectional neuroimaging studies of executive control that have reported higher frontal cortex activation in older adults compared to younger adults (Cabeza, et al., 2004; Colcombe, Kramer, Erickson, & Scalf, 2005; Langenecker, et al., 2004; Madden, et al., 2007; Milham, et al., 2002; Nielson, et al., 2002; Townsend, Adamo, & Haist, 2006). Frontal over-recruitment in these previous cross-sectional studies has been observed in a number of regions but appear to be especially consistent in lateral PFC and pre-motor cortex (PMC) regions (c.f. Turner & Spreng, 2012). Here again, our longitudinal findings of increased activation in bilateral VLPFC and PMC are consistent with the pattern reported in cross-sectional studies of executive control.

Increased VLPFC activation is generally thought to reflect recruitment of cognitive control processes (Aron, Robbins, & Poldrack, 2004; Badre, 2008; Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004). Similarly, age-related over-recruitment of PMC regions has frequently been observed in studies employing modified Stroop and response inhibition paradigms which place demands on reactive control over response conflict (Langenecker, et al., 2004; Milham, et al., 2002; Nielson, et al., 2002). Given the overlap of stimuli and response mappings across task sets in our task switching paradigm, our fMRI results appear to be generally in-line with the interpretation that age-related increases in VLPFC and PMC may reflect increased demands on cognitive control and response conflict processes with aging (see also Campbell, Grady, Ng, & Hasher, 2012).

We chose to focus specifically on longitudinal changes in frontal cortex activation in the current study given the importance of frontal recruitment to neurocognitive theories of aging (Grady, 2012; Lindenberger, 2014; Reuter-Lorenz & Cappell, 2008). To date, support for compensation and dysfunction theories has come from cross-sectional studies showing increased frontal recruitment among older adults. Frontal BOLD increases were consistent

in our participants (Figure S3) but contrast with a frontal decrease reported in a previous longitudinal study (Nyberg, et al., 2010). Frontal under-recruitment has typically been thought to reflect cognitive deficits (Grady, 2012) and was reported in the context of semantic memory declines in this previous longitudinal study of older adults enriched for the risk of Alzheimer's disease.

An influential theory suggests that frontal increases in older adults may reflect a compensatory attempt to match increasing task demands in the context of declining cerebral resources, while frontal under-recruitment may reflect reduced ability to engage this mechanism as cerebral resources deplete beyond some threshold (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008). Future research should test this possibility more directly by assessing relationships between longitudinal changes in BOLD response and cognitive performance in larger samples of older adults as a function of task difficulty.

We further observed longitudinal reductions in WM microstructure (fractional anisotropy; FA) in frontal regions. These findings are consistent with results from both volumetric and DTI studies. For example, previous longitudinal and cross-sectional evidence have shown that frontal WM volume declines significantly with aging, contributing to age-related declines in executive functions (Colcombe, et al., 2005; Raz & Kennedy, 2009; Raz, et al., 2005; Salthouse, 2011; West, 1996). Age-related declines in WM microstructure have been demonstrated by longitudinal studies over periods as short as one year (Barrick, et al., 2010; Teipel, et al., 2010). Consistent with these findings, we found longitudinal decreases in FA over a three year period in frontal WM. The most prominent and spatially coherent reductions in the present study were observed in the body of the corpus callosum (CC-body) and genu of the corpus callosum (CC-genu) with additional reductions in long projection and association tracts.

Of particular relevance to our study goals, we found that longitudinal declines in frontal WM microstructure significantly correlated with longitudinal increases in frontal BOLD response. Specifically, longitudinal FA decreases in anterior portions of the CC-body were significantly correlated with longitudinal BOLD increases in left pVLPFC, right pVLPFC, and left aVLPFC regions. In addition, our probabilistic tractography results indicated the existence of direct anatomical connections (within our participant sample) between these three VLPFC regions that passed through the frontal portion of the CC-body. Our findings suggest that alterations in the quality of structural connections between brain regions may influence functional activation response levels within those regions. In particular, our results are consistent with a view that age-related frontal activation increases may in part arise from reduced cortico-cortical signaling.

Functional neuroimaging techniques cannot distinguish between excitatory or inhibitory signals (Logothetis, 2008). A decrease in WM microstructure accompanied by an increase in BOLD magnitude could thus reflect a regulatory mechanism intended to maintain the fidelity of signal processing (e.g. local BOLD increases in response to a noisier signaling environment), or reduced inhibitory signaling between regions. In either case, our findings suggest that age-related changes in WM microstructure as a potential moderator of frontal cortex activation increases in aging. Recent findings suggest that age-related declines in

WM microstructure are not immutable (Engvig, et al., 2012; Lövdén, et al., 2010). For example, microstructure in the CC-body—the structure linked with increased frontal recruitment in the present study—has been found to be positively correlated with aerobic fitness in CN older adults (Johnson, et al., 2012). It would thus be of interest for future longitudinal research to determine if cognitive reserve variables that offset age-related WM changes may also affect age-related frontal cortex recruitment.

We do not conclude that age-related activation increase in frontal cortex necessarily represents a dysfunctional response. Here we observed a significant correlation between longitudinal increase in left pVLPFC activation and longitudinal increase in response latencies during task performance. However, not every region showing a significant longitudinal increase in activation was associated with changes in task performance. As noted, there is some cross-sectional evidence suggesting that higher frontal cortex response in older adults can be associated with better performance in some contexts (Cabeza, Anderson, Kester, & McIntosh, 2002; Davis, et al., 2008). It may be the case that frontal activation increases may benefit performance in some contexts but not others, depending upon a number of factors including but not limited to the specific frontal region and task domain. What can be said here is that in the context of a task switching paradigm those older adults who showed the greatest increases in BOLD response in pVLPFC over time tended to show the highest task performance declines.

Our longitudinal findings thus seem to suggest that while age-related frontal increases may represent an attempt at compensation, they may not always lead to improved performance (Cabeza & Dennis, 2012; Reuter-Lorenz & Cappell, 2008). An alternative interpretation of our findings is that efficiency of brain function declines with age (Rypma, Berger, Genova, Rebbechi, & D'Esposito, 2005; Stern, 2009; Zarahn, et al., 2007). It should be emphasized that the potential cellular, metabolic and synaptic mechanisms underlying both compensation and efficiency theories remain to be elucidated (Lindenberger, 2014). Microstructural properties of WM represent one potential contributing mechanism given the importance of heavily myelinated axons in signal transmission between neurons (Bartzokis, et al., 2010).

It is worth noting that the performance slowing observed here concerned both single and switching task conditions and were not specific to task-switching, per se. This pattern of behavior suggests two potential sources of longitudinal declines: generalized slowing (Salthouse, 2000) or decline in a cognitive process common to both task conditions. While generalized slowing is a well-established aging phenomenon, one nuance regarding the parameters of the current task switching paradigm suggests additional involvement of declines in cognitive processes common to both task conditions. Specifically, stimuli for both task conditions were bivalent (i.e. included a feature from each task dimension; a color and a shape) and thus afforded a response associated with each task set even during the single task condition. Given that aging is associated with marked declines in the ability to ignore irrelevant visual information (Gazzaley, Cooney, Rissman, & D'Esposito, 2005) and inhibit irrelevant information within working memory (Hasher & Zacks, 1988), performance slowing observed here could relate to demands imposed by the irrelevant stimulus feature common to both single and task switching conditions.

Our study has caveats. First, our relatively small sample size likely resulted in identification of only the most statistically robust relationships between BOLD, WM, and performance variables with statistically weaker relationships possibly being missed. In addition, the effects we observed should be considered preliminary and should be confirmed with larger sample sizes. In particular, more powerful approaches to measuring longitudinal change, including latent change modeling (e.g. Bender & Raz, 2015; Raz, et al., 2005), will be necessary to confirm and further characterize this phenomenon in larger samples.

Second, it should be noted that our longitudinal study does not represent a random sample of individuals selected to return for a follow-up scan. Instead, as with most longitudinal studies, returning participants were those who continued to meet inclusion criteria and were willing to return for a follow-up session. In the present study, returner and non-returner groups did not differ significantly demographically or on IQ scores. Still, the returners may be higher functioning, or more motivated/energetic than the non-returners. As noted above, age-related frontal over-recruitment may be more likely in higher functioning CN older adults than in their lower functioning peers. It may be possible to address this issue in future studies in which returners are randomly selected from the initial sample.

It should also be emphasized that age-related frontal over-recruitment is likely to emerge from synergistic effects of multiple age-related neurodegenerative changes likely to affect the BOLD response including but not limited to synapse alterations affecting local field potentials (Lauritzen, 2005), alterations in metabolite ratios reflecting various molecular and cellular processes (Kantarci, et al., 2011), and/or neuronal-glial interactions expected to affect neurovascular coupling (Takano, et al., 2006). We focused on WM microstructure given its established importance in neuronal signaling but note that substantial further research will be required to delineate the broad range of structural contributors to age-related changes in frontal cortex activation and its relationship to performance.

5 CONCLUSIONS

Our results provide the first longitudinal evidence to our knowledge for an association between age-related declines in WM microstructure and age-related alterations in functional brain activation in CN older adults. Our results suggest that age-related frontal activation increases may represent a mechanistic response to reduced WM regulatory signaling. Whether such frontal activation increases represent a successful form of compensation to structural declines remains to be elucidated by future longitudinal studies with larger sample sizes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Longitudinal increases in frontal activation were observed in healthy older adults
- Declines in white matter microstructure and cognitive performance were observed
- Correlated change was observed between frontal function, structure, and performance
- Regions showing correlated structure-function change were connected anatomically

Figure 1. Longitudinal Increases in RT

(A) No change in accuracy was observed for either task condition between TPs. (B) Significant longitudinal increases in RT were observed for both the single and switching task conditions. TP = time point. Note, * = $p < 0.05$.

Figure 2. fMRI Increases at TP2 Compared to TP1

Longitudinal increases in functional activation were observed from TP1 to TP2 in several frontal regions: (A) the PMC and posterior VLPFC (pVLPFC), (B) a second distinct cluster within a more anterior aspect of the left VLPFC (aVLPFC).

Figure 3. FA Decreases at TP2 Compared to TP1

Longitudinal reductions in FA were observed in multiple frontal WM regions, with the most prominent and spatially coherent reductions observed in the body of the corpus callosum (CC-body) and genu of the corpus callosum (CC-genu).

Figure 4. Correlated Change between FA in the CC-body, Frontal Cortex Activation, and RT Longitudinal FA reduction in the CC-body was significantly correlated with longitudinal increase in fMRI activation in the (A) left pVLPFC, (B) right pVLPFC, and (C) left aVLPFC. Note, more positive values on x-axis indicate greater FA reduction between TP1 and TP2. (D) Longitudinal fMRI increase in the left pVLPFC was significantly associated with longitudinal increase in mean RT. Scatter-plots are standardized (mean-centered) residual plots from separate partial correlation analyses. aVLPFC = anterior ventrolateral prefrontal cortex; pVLPFC = posterior ventrolateral prefrontal cortex.

Figure 5. A Common White Matter Tract Connecting Regions of the VLPFC

(A) A representation of the CC-Body (green) used as the seed for probabilistic tractography (only CC-body voxels falling within the study-specific white matter skeleton were included in the tractography analysis). The white line indicates the y-axis (and corresponding MNI coordinate) of the coronal cut in panel B. (B) Waypoint tractography probability map results (blue), overlaid on a 1mm resolution MNI standard template. A common anterior portion of the CC-Body (blue) within the frontal lobe was found to inter-connect all three frontal cortical regions (red) in which longitudinal FA-BOLD change correlations were observed (see Figure 4). (C) Classification tractography results thresholded at 95th percentile of all successful tracts, overlaid on a 1mm resolution MNI standard template. Successful tracts connecting bilateral pVLPFC ROI clusters were limited to the frontal portion of the CC-body.

Table 1

Participant Demographics and Neuropsychological Scores at Each Visit

	Visit 1	Range	Visit 2	Range	Change
Mean Age	62.4 (5.4)	52-70	65.6 (5.4)	55-73	3.33 (0.17)
N (gender)	18 (9M; 9F)	-	-	-	N/A
Education (Yrs)	16.4 (2.8)	13-22	-	-	N/A
ISP	26.1 (9.6)	11-40	-	-	N/A
MMSE	-	-	29.1 (1.02)	27-30	N/A
IQ	132.5 (20.6)	81-164	133.7 (20.2)	93-184	0.32 (0.75)

Notes: M = male; F = female; Standard deviations in parentheses; ISP = Index of Social Position; MMSE = Mini Mental Status Exam; IQ = Cattell Culture Fair Intelligence Test; Values for IQ are age-scaled scores; Change in Mean Age = Mean and standard deviation of number of years between visits; Change in IQ = t- and p-value in parentheses.

Table 2

Peak fMRI Activation Coordinates for Main-effect of Time Point

Region	Gyrus	Z-max	X	Y	Z	BA	k
Left Hemisphere							
<i>PMC</i>	<i>MFG</i>	4.26	-26	4	36	6	38
<i>pVLPFC</i>	<i>IFG, pars opercularis</i> *	4.18	-50	20	18	44	45
<i>aVLPFC</i>	<i>IFG, pars triangularis</i> *	5.12	-50	30	6	45/46	157
Right Hemisphere							
<i>PMC</i>	<i>MFG</i>	4.61	38	0	42	6	96
<i>pVLPFC</i>	<i>IFG, pars opercularis</i> *	4.46	50	20	20	44	384

Notes: PMC = premotor cortex; MFG = middle frontal gyrus, IFG = inferior frontal gyrus

* = longitudinal increase in this region was significantly predicted by longitudinal FA decline in CC-body; k = spatial extent at ROI-definition threshold of $p < 0.0001$.