Correspondence of executive function related functional and anatomical alterations in aging brain

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ABSTRACT

Neurocognitive aging studies have focused on age-related changes in neural activity or neural structure but few studies have focused on relationships between the two. The present study quantitatively reviewed 24 studies of age-related changes in fMRI activation across a broad spectrum of executive function tasks using activation likelihood estimation (ALE) and 22 separate studies of age-related changes in gray matter using voxel-based morphometry (VBM). Conjunction analyses between functional and structural alteration maps were constructed. Overlaps were only observed in the conjunction of dorsolateral prefrontal cortex (DLPFC) gray matter reduction and functional hyperactivation but not hypoactivation. It was not evident that the conjunctions between gray matter and activation were related to task performance. Theoretical implications of these results are discussed.

1. Introduction

As individuals age, many aspects of cognitive function become less efficient most notably working memory, inhibitory function, and long-term memory (e.g., Craik and McDowd, 1987; Gazzaley et al., 2008; Hasher et al., 1991; Nyberg et al., 2003; Rypma et al., 2007; see Nyberg and Backman, 2010). Gray matter (GM) reductions have been reported in regions associated with these functions most notably prefrontal cortex, caudate, cerebellum, and hippocampus (Dennis and Cabeza, 2008; Raz and Rodrigue, 2006). To confront these increased endogenous challenges (i.e., those brought on by changes to neural anatomy and physiology), as well as exogenous challenges (i.e., those brought on by changes to the environment), older adults must flexibly adapt. Changes in neural activity associated with neuroanatomic changes could be thought of as manifestations of this “neural plasticity” (i.e., adaptation-related skill reacquisition; Greenwood, 2007; Park and Bischoff, 2010; Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Park, 2010; Schneider-Garces et al., 2010) if it were observed (1) that age-related GM changes corresponded spatially with age-related neural activation (as measured by fMRI) and (2) that these age-related structure–function changes corresponded to improvements in performance (Grady, 2012; Rypma and D’Esposito, 2001).

Studies of brain function in older adults using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have demonstrated consistent patterns of neural activity alterations (Davis et al., 2008; Spreng et al., 2010, but see Nyberg et al., 2010). These alterations generally take the form of age-related increases in frontal activity (i.e., hyperactivation). These hyperactivations have been interpreted as reflecting compensation, (i.e., adaptation to the decline of some cognitive functions; Grady, 1998), de-differentiation of cognitive processes (Baltes and Lindenberger, 1997), and reduced efficiency of cognitive processes (Motes et al., 2010; Rypma and D’Esposito, 2000; Rypma et al., 2005).

Age-related neural increases in activity might be related to anatomic degeneration (e.g., Bennett et al., 2012). Specifically, it might be that local anatomic deficits lead to neural inefficiency as reflected by enhanced functional responses (e.g., Bennett et al., 2012; Greenwood, 2007). Structural alterations have been extensively investigated in previous work using manual volumetric measurement (e.g., Raz et al., 2005), voxel-based morphometry (VBM; Good et al., 2001), and cortical thickness techniques (e.g., Salat et al., 2004). Age-related gray matter reductions occur over the entire cortex, but disproportionately in regions associated with age-related functional deficits (i.e., prefrontal cortex, caudate, cerebellum, and hippocampus, Dennis and Cabeza, 2008; Raz and Rodrigue, 2006).
In the present study we sought to characterize relationships between age-related neuroanatomic changes and functional activity changes. We focused on age-related activation changes related to general cognitive processes of executive function drawn from studies in the literature. Activation likelihood estimation (ALE, Turkeltaub et al., 2002) was used to identify age-related activation changes over a range of different types of executive function tasks (e.g. working memory, executive control, and delayed response task). Based on similar consideration, Spreng et al. (2010) quantitatively reviewed 77 neuroimaging studies of aging effects using the ALE technique. Their results showed age-related increases in prefrontal activity and performance-dependent age differences in activation laterality. In contrast, we analyzed data only from articles that directly compared activity differences between older and younger groups. In addition, another ALE analysis was conducted to examine consistent anatomical alterations using VBM analysis (Ashburner and Friston, 2000; Chan et al., 2011; Di et al., 2009). Conjunction analyses were then conducted to examine age-related structural and functional correspondence.

Four patterns of structure–function associations could be expected. First, age-related GM decreases would correspond with reductions in functional activity. This result would suggest that, with aging, neural loss is associated with reductions in the neural metabolic activity that gives rise to the BOLD signal. Second, age-related GM decreases would be associated with increases in functional activity. This result would suggest that neural loss is associated with increases in neural metabolic activity. Third, GM preservation would be associated with decreases in functional activity. Finally, age-related GM preservation might be associated with increases in functional activity. These latter outcomes would suggest more complex relationships between age-related GM changes and changes in neural metabolic activity. Interpretation of these results would be contingent upon their relationships to performance. Based on plasticity theories of neurocognitive aging (Greenwood, 2007; Park and Reuter-Lorenz, 2009), we predicted that regions that showed consistent hyperactivation but not hypoactivation in older group would overlap with regions that showed consistent GM reductions. In addition, observations of overlap between age-related activation changes and GM changes would be associated with age-related changes in performance.

2. Methods

2.1. Article selection

2.1.1. Functional imaging studies

Studies were searched in the PubMed database using “aging” combined with task keywords and imaging modality keywords (functional magnetic resonance imaging, fMRI or PET). The task keywords included delayed match-to-sample, delayed response, go/no-go, mental arithmetic, N-back, oddball, sequence recall, Stroop, Wisconsin Card Sort, and word generation task, which was consistent with a previous meta-analysis on executive function of patients with schizophrenia (Minzenberg et al., 2009). In addition, we searched the reference lists of the studies identified and recent ALE studies (Spreng et al., 2010; Turner and Spreng, 2012) for potential inclusion. The inclusion criteria were as follows: 1) they were research articles; 2) they studied linear correlations between the age and task related activations, or compared differences in activations between a group of older subjects and a group of younger subjects; 3) the results were normalized to a stereotactic standardized space such as the MNI space or Talairach space (Talairach and Tournoux, 1988), and the coordinates of the activation areas were explicitly reported. Twenty-four articles with a total of 860 subjects were included in the fMRI meta-analysis (Table 1). Paxton et al. (2008) reported two experiments with independent subject samples, so the two experiments were treated as independent. Esposito et al. (1999) and Nagels et al. (2012) examined linear correlation between task related activation and age, while the other experiments directly compared the task related activations between the older and younger groups. All of the included studies but Prakash et al. (2012) reported hyperactivation for the older group, and fifteen studies also reported hypoactivation. The task used in each experiment was listed in Table 1. Task performance was determined based on accuracy but not reaction time, consistent with a previous meta-analysis (Spreng et al., 2010). Equivalent performance describes experiments where the accuracy of a given task performance was not statistically significant between young and old group. Twelve experiments did not report significant different performance between young and old groups (denoted as ‘~’ in Table 1), whereas 13 experiments reported significantly poorer performance in old adults (denoted as ‘*’ in Table 1).

2.1.2. VBM studies

PubMed search used the key words “Voxel Based Morphometry” and “aging,” or “VBM” and “aging,” respectively. In addition, we searched the reference lists of the studies identified for potential inclusion. From the about 150 resultant articles, we included the studies considering the following criteria: 1) they were empirical articles; 2) they used the voxel-based morphometry analysis to test the GM concentration or volume changes of the MRI dataset; 3) they studied linear correlations between the GM alterations and age, or compared GM differences between the older and younger individuals; 4) the results were normalized to a stereotactic standardized space such as the MNI space or Talairach space (Talairach and Tournoux, 1988), and the coordinates of the activation areas were explicitly reported.

Twenty-two articles with a total of 2657 subjects were included in the VBM meta-analysis (Table 2). One paper by Takahashi et al. (2011) reported separately the male and female results, so the two results were treated as two independent experiments. These studies used different software such as (SPM99, SPM2, SPM5, and SPM8, http://www.fil.ion. ucl.ac.uk/spm/), FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/), and house software (Tisserand et al., 2002, 2004) to conduct VBM analyses. In addition, different algorithms were used, including traditional VBM (Ashburner and Friston, 2000), optimized segmentation (Good et al., 2001), unified segmentation (Ashburner and Friston, 2005), and DARTEL (Ashburner, 2007). Sixteen studies compared age-related differences using modulated GM images (i.e. GMV, gray matter volume), while seven studies used unmodulated GM images (i.e., GMC gray matter concentration). Good et al. (2001) used both GMV and GMC images, but we only included the GMV results in the current analysis. All of the included studies reported a GM reduction across aging, while ten studies also reported relative GM preservation after controlling for global GM loss. Seventeen studies examined the linear correlation between the GM volume/concentration and age, and the other six studies directly compare GM measures between older and younger groups. There was no overlap of subject samples between the fMRI meta-analysis and the VBM meta-analysis.

2.2. Activation likelihood estimation analysis

Because most of the studies reported results in MNI space, the ALE analyses were also conducted in MNI space. For papers whose results had been converted from MNI to Talairach space using Brett’s transformation (Brett, 1999), or a simple affine transformation (e.g. in Lamar et al., 2004), results were converted back to MNI space using the corresponding method. For the studies whose results were originally in Talairach space, anatomical coordinates were converted into MNI space using the Lancaster transform (Lancaster et al., 2007).

The activation likelihood estimation meta-analysis (Turkeltaub et al., 2002) was carried out using GingerALE 2.1.1 software with revised random effect algorithm (Eickhoff et al., 2009), and non-additive method (Turkeltaub et al., 2012). The idea behind ALE analysis is that the peak coordinates reported in VBM studies should be viewed as probability distributions around these coordinates (Turkeltaub et al., 2002). Accordingly, the coordinates were convolved with a three-dimensional
Gaussian kernel, whose full width at half maximum (FWHM) was a function of the sample size of a particular study. An algorithm was used to model the spatial uncertainty of each focus using an estimation function of the sample size of a particular study. An algorithm was constructed based on 159 foci from 24 independent comparisons.

Four ALE maps were constructed. First, an fMRI hyperactivation map for each study, the convergence of activations across experiments was assessed quantitatively.

Table 1
List of VBM studies included in the anatomical ALE analysis.

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<thead>
<tr>
<th>Study #</th>
<th>First author &amp; year</th>
<th>Task</th>
<th>Category</th>
<th>Performance</th>
<th>Modality</th>
<th>Effect of age</th>
<th>Young</th>
<th>Old</th>
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<td>Anguera 2011</td>
<td>Spatial working memory task</td>
<td>WM</td>
<td>≠</td>
<td>fMRI</td>
<td>↑</td>
<td>18</td>
<td>21.1</td>
</tr>
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<td>2</td>
<td>Cabrera 2004</td>
<td>Delayed-response</td>
<td>WM</td>
<td>=</td>
<td>fMRI</td>
<td>↑</td>
<td>20</td>
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<tr>
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<td>Colcombe 2005</td>
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<td>=</td>
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<td>↑</td>
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<tr>
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<td>Esposito 1999</td>
<td>Wisconsin card sorting task</td>
<td>Other</td>
<td>≠</td>
<td>PET</td>
<td>↑</td>
<td>n = 41; range: 18–80</td>
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↑↑ represents that the paper reported both higher and lower activations in older group compared with younger group. WM represents working memory.

Table 2
List of fMRI and PET studies on executive functions that are included in the functional ALE analysis.

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</tbody>
</table>

↑↑ represents that the paper reported both decreased and relative preservation of gray matter volume/concentration in older group compared with younger group. WM represents working memory.
Second, an fMRI hypoactivation map was constructed based on 84 foci from 15 independent comparisons. Third, the GM reduction map was constructed according to 312 coordinates from 23 independent comparisons. And last, the GM relative preservation map was constructed according to 77 coordinates from ten studies. The resultant ALE maps were thresholded using a false discovery rate (FDR)-corrected threshold of p < 0.05, with a recommended cluster extent threshold obtained from the FDR-correction procedure. Results-clusters were identified according to the peak locations using an anatomical label assigned by the Talairach Daemon (Lancaster et al., 2000).

We first binarized the thresholded ALE maps and then performed conjunction analysis on these maps. Four conjunction analyses were conducted: (1) between GM reductions and functional hyperactivations; (2) between GM reductions and functional hypoactivations; (3) between GM relative increases and functional hyperactivations; and (4) between GM relative increases and functional hypoactivations. An AND operation was performed to find voxels that were commonly activated in both ALE maps. Number of voxels and mean coordinates of the resulting clusters were calculated. It is noteworthy that the purpose of conjunction analysis is to find common activations of two statistical maps, thus the number of subjects, foci and studies of the two maps will not affect the results of conjunction analysis.

Finally, we examined the characteristics of studies contributing to clusters of significant conjunction effects. The variables of interests included the effects of task performance (equal vs. unequal), executive function components (working memory, inhibition and others) and imaging modality (fMRI vs. PET) for functional studies. The studies that contributed to these two clusters were pooled together (10 studies). For each variable, the number of contributing studies of each category was calculated and compared with the expected number of studies of each category, which were calculated from the whole studies sample of the current meta-analysis. Chi square was calculated to determine statistical significance (Laird et al., 2009).

### 3. Results

#### 3.1. ALE analyses of functional imaging studies

As illustrated in Fig. 1 and Table 3, the older group showed consistent enhanced activation related to executive function than the younger group in distributed networks, including the bilateral dorsolateral prefrontal cortex (DLPFC) (BA 6/9), anterior cerebellum, and left inferior frontal gyrus (BA 13) (cluster extent threshold was 432 mm³ for FDR correction). In contrast, the younger group conveyed consistent greater activation related to executive function than the older group in the bilateral insula (BA 13), medial frontal gyrus/cingulate gyrus (BA 32/24), and cuneus (BA 18) (cluster extent threshold was 296 mm³ for FDR correction).

#### 3.2. ALE analyses of VBM studies

As illustrated in Fig. 2 and Table 4, there were consistent age related GM reductions in the left sensorimotor cortex (BA 1/2/3/4), bilateral insula (BA 13), medial frontal gyrus (BA 6) caudate/thalamus, bilateral

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**Table 3**

Regions reveal consistent age differences of executive function related activations.

<table>
<thead>
<tr>
<th>Volume (mm³)</th>
<th>Label</th>
<th>MNI coordinates</th>
<th>Extrema value</th>
<th>Contributed studies #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old &gt; young</td>
<td>L. inferior frontal gyrus, BA 9</td>
<td>−40 12 22</td>
<td>0.0132</td>
<td>3, 5, 8, 13, 16, 17, 22, 24</td>
</tr>
<tr>
<td></td>
<td>L. inferior frontal gyrus, BA 9</td>
<td>−46 6 30</td>
<td>0.0129</td>
<td>5, 7, 14, 16, 24</td>
</tr>
<tr>
<td></td>
<td>L. inferior frontal gyrus, BA 9</td>
<td>−48 6 14</td>
<td>0.0109</td>
<td>1, 5, 13</td>
</tr>
<tr>
<td></td>
<td>L. middle frontal gyrus, BA 9</td>
<td>−46 12 36</td>
<td>0.0104</td>
<td>1, 5, 13</td>
</tr>
<tr>
<td></td>
<td>R. inferior frontal gyrus, BA 9</td>
<td>54 10 32</td>
<td>0.0137</td>
<td>2, 3, 13, 15</td>
</tr>
<tr>
<td></td>
<td>R. middle frontal gyrus, BA 9</td>
<td>46 20 28</td>
<td>0.0115</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L. inferior frontal gyrus, BA 9</td>
<td>−40 34 2</td>
<td>0.0120</td>
<td>5, 7, 14, 16, 24</td>
</tr>
<tr>
<td></td>
<td>L. inferior frontal gyrus, BA 13</td>
<td>−48 28 4</td>
<td>0.0103</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L. fusiform gyrus, BA 37</td>
<td>−48 58 16</td>
<td>0.0160</td>
<td>7, 16, 21</td>
</tr>
<tr>
<td></td>
<td>L. cerebellum, anterior lobe, culmen</td>
<td>−20 52 12</td>
<td>0.0152</td>
<td>1, 5, 13</td>
</tr>
<tr>
<td></td>
<td>R. parahippocampal gyrus, BA 30</td>
<td>16 52 6</td>
<td>0.0147</td>
<td>11, 18, 24</td>
</tr>
<tr>
<td>Young &gt; old</td>
<td>L. insula, BA 13</td>
<td>−40 14 14</td>
<td>0.0123</td>
<td>6, 20, 21, 22</td>
</tr>
<tr>
<td></td>
<td>L. middle frontal gyrus, BA 9</td>
<td>−44 18 28</td>
<td>0.0095</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R. insula, BA 13</td>
<td>40 24 12</td>
<td>0.0124</td>
<td>6, 19a, 22</td>
</tr>
<tr>
<td></td>
<td>L. medial frontal gyrus, BA 32</td>
<td>0 10 48</td>
<td>0.0113</td>
<td>4, 11, 19b, 22</td>
</tr>
<tr>
<td></td>
<td>R. cingulate gyrus, BA 24</td>
<td>10 8 44</td>
<td>0.0103</td>
<td></td>
</tr>
</tbody>
</table>

The clusters in bold represent the two clusters that overlap with consistent gray matter reductions. Contributed studies # refers to the study # in Table 1. L, left; R, right; BA, Brodmann’s Area.

---

Fig. 1. Regions show consistent greater (hot) and smaller (cold) activations of executive function tasks in older subjects as compared to younger subjects. Clusters were displayed using a threshold at p < 0.05 (FDR corrected). Z represents z coordinates in MNI space. L, left; R, right.
and cingulate gyrus (BA 24) (cluster extent threshold was 320 mm³ for FDR correction). There was also consistent age related relative GM preservation in the bilateral parahippocampal gyrus/amgydala, bilateral thalamus, and cingulate gyrus (BA 24) (cluster extent threshold was 320 mm³ for FDR correction).

3.3. Conjunction analysis

As illustrated in Fig. 3, conjunction analysis of fMRI hyperactivation and GM reduction in the old group revealed two clusters located in the bilateral dorsolateral prefrontal cortex (BA6/9; centered coordinates: −47, 7, 32, 408 mm³ for the left cluster, and at 52, 12, 30, 216 mm³ for the right cluster). No overlap was observed in the other three conjunction analyses.

3.4. Regions of interest analysis

For the two clusters of hyperactivation that overlap with GM reduction clusters, totally 10 studies were identified that contribute to these two clusters (shown in bold in Table 3). The number of equal and unequal performance studies from the contributed studies was not significantly different from the expected number of studies with different task performance from the whole study sample (Chi square = 1.94, p = 0.16). The number of working memory, inhibition, and other studies from the contributing studies was not significantly different from the expected number of studies of each executive function component from the whole study sample (Chi square = 0.80, p = 0.67). The number of PET and fMRI studies from the contributed studies was not significantly different from the expected number of studies from different imaging modalities from the whole study sample (Chi square = 0.63, p = 0.43).

4. Discussion

The present study suggested that regions with disproportionate age-related GM loss overlapped with regions wherein older adults showed greater activation than younger adults during performance of executive function tasks. Thus, neural loss in DLPCF was associated with increases in neural metabolic or BOLD activity. Additional analyses did not indicate that DLPCF hyperactivation was biased to specific PET or fMRI modalities. These overlaps highlight a central role for bilateral DLPCF in the process of neurocognitive aging.

Table 4

Regions show consistent gray matter reduction and relative preservation in the old group relative to the young group.

<table>
<thead>
<tr>
<th>Volume (mm³)</th>
<th>Label</th>
<th>MNI coordinates</th>
<th>Extrema value</th>
<th>Contributed studies #</th>
</tr>
</thead>
<tbody>
<tr>
<td>2936 L. postcentral gyrus, BA 2</td>
<td>−56 −26 46</td>
<td>0.0241</td>
<td>2, 3, 5, 9, 10, 11, 17</td>
<td></td>
</tr>
<tr>
<td>1720 L. inferior frontal gyrus, BA 9</td>
<td>−48 12 32</td>
<td>0.0243</td>
<td>2, 4, 6, 12, 13, 17</td>
<td></td>
</tr>
<tr>
<td>1360 L. insula</td>
<td>−44 −4 0</td>
<td>0.0275</td>
<td>5, 13, 15, 16, 17, 19</td>
<td></td>
</tr>
<tr>
<td>1304 R. insula</td>
<td>−40 −22 8</td>
<td>0.0152</td>
<td>18a, 18b, 22</td>
<td></td>
</tr>
<tr>
<td>1296 L. medial frontal gyrus, BA 6</td>
<td>−44 −12 20</td>
<td>0.0177</td>
<td>2, 5, 10, 16, 17</td>
<td></td>
</tr>
<tr>
<td>1232 R. insula, BA 13</td>
<td>−42 −16 12</td>
<td>0.0185</td>
<td>2, 6, 11, 15, 16, 17</td>
<td></td>
</tr>
<tr>
<td>1224 L. caudate body</td>
<td>−2 4 6</td>
<td>0.0188</td>
<td>5, 13, 17, 18a, 18b, 22</td>
<td></td>
</tr>
<tr>
<td>1136 R. Inferior Frontal Gyrus, BA 9</td>
<td>−28 24 20</td>
<td>0.0176</td>
<td>2, 5, 10, 17, 20, 21</td>
<td></td>
</tr>
<tr>
<td>944 L. inferior frontal gyrus, BA 47</td>
<td>−46 16 −10</td>
<td>0.0205</td>
<td>5, 10, 20, 21, 22</td>
<td></td>
</tr>
<tr>
<td>1040 L. thalamus, ventral posterior medial nucleus</td>
<td>−16 −20 6</td>
<td>0.0297</td>
<td>5, 10, 11, 17</td>
<td></td>
</tr>
<tr>
<td>1000 L. parahippocampal gyrus, amygdala</td>
<td>−26 −4 −22</td>
<td>0.0205</td>
<td>9, 17, 19</td>
<td></td>
</tr>
<tr>
<td>982 L. thalamus, ventral posterior medial nucleus</td>
<td>−20 −8 0</td>
<td>0.0282</td>
<td>5, 10, 11, 17</td>
<td></td>
</tr>
<tr>
<td>696 R. cingulate gyrus, BA 24</td>
<td>−6 −14 36</td>
<td>0.0163</td>
<td>1, 10, 19</td>
<td></td>
</tr>
<tr>
<td>336 L. cingulate gyrus, BA 24</td>
<td>−6 −14 36</td>
<td>0.0163</td>
<td>1, 5</td>
<td></td>
</tr>
</tbody>
</table>

The clusters in bold represent the clusters which overlap with executive function related hyper-activations in the old individuals. Contributed studies # refers to the study # in Table 2, L, left; R, right; BA, Brodmann’s Area.

Fig. 2. Thresholded ALE maps of gray matter reduction (hot) and relative preservation (cold) in aging. Clusters are displayed using a threshold at p < 0.05 (FDR corrected). Z represents z coordinates in MNI space. L, left; R, right.
A central question in neurocognitive aging is whether age-related increases in activation reflect processes in the service of optimizing performance or whether they reflect deterioration. Although cortical volume decrease is broad-spread in aging (Good et al., 2001; Raz et al., 2005), the present study revealed consistent regions of disproportionate GM loss. Importantly, the most impaired GM regions overlapped with regions of age-related activation increases, but not decreases, during executive task performance. These results suggest on the one hand, that age-related activation increases might be associated more with deterioration than with performance optimization. On the other hand, the increased neural activity in regions of neural atrophy could reflect a number of changes in cognitive function aimed at optimizing performance.

Age-related increases in frontal activity have been interpreted as support for the idea that older adults cognitively compensate for loss of function, due to neuroanatomic loss either within the region showing increased activity or in a region distal to that showing increased activity (Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Cappell, 2008). DLPFC has been posited as the locus of compensation in the neurocognitive aging process. In these theories, hyperactivation in DLPFC reflects the erection of temporary skill-acquisition mechanisms (i.e., “scaffolds”) to compensate for anatomical deficits that develop with age and maintain cognitive performance. The effectiveness of such scaffolds might be limited by older adults’ reduced cognitive capacity leading ultimately to age-related reductions in DLPFC activity when tasks are sufficiently difficult (Cappell et al., 2010; but see Bennett et al., 2012). Evaluation of the extent to which the present results reflect such compensatory processes would require assessment of performance-related changes associated with phenomena such as those we have observed here. Such tests of association were not significant in the present study. Thus the hypothesis that the relationships we observed between GM and activation represented any form of compensation was not supported.

When considering how the relationships between structural and functional measures might reflect cognitive function, the relationships between these measures and task performance are a vital factor in assessing whether or not one could attribute the functional hyperactivation we observed to cognitive constructs like compensation or de-differentiation (Berlinger et al., 2010; Grady, 2012; Rypma and D’Esposito, 2001). Some studies have suggested a pattern of “hemispheric asymmetry reduction in older adults” (Cabeza, 2002). Better-performing older adults sometimes activate bilateral frontal regions, while poor performing elderly only activates the right frontal region (Cabeza et al., 2002). Such a pattern was observed by Spreng et al. (2010). They observed right DLPFC hyperactivation in older subjects who performed similar to young subjects, but not for those whose performance was poorer. This pattern, however, was not observed in the present study (Fig. 4A/ B). The effect of task performance on age-related activation changes requires further meta-analytic investigation to resolve these empirical ambiguities.

It is possible to speculate that processing deficits due to regional atrophy might drive neuronal plasticity through strategy changes and training similar to that observed as patients’ performance improves in the process of the performance improvements that accompany development of skilled performance (Greenwood, 2007). FMRI studies of the neural basis of cognitive training indicate that prefrontal cortex activity changes in the training process. Some studies have shown training-related activation increases in PFC (e.g., Callan et al., 2003; Olesen et al., 2004; Westerberg and Klingberg, 2007) but others have shown training-related decreases (e.g., Babiloni et al., 2009; Del Percio et al., 2009; Gobel et al., 2011; Wartenburger et al., 2009). The role of prefrontal cortex is not yet well-understood but its versatility suggests that it probably supports a number of plasticity-related processes associated with training-related performance improvements (e.g., Fuster, 2002). The present results, however, while indicating relationships between age-related structural changes and activation changes, did not indicate any consequence of these relationships to performance.

Age-related activation increases have been posited to reflect de-differentiation (Baltes and Lindenberger, 1997). However, even though a causal relationship of structural alteration and functional hyperactivation seems reasonable, most of the evidence at hand (like the present results) is only correlational. It is also possible that structural and functional alterations are independent processes during aging, and only show epiphenomenal overlap (e.g., Steffener and Stern, 2012). As with other studies, we cannot rule out the possibility of some third factor that contributes to both of functional and structural alterations, such as hypertension or diabetes (D’Esposito et al., 2003). Several reports have demonstrated age-related coupling changes between cerebral blood flow (CBF) and cerebral–metabolic rate of oxygen consumption (CMRO2). Regional reductions in gray matter could lead to CMRO2 decreases that could, combined with age-related CBF increases, lead to apparent increases in BOLD signal (e.g., Ances et al., 2009; Hutchison et al., 2012; Restom et al., 2007). Further studies using longitudinal designs and pharmacologic manipulations will be required to provide the kind of direct evidence required to infer causal structure–function relationships.

In terms of function, bilateral DLPFC is not the only part of the distributed network that supports executive function (Minzenberg et al., 2009; Smith and Jonides, 1999), bilateral DLPFC is also involved in a broad range of tasks including perception (Spreng et al., 2010) and memory (Grady et al., 2003; Spreng et al., 2010). A parsimonious explanation of this age-related activation increase in DLPFC is that it provides some general task functions that provide support for cognition (e.g., Zarahn et al., 2007).

In terms of connectivity, the DLPFC is intensively connected to other brain regions. The DLPFC constitutes part of a task positive network (Fox et al., 2005; Torro et al., 2008), which includes distributed brain regions such as DLPFC, ventrolateral prefrontal cortex (VLPFC), supplementary motor area (SMA), inferior parietal lobe (IPL), ventral occipital cortex, and middle temporal region. The regions within the task positive network are extensively interconnected between each other. In contrast to the DLPFC, however, the posterior task-positive network regions, such as the ventral occipital cortex and middle temporal regions, generally have shown decreased activation in perceptual tasks in older adults (Spreng et al., 2010). The scaffolding theory proposes that age-related hyperactivation of DLPFC reflects compensation for functional deficits in these posterior regions. Evidence to support this speculation includes that increased PFC activation was correlated with the extent of deficient ventral visual and sensory activations (Davis et al, 2008). Greater connectivity has also been observed between DLPFC and hippocampus in older subject during memory task performance (Grady et al., 2003). Thus it is possible that, in the face of age-related processing deficits, older individuals might rely on more controlled processing, supported by...
mainly by prefrontal brain regions, rather than on more automatic processing, supported mainly by posterior brain regions (cf. Rypma and Prabhakaran, 2009; Shiffrin and Schneider, 1984).

Although the present study focused on general processes of executive function, recent studies have considered executive function to be comprised of three independent components: working memory (updating), inhibition, and task-switching (Miyake et al., 2000). Turner and Spreng (2012) have shown a dissociation of working memory and inhibition related hyperactivation in aging in the anterior and posterior parts of the DLPFC. The present analyses, however, failed to show any selective association between the hyperactivation results and either working memory or inhibition processes. Although a parsimonious explanation is that the DLPFC clusters observed in the present study involve general processes of executive function, further research is certainly needed to understand the functional significance of age-related prefrontal hyperactivation.

It has been demonstrated that GM volume generally declines with aging (Kennedy et al., 2009; Raz and Rodrigue, 2006). Regional specific alterations of the GM structure, however, can provide insight to relatively independent neural mechanisms of cognitive aging. The ALE analysis of VBM studies identified distributed networks, which were generally consistent with other types of structural measures such as cortical thickness (Salat et al., 2004), and longitudinal volumetric studies (Raz et al., 2005). The most consistent GM reduction across the studies considered here was in the left sensorimotor area (BA1/2/3/4), which has also been reported using cortical thickness measures (Salat et al., 2004). However, regional atrophy of the left sensorimotor cortex has also been observed (Salat et al., 2004) but has not drawn much attention. Parallel to the anatomical studies, functional imaging studies of motor function have revealed hyperactivation in contralateral sensorimotor area (Mattay et al., 2002; Ward and Frackowiak, 2003). Consistent with these studies, we could hypothesize that the hyperactivation in left SMC might reflect compensatory processes to account for reduced motor function (Ward, 2006), driven by focal anatomical de

There are some limitations in the current study. First, brain activation patterns differ across various task domains (e.g. memory and perception (Biswal et al., 2010; Spreng et al., 2010)); therefore, it is highly possible that age-related alteration in brain activation patterns and thus, the structure–function correspondence may differ depending on the task domain at hand. Conceivably, the structure–function correspondence in the DLPFC may be specific to executive function tasks. Secondly, our result is based on a spatial overlap between structural and functional alterations; thus, a solid evidence of structure–function relationship may be gained from directly examining individual differences between the brain activations and regional gray matter. Further studies with a large number of subjects are needed to explore this direct relationship.

5. Conclusion

The present study illustrated the correspondence of the functional hyperactivation in the executive function and the GM reduction in the bilateral DLPFC. Many of the studies that contributed to the DLPFC clusters showed age-equivalent behavioral performance. Taken together, the results suggest that intrinsic age-related anatomical deficits in DLPFC are associated with increases in activation. Further research will be required to understand the relationship between these age-related structure–function relationship changes and cognitive function.

Acknowledgments

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Appendix A. Articles included in the functional meta-analysis


Appendix B. Articles included in the VBM meta-analysis


