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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 dorsalateral 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.

Keywords

aging; dorsolateral prefrontal cortex; efficiency; executive function; meta-analysis; plasticity

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., Rypma, Eldreth & Rebbechi, 2007; Hasher, et al., 1991; Gazzaley et al., 2008; Craik & McDowd, 1987; Nyberg et al., 2003; see Nyberg & Backman, 2010). Gray matter (GM) reductions have been reported in regions associated with these functions most notably prefrontal cortex, caudate, cerebellum, and hippocampus (Raz & Rodrigue, 2006; Dennis & Cabeza, 2008). 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 & Reuter-

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Lorenz, 2009; Reuter-Lorenz & Park, 2010; Park & Bischoff, 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 & 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 & Lindenberger, 1997), and reduced efficiency of cognitive processes (Motes, Biswal & Rypma, 2010; Rypma et al., 2005, Rypma & D'Esposito, 2000).

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., Greenwood; 2007, Bennett et al., 2012). 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, Raz & Rodrigue, 2006; Dennis & Cabeza, 2008).

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 & Friston, 2000; Di et al., 2009; Chan et al., 2011). 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 change 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 & 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 & 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 Montreal Neurological Institute (MNI) space or Talairach space (Talairach & 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 investigate the GM concentration or volume changes of 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 & 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 in house software (Tisserand et al.,

2002; 2004) to conduct VBM analyses. In addition, different algorithms were used, including traditional VBM (Ashburner & Friston, 2000), optimized segmentation (Good et al., 2001), unified segmentation (Ashburner & 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 of the spatial variability. For the correlation studies that calculate correlations between the imaging variables and subjects' age, the study N was set as the total number of subjects. Study Ns were set as the number of the smaller group when studies reported group differences between the older and younger groups. After obtaining the activation map for each study, the convergence of activations across experiments was assessed quantitatively.

Four ALE maps were constructed. First, an fMRI hyperactivation map was constructed based on 159 foci from 24 independent comparisons. 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 Figure 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 dorsalateral prefrontal cortex (DLPFC) (BA 6/9), anterior cerebellum, and left inferior frontal gyrus (BA 13) (cluster extent threshold was 432 mm^3 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 mm^3 for FDR correction).

3.2 ALE analyses of VBM studies

As illustrated in Figure 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 dorsolateral prefrontal cortex (BA 6/9), and left ventrolateral prefrontal cortex (BA 47) (cluster extent threshold was 912 mm^3 for FDR correction). There was also consistent age related relative GM preservation in the bilateral parahippocampal gyrus/amygdala, bilateral thalamus, and cingulate gyrus (BA 24) (cluster extent threshold was 320 mm^3 for FDR correction).

3.3 Conjunction analysis

As illustrated in Figure 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 mm^3 for the left cluster, and at 52, 12, 30, 216 mm^3 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 were 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 were 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 were not significantly different from the expected

number of studies from different imaging modality 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 DLPFC was associated with increases in neural metabolic or BOLD activity. Additional analyses did not indicate that DLPFC hyperactivation was biased to specific PET or fMRI modalities. These overlaps highlight a central role for bilateral DLPFC in the process of neurocognitive aging.

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 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 (Reuter-Lorenz & Cappell, 2008; Park & Reuter-Lorenz, 2009). 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 is a vital factor in assessing whether or not one could attribute the functional hyperactivation we observed to cognitive constructs like compensation or de-differentiation (Rypma & D'Esposito, 2001; Berlingeri et al., 2010; Grady, 2012). 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 activate 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 (Figure 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., Olesen et al., 2004; Westerberg & Klingberg, 2007; Callan et al., 2003) but others have shown training-related decreases (e.g., Gobel, Parrish & Reber, 2011; Babiloni et al., 2009; Del Percio et al., 2009; 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 & 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) are only correlational. It is also possible that structural and functional alterations are independent processes during aging, and only show epiphenomenal overlap (e.g., Steffener et al., 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 ($CMRO_2$). Regional reductions in grey matter could lead to $CMRO_2$ decreases that could, combined with age-related CBF increases, lead to apparent increases in BOLD signal (e.g., Restom et al., 2007; Ances et al., 2009; Hutchison et al., 2012). 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 (Smith &Jonides, 1999: Minzenberg et al., 2009), 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; Toro et al., 2008), which includes distributed brain regions such as DLPFC, ventrolateral prefrontal cortex (VLPFC), supplementary motor area (SMA), inferior parietal lobule (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 mainly by prefrontal brain regions, rather than on more automatic processing,

supported mainly by posterior brain regions (cf. Shiffrin & Schneider, 1984; Rypma & Prabhakaran, 2009).

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 & Spreng (2012) have shown a dissociation of working memory and inhibition related hyperactivation in aging in the anterior and posterior part 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 (Raz & Rodrigue, 2006; Kennedy et al., 2009). 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 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 & 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 deficits in the same area. The absence of performance changes associated with this hyperactivation suggests that it might also reflect age-related CBF/$CMRO_2$ coupling dysregulation. More research is required to understand the relations between the age-related SMC activation increases we observed here and performance.

It is possible that updates to improve VBM algorithm (e.g. optimized segmentation (Good et al., 2001), unified segmentation (Ashburner & Friston, 2005), and DARTEL (Ashburner, 2007)) may introduce variance across all studies. Differences in other processing steps such as carrying out GM modulation or not that result in GMC or GMV, respectively, are other possible source of variance across these studies. For example, a meta-analysis have reported discrepancies of structural alterations in schizophrenia patients when measuring with GMV and GMV (Fornito et al., 2009). Although their effects on age-related structural changes need further exploration, we didn't observe systematic bias of VBM algorithms and GM modulation in the current data.

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.

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Abbreviations

ALE	activation likelihood extimation
CBF	cerebral blood flow
$CMRO_2$	cerebral-metabolic oxygen rate of oxygen
DLPFC	dorsalateral prefrontal cortex
FDR	false discovery rate
fMRI	functional magnetic resonance imaging
FWHM	full width at half maximum
GM	gray matter
IPL	inferior parietal lobule
MNI	Montreal Neurological Institute
PET	positron emission tomography
SMA	supplementary motor area
VBM	voxel-based morphometry
VLPFC	ventrolateral prefrontal cortex

Highlights

- A series of meta-analyses were conducted to study age related brain alterations.
- Functional alterations related to executive function were examined.
- Anatomical reductions and relative preservations of gray matter were examined.
- Only hyperactivations and gray matter reductions overlapped in the bilateral DLPFC.

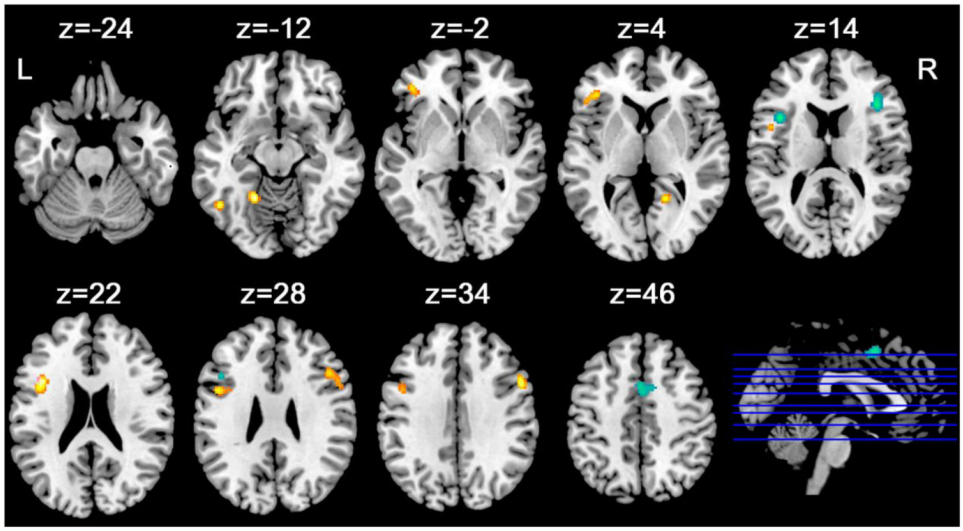

Figure 1.
Regions show consistent greater (hot) and smaller (cold) activations of executive function tasks in older subjects as compared to younger subjects. Clusters were displayed using a threshold at $p<0.05$ (FDR corrected). Z represents z coordinates in MNI space. L, left; R, right.

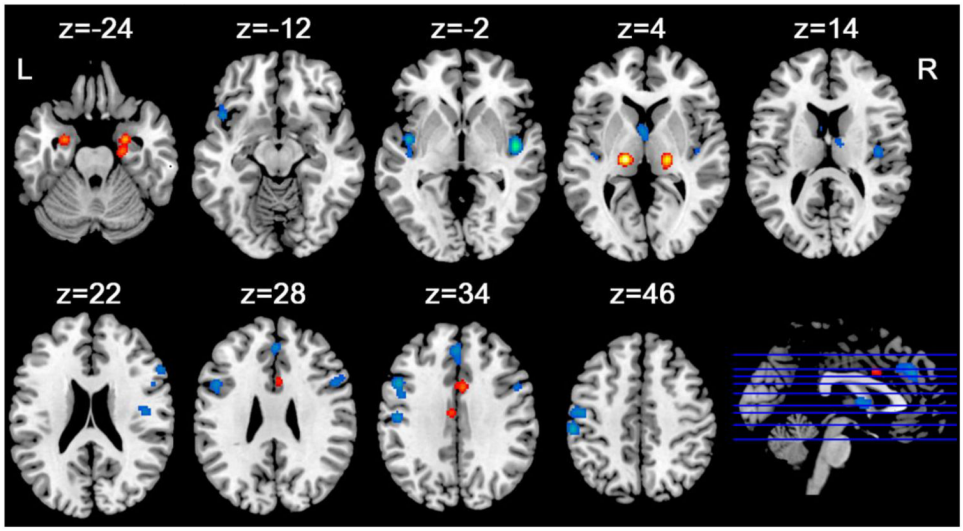

Figure 2.
Thresholded ALE maps of gray matter reduction (hot) and relative preservation (cold) in aging. Clusters are displayed using a threshold at $p<0.05$ (FDR corrected). Z represents z coordinates in MNI space. L, left; R, right.

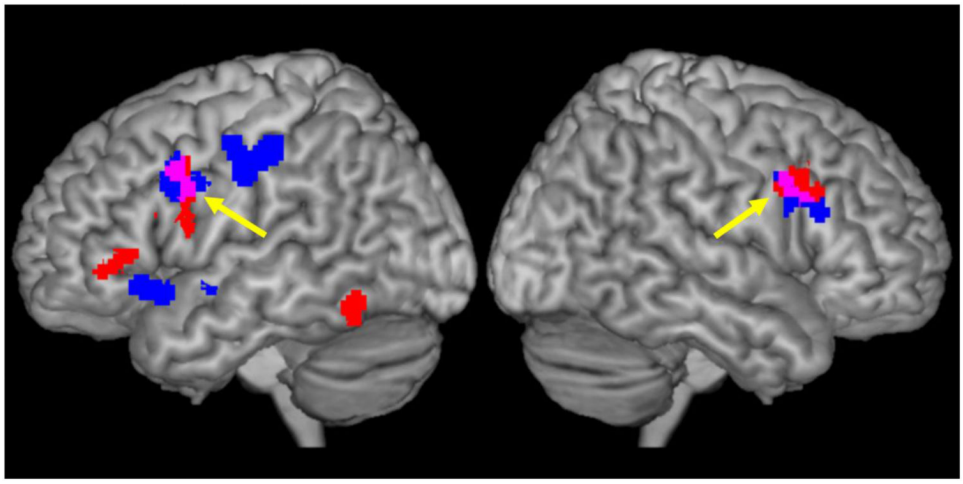

Figure 3.
Illustration of overlap between hyperactivation of executive function tasks and gray matter reduction in the older group than younger group. Clusters in red represent hyper-activation of executive function tasks, and clusters in blue represent gray matter reduction. The yellow arrows highlight the overlaps of the hyperactivation and gray matter reduction (in violate).

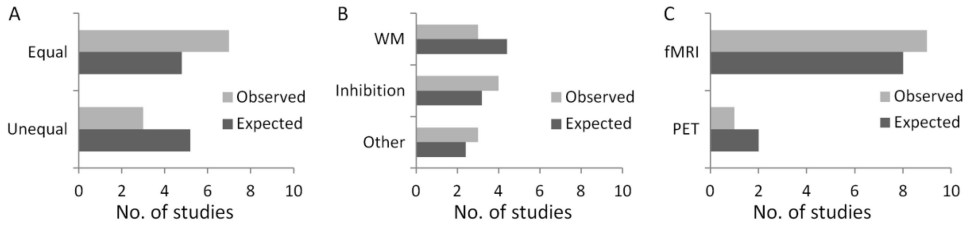

Figure 4.

Results of regions of interest analysis for the bilateral DLPFC that consistent hyperactivations overlap with consistent GM reductions. Numbers of studies of task performance (A), executive function category (B), and imaging modality (C) from the two hyperactivation clusters were not significantly different from the number of studies from all the functional studies included in the meta-analysis.

Table 1

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

Study #	First author & year	Task	Category	Performance	Modality	Effect of age	Young		Old	
							N	Age	N	Age
1	Anguera 2011	Spatial working memory task	WM	≠	fMRI	↑↓	18	21.1	18	71.4
2	Cabeza 2004	Delayed-response	WM	=	fMRI	↑↓	20	22.6	20	70.3
3	Colcombe 2005	Flanker task	Inhibition	=	fMRI	↑	20	23.5	40	67.5
4	Esposito 1999	Wisconsin card sorting task	Other	≠	PET	↑↓	n = 41; range:18-80			
5	Freo 2005	Delayed match to sample	WM	=	PET	↑↓	13	27	13	65
6	Grady 1998	Delayed match to sample	WM	≠	PET	↑↓	13	25	16	66
7	Grady 2008	N-back task	WM	≠	fMRI	↑	16	26.1	18	65.8
8	Grossman 2002	Sentence comprehension task	WM	=	fMRI	↑↓	13	22.6	11	63.5
9	Huang 2012	Stroop-like Task	Inhibition	=	fMRI	↑	15	25.5	18	66.1
10	Hubert 2009	Tower of Toronto task	Other	≠	PET	↑	12	22.4	12	65
11	Lamar 2004	Delayed match to sample	WM	≠	fMRI	↑↓	16	27.9	16	69.1
12	Lee 2006	Response regulation task	Inhibition	≠	fMRI	↑	12	29.8	9	65.2
13	Madden 2010	Task switching	Other	≠	fMRI	↑↓	20	22.4	20	69.6
14	Mathis 2009	Stroop task	Inhibition	≠	fMRI	↑	12	26.8	24	51.7
15	Mell 2009	Probabilistic object reversal task	Inhibition	=	fMRI	↑↓	14	26.5	14	67.8
16	Nagels 2012	Word generation	Other	=	fMRI	↑	n = 56; range:22-56			
17	Onur 2011	Stroop task	Inhibition	≠	fMRI	↑↓	15	24.2	13	63.8
18	O'Connell 2012	Oddball task	Other	=	fMRI	↑	15	22	14	70.6
19a	Paxton 2008	AX Continuous performance task	WM	=	fMRI	↑↓	21	22.8	20	73
19b	Paxton 2008	AX Continuous performance task	Inhibition	≠	fMRI	↑↓	16	21.6	16	72.4
20	Prakash 2012	N-back task	WM	≠	fMRI	↓	25	23.4	25	72.2
21	Ricciardi 2009	Delayed match to sample	WM	=	PET	↑↓	10	26.2	10	68.4
22	Rypma 2001	Item-recognition task	WM	=	fMRI	↑↓	6	25.3	6	68.6
23	Van Impe 2011	Mental arithmetics	Other	≠	fMRI	↑	20	25.2	21	68.0
24	Zysset 2006	Stroop task	Inhibition	=	fMRI	↑	23	26.6	24	57.1

'↑' represents that the paper reported higher activations in older group compared with younger group, whereas '↓' denotes that older group demonstrated lower activations compared with younger group. '↑↓' 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 VBM studies included in the ALE analysis.

Study #	First author & year	No. of subjects [a]	male	female	Mean age	Age range [b]	Software	Algorithm	Modulation	Measure	Effect of age
1	Abe 2008	73		73	39.2	22-70	SPM2	Optimized	GMV	Linear	↓↑
2	Alexander 2006	26	15	11	50.7	22-77	SPM2	Optimized	GMV	Linear	↓↑
3	Antonova 2009	10o/10y	20		47.9	23.6-72.1	SPM2	Optimized	GMV	group difference	↓
4	Bauer 2012	18o/18y	N.A		42.3	24.4-60.2	SPM8	DARTEL	GMV	group difference	↓
5	Bergfield 2010	29	11	18	47.7	23-84	SPM5	Unified	GMV	Linear	↓↑
6	Berlingeri 2010	24o/24y	24	24	44.3	26.5-62	SPM2	Optimized	GMV	group difference	↓
7	Curiati 2009	45	45		70.1	~67-75	SPM2	Optimized	GMV	Linear	↓↑
8	Giorgio 2010	66	31	35	36.7	23.0-81.6	FSL	Optimized	GMV	Linear	↓
9	Good 2001	465	265	200	~30	17-79	SPM99	Optimized	GMV [c]	Linear	↓↑
10	Grieve 2005	223	117	106	34.5	Aug-79	SPM2	Optimized	GMV	Linear	↓↑
11	Kalpouzos 2009	45	21	24	49.4	20-83	SPM2	Optimized	GMV	Linear	↓↑
12	Kalpouzos 2012	20o/16y	8	28	45.2	25-61.3	SPM5	Unified	GMV	group difference	↓
13	Kennedy 2009	200	81	119	46.9	18-81	FSL	Optimized	GMV	Linear	↓
14	Lehmbeck 2006	17o/17y		34	46.5	25.9-67.1	SPM2	Optimized	GMC	group difference	↓
15	Lemaître 2005	662	331	331	69.5	63.7-75.6	SPM99	Optimized	GMV	Linear	↓
16	Maguire 2003	12o/12y	12	12	53.6	32.4-74.8	SPM99	Traditional	GMC	group difference	↓
17	Nunnemann 2007	133	60	73	55	29-80	SPM2	Optimized	GMV	Linear	↓↑
18a	Takahashi 2011	111	111		48.3	~20-79	SPM8	Optimized	GMC	Linear	↓
18b	Takahashi 2011	116		116	55.4	~20-79	SPM8	Optimized	GMC	Linear	↓
19	Terribilli 2011	89	48	41	30.2	~18-50	SPM2	Optimized	GMV	Linear	↓↑
20	Tisserand 2002	57	34	23	55.7	21-81	In house	Traditional	GMC	Linear	↓
21	Tisserand 2004	38	18	20	71.8	52-82	In house	Traditional	GMC	Linear	↓
22	Van Laere 2001	81	40	41	44.2	20-81	SPM99	Traditional	GMC	Linear	↓↑

'↓' represents that the paper reported decreased gray matter volume / concentration in older group compared with younger group, whereas '↑' denotes that the paper reported relative preservation of gray matter volume / concentration with age. '↑↓' represents that the paper reported both decreased and relative preservation of gray matter volume / concentration in older group compared with younger group. GMV, gray matter volume; GMC, gray matter concentration.

[a] For studies that examined linear trend of aging, number of subjects for each groups are reported separately. O represents old group, while y represents young group.

[b] For studies that examined linear trend of aging, age range represents minimum and maximum of the whole sample, whereas for the studies that directly compared between two groups of old young subjects, the age range represents the mean age of each group. ~ denotes that the studies did not explicitly report the age range in their papers, we made an approximation of the age range based on the description of the original paper.

[c] Good et al., (2001) reported both GMV and GMC in the paper. We only used the GMV results in the current analysis.

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Table 3

Regions reveal consistent age differences of executive function related activations.

Volume (mm^3)	Label	MNI coordinates			Extrema Value	Contributed studies #
		x	y	z		
Old > Young						
2032	**L. Inferior Frontal Gyrus, BA 9**	**− 40**	**12**	**22**	**0.0132**	**3, 5, 8, 13,**
	L. Inferior Frontal Gyrus, BA 6	**−46**	**6**	**30**	**0.0129**	**16, 17, 23, 24**
	L. Inferior Frontal Gyrus, BA 44	**−48**	**6**	**14**	**0.0109**	
	L. Middle Frontal Gyrus, BA 9	**−46**	**12**	**36**	**0.0104**	
1240	**R. Inferior Frontal Gyrus, BA 9**	**54**	**10**	**32**	**0.0137**	**2, 3, 13, 15**
	R. Middle Frontal Gyrus, BA 9	**46**	**20**	**28**	**0.0115**	
864	L. Inferior Frontal Gyrus, BA 13	−40	34	2	0.0120	5, 7, 14, 16,
	L. Inferior Frontal Gyrus, BA 13	−48	28	4	0.0103	24
832	L. Fusiform Gyrus, BA 37	−48	−58	−16	0.0160	7, 16, 21
592	L. Cerebellum, Anterior Lobe, Culmen	−20	−52	−12	0.0152	1, 5, 13
584	R. Parahippocampal Gyrus, BA 30	16	−52	6	0.0147	11, 18, 24
Young > Old						
1056	L. Insula, BA 13	−40	14	14	0.0123	6, 20, 21, 22
	L. Middle Frontal Gyrus, BA 9	−44	18	28	0.0095	
976	R. Insula, BA 13	40	24	12	0.0124	6, 19a, 22
960	L. Medial Frontal Gyrus, BA 32	0	10	48	0.0113	4, 11, 19b, 22
	R. Cingulate Gyrus, BA 24	10	8	44	0.0103	

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.

Table 4

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

Volume (mm^3)	Label	MNI coordinates			Extrema Value	Contributed studies #
		x	y	z		
Gray matter reduction						
2936	L. Postcentral Gyrus, BA 2	−56	−26	46	0.0241	2, 3, 5, 9, 10, 11,
	L. Postcentral Gyrus, BA 3	−50	−16	36	0.0232	14, 15, 16, 17
	L. Precentral Gyrus, BA 4	−48	−14	44	0.0200	
1720	**L. Inferior Frontal Gyrus, BA 9**	**−48**	**12**	**32**	**0.0243**	**2, 4, 6, 12, 13, 15,**
	L. Precentral Gyrus, BA 6	**−46**	**2**	**32**	**0.0188**	**17**
1360	L. Insula, BA 13	−44	−4	−4	0.0275	5, 13, 15, 16, 17,
	L. Insula, BA 13	−44	−16	0	0.0155	18a, 18b, 22
	L. Insula, BA 13	−40	−22	8	0.0152	
1304	R. Insula	44	−10	−2	0.0355	5, 13, 17, 18a, 18b, 22
1296	L. Medial Frontal Gyrus, BA 6	0	40	32	0.0210	2, 5, 9, 16, 20, 21, 22
1232	R. Insula, BA 13	42	−16	12	0.0185	2, 6, 11, 15, 16, 17
	R. Insula, BA 13	44	−12	20	0.0177	
1224	L. Caudate Body	−2	4	6	0.0188	1, 3, 6, 11, 17, 18a,
	L. Thalamus	0	−2	6	0.0185	18b
	R. Thalamus	8	−6	14	0.0139	
1136	**R. Inferior Frontal Gyrus, BA 9**	**58**	**24**	**20**	**0.0176**	**2, 5, 10, 17, 20, 21**
	R. Inferior Frontal Gyrus, BA 9	**50**	**12**	**28**	**0.0173**	
	R. Precentral Gyrus, BA 6	**50**	**8**	**34**	**0.0150**	
944	L. Inferior Frontal Gyrus, BA 47	−46	16	−10	0.0205	5, 10, 20, 21, 22
	L. Inferior Frontal Gyrus, BA 47	−48	24	−8	0.0193	
Gray matter relative preservation						
1368	R. Parahippocampal Gyrus, Amygdala	24	−4	−22	0.0197	9, 11, 17, 19
	R. Uncus, BA 28	20	−8	−30	0.0194	
	R. Parahippocampal Gyrus, BA 34	22	−14	−24	0.0164	
1040	L. Thalamus, Ventral Posterior Medial Nucleus	−16	−20	6	0.0297	5, 10, 11, 17
1000	L. Parahippocampal Gyrus, Amygdala	−26	−4	−22	0.0205	9, 17, 19

Volume (mm^3)	Label	MNI coordinates			Extrema Value	Contributed studies #
		x	y	z		
992	R. Thalamus, Ventral Posterior Medial Nucleus	18	−20	6	0.0282	5, 10, 11, 17
696	R. Cingulate Gyrus, BA 24	4	10	32	0.0160	1, 10, 19
336	L. Cingulate Gyrus, BA 24	−6	−14	36	0.0163	1, 5

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.