Progress in Neuro-Psychopharmacology & Biological Psychiatry 48 (2014) 41–50

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

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

Xin Di [a,*], Bart Rypma [b], Bharat B. Biswal [a]

[a] Department of Biomedical Engineering, New Jersey Institute of Technology, Newark, NJ 07101, USA
[b] School of Behavioral and Brain Sciences, University of Texas at Dallas, Richardson, TX 75080, USA

ARTICLE INFO

Article history:
Received 25 June 2013
Received in revised form 19 August 2013
Accepted 3 September 2013
Available online 12 September 2013

Keywords:
Aging
Dorsolateral prefrontal cortex
Efficiency
Executive function
Meta-analysis
Plasticity

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).

Abbreviations: ALE, activation likelihood estimation; CBF, cerebral blood flow; $CMRO_2$, cerebral-metabolic oxygen rate of oxygen; DLPFC, dorsolateral 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.

* Corresponding author at: Department of Biomedical Engineering, New Jersey Institute of Technology, Fenster Hall, University Heights, Newark, NJ 07102, USA. Tel.: +1 201 628 5188.
E-mail address: synge.x.d@gmail.com (X. Di).

0278-5846/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pnpbp.2013.09.001

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 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 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 Montreal Neurological Institute (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 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 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 in 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