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Research Report

Relationship between grey matter integrity and executive abilities in aging

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ABSTRACT

This cross-sectional study was designed to investigate grey matter changes that occur in healthy aging and the relationship between grey matter characteristics and executive functioning. Thirty-six young adults (18–30 years old) and 43 seniors (60–75 years old) were included. A general executive score was derived from a large battery of neuropsychological tests assessing three major aspects of executive functioning (inhibition, updating and shifting). Age-related grey matter changes were investigated by comparing young and older adults using voxel-based morphometry and voxel-based cortical thickness methods. A widespread difference in grey matter volume was found across many brain regions, whereas cortical thinning was mainly restricted to central areas. Multivariate analyses showed age-related changes in relatively similar brain regions to the respective univariate analyses but appeared more limited. Finally, in the older adult sample, a significant relationship between global executive performance and decreased grey matter volume in anterior (i.e. frontal, insular and cingulate cortex) but also some posterior brain areas (i.e. temporal and parietal cortices) as well as subcortical structures was observed. Results of this study highlight the distribution of age-related effects on grey matter volume and show that cortical atrophy does not appear primarily in "frontal" brain regions. From a cognitive viewpoint, age-related executive functioning seems to be related to grey matter volume but not to cortical thickness. Therefore, our results also highlight the influence of methodological aspects (from preprocessing to statistical analysis) on the pattern of results, which could explain the lack of consensus in literature.

1. Introduction

During healthy aging, many changes are observed in cognitive and neurobiological domains. Concerning cognition, aging is known to involve declines in several cognitive processes (see Hedden and Gabrieli (2004) or Park and Gutchess (2002) for a review). From a biological viewpoint, structural changes such as white matter hyperintensities, reduced grey and/or white matter volume, and cortical thinning have been reported (Raz and Rodrigue, 2006). A very popular theory linking cerebral to cognitive age-related decline is the *Frontal Aging Hypothesis* proposed by West (1996), which suggests that the age-related decline in cognitive functioning may be mediated by frontal and executive impairments. That theory was supported by the following findings: (1) the presence of age-related executive impairments, (2) a predominant age-related atrophy in the prefrontal cortex, (3) white matter deterioration mainly localized in anterior brain regions encompassing the prefrontal cortex, and (4) age-related impairments in dopamine function affecting frontal regions (see Cabeza and Dennis (2012)).

Although these observations seem well established, some debate remains on the importance of age-related grey matter atrophy and, by extension, its influence on executive functioning. The objectives of this study are therefore twofold: (1) to investigate grey-matter atrophy related to healthy aging (assessed by volumetric and thickness measures), using both univariate (Statistical Parametric Mapping 8, SPM8 (Wellcome Department of Imaging Neuroscience, London)) and multivariate (Partial Least Square, PLS (McIntosh et al., 1996; McIntosh and Lobaugh, 2004)) methods; (2) to specify the relationship between executive functioning and both grey matter volume and thickness in healthy elderly individuals by the multivariate PLS procedure.

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1.1. Executive functions: definition and brain correlates

Executive functioning refers to the high level cognitive processes needed for efficient adaptation to new and/or complex situations. These processes take place when highly practiced cognitive abilities no longer suffice to respond correctly to environmental demands (Shallice, 1982). Among executive processes, shifting, updating and inhibition have been identified as three clearly separate functions (although they have some common features at both cognitive and cerebral levels (Collette et al., 2005; Miyake et al., 2000)).

Since the initial observations of Luria (1966), the cerebral localization of executive processes has been a focus of research in cognitive neuroscience. At first, studies of brain damaged patients evidenced a main involvement of frontal areas. However, with the emergence of modern neuroimaging tools (e.g. positron emission tomography (PET) and functional magnetic resonance imaging (fMRI)), it became clear that the frontal cortex was not the only region involved in executive functioning but that these processes in fact depended on a large network of distributed antero-posterior areas (see Collette and Van der Linden (2002), Collette et al. (2006), and Collette and Salmon (2014b) for reviews). More specifically, the dorsolateral prefrontal cortex and the anterior cingulate gyrus are activated by a wide variety of executive tasks, suggesting their involvement in general executive processes (see Collette and Van der Linden (2002) and Duncan and Owen (2000) for a similar interpretation). Nevertheless, the involvement of posterior (mainly parietal) areas as well as the importance of functional connectivity within a fronto-parietal network was also emphasized (e.g. Cole et al., 2013; Reineberg et al., 2015; Seeley et al., 2007). In addition, Shaw et al. (2015) observed that the fronto-parietal network is also particularly involved during executive processes in healthy older adults (see also Hedden and Gabrieli (2010) and Hedden et al. (2012)).

1.2. Age-related executive differences

Many studies of healthy aging have pointed out an age-related decline in several cognitive functions, whereas others seem to remain stable (see Dujardin and Lemaire (2008) for a review). The executive decline hypothesis of cognitive aging (Dempster, 1992; West, 1996) posits that the pattern of cognitive changes associated with normal aging may be a consequence of an age-related decline in the efficiency of the frontal lobes, known to play a major role in executive functioning. Indeed, executive processes appear to be particularly sensitive to age (Collette and Salmon, 2014b; Nagahama et al., 1997; Wecker et al., 2000; Zacks et al., 2000; Zelazo et al., 2004). According to the three components model of executive functioning proposed by Miyake et al. (2000), age-related changes have been observed in shifting (e.g. Gamboz et al., 2009), updating (e.g. Fisk and Sharp, 2004; Leonards et al., 2002; Podell et al., 2012) and inhibition abilities (e.g. Andrés et al., 2008; Darowski et al., 2008; West, 2004).

1.3. Grey matter changes with aging

Neuroimaging (and post mortem) studies have shown structural grey matter changes with aging (e.g. Bartzokis et al., 2001; Convit et al., 2001; Jernigan et al., 2001; Raz et al., 1997; Raz, 2000; Raz et al., 2004; Tisserand et al., 2002; Tisserand et al., 2004; Xu et al., 2000). In a review of the literature on volumetric studies, Raz and Rodrigue (2006) suggested that prefrontal cortices showed greater deleterious age-related effects (median correlation between age and volume: $r = -.56$) than other neocortical areas (temporal: $r = -.37$; parietal: $r = -.20$; occipital: $r = -.19$). In addition, a moderate decline was observed in hippocampal volume, amygdala, cerebellum and neostriatum (correlations ranging from $-.30$ to $-.43$) as in the globus pallidus ($r = -.20$) and the thalamus ($r = -.28$).

Using Voxel-Based Morphometry (VBM), Good et al. (2001) showed both an age-related decline in global grey matter volume ($R^2 = 0.489$[1]) and regional age-related effects (for similar results see also Bergfield et al. (2010), Giorgio et al. (2010), and Kennedy et al. (2009)). The regional effects correspond to larger grey matter losses bilaterally in the superior parietal gyri, pre- and postcentral gyri, insula and frontal operculum, right cerebellum and anterior cingulate when volume analysis was performed, and an accelerated decrease in grey matter in the left middle frontal gyrus, Heschl's gyri bilaterally, and left planum temporal based on density measures. In contrast, regions showing relative preservation of grey matter volume were found in the lateral thalamus, amygdala, hippocampus and entorhinal cortex while measures of density in the thalamus appeared more diffuse. The results of these studies showed that VBM generally led to similar findings to those obtained with volumetric studies, although discrepancies were sometimes reported. For instance, age-related grey matter decline in the anterior cingulate cortex (Good et al., 2001) or in the striate cortex (Tisserand et al., 2002) was not reported in volumetric studies (see Kennedy et al. (2009) or Tisserand et al. (2002) for a direct comparison of volumetric and VBM methods).

Studies using cortical thickness methods tended to show age-related grey matter thinning in several brain regions also observed with volumetric and morphometric analyses but also led to different results. For example, Salat et al. (2004) found an age-related thinning particularly pronounced in the prefrontal cortex, similarly to volumetric studies, but also in precentral and supramarginal regions, as well as in postcentral and occipital areas (see also Hurtz et al. (2014) or McGinnis et al. (2011) for similar results). More recently, Fjell et al. (2009), by comparing the age-related cortical thinning in six samples of healthy adults (from 18 to 94 years old), found that regions such as the lateral and superior medial prefrontal cortices as well as the superior and middle temporal gyri showed a consistent decline across samples. However, age-related thinning of grey matter was less consistently observed in occipital, motor, inferior temporal and cingulate regions.

To summarize, grey matter atrophy in aging has been reported with a plethora of methods. However, some of the regions showing atrophy varied according to the procedure used. Consequently, this study was designed to investigate the grey matter atrophy using voxel-based morphometry and cortical thickness as complementary methods to finely address this major issue in healthy aging.

1.4. Influence of grey matter on the age-related decline of executive abilities

Cabeza and Dennis (2012) have reported several studies revealing significant correlations between executive functioning and prefrontal atrophy in older adults. For instance, using the classical Wisconsin Card Sorting Test (WCST), Gunning-Dixon and Raz (2003) showed a negative correlation between the number of perseverative errors and the prefrontal cortex volume (see also Head et al. (2009) for similar results). In a very interesting study, Tisserand et al. (2004) used VBM to investigate the relationship between grey matter density and age, as well as cognitive decline over a three-year period. Grey matter density was compared

[1] Multiple regression applied on the sum of voxel values extracted from grey, white matter, cerebrospinal fluid and total intracranial volume with linear and quadratic expansions of age for both gender types.