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Local brain atrophy accounts for functional activity differences in normal aging

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Abstract

Functional brain imaging studies of normal aging typically show age-related under- and overactivations during episodic memory tasks. Older individuals also undergo nonuniform gray matter volume (GMv) loss. Thus, age differences in functional brain activity could at least in part result from local atrophy. We conducted a series of voxel-based blood oxygen level-dependent (BOLD)-GMv analyses to highlight whether age-related under- and overrecruitment was accounted for by GMv changes. Occipital GMv loss accounted for underrecruitment at encoding. Efficiency reduction of sensory-perceptual mechanisms underpinned by these areas may partly be due to local atrophy. At retrieval, local GMv loss accounted for age-related overactivation of left dorsolateral prefrontal cortex, but not of left dorsomedial prefrontal cortex. Local atrophy also accounted for age-related overactivation in left lateral parietal cortex. Activity in these frontoparietal regions correlated with performance in the older group. Atrophy in the overrecruited regions was modest in comparison with other regions as shown by a between-group voxel-based morphometry comparison. Collectively, these findings link age-related structural differences to age-related functional under- as well as overrecruitment.

Keywords: Activation; Atrophy; Compensation; Episodic memory; Frontal lobe; Functional magnetic resonance imaging; Normal aging; Multimodal neuroimaging; Occipital lobe; Parietal lobe; Preservation; Structural magnetic resonance imaging; Voxel-based morphometry

1. Introduction

Functional neuroimaging studies have shown both age-related under- and overrecruitment of brain regions during episodic memory tasks, with a focus on the prefrontal cortex (PFC), the medial temporal lobe (MTL) including the hippocampus, and the occipital cortex. Underrecruitment has been linked to less efficient neural networks and corresponding episodic memory performance decline. Overrecruitment is being a matter of debate, where different hypotheses have been suggested such as inhibition deficit, dedifferentiation, and compensation (Cabeza, 2002) leading in some cases to preserved cognitive performance. Recently, Park and Reuter-Lorenz (2009) integrated this notion of compensation by the PFC by elaborating the "Scaffolding theory" of the aging brain. This theory stipulates that increased prefrontal activity is a marker of compensatory mechanisms, adaptively elaborated in response to structural and molecular deterioration of the brain in order to optimize cognitive performance. Thus, this account assumes relationships between structural integrity and brain function. However, little is known about such links, as most previous neuroimaging studies on aging were modality-specific, examining either brain structure or function, possibly in relation to cognitive performance (Reuter-Lorenz and Cappell, 2008). Simultaneous assessment and integra-

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tion of structural and functional data would be critical for furthering the understanding of whether age-related atrophy may account for functional brain differences.

Three kinds of structure-function relationships can be examined: (1) effect of global atrophy on local functional changes (Brodtmann et al., 2009; Solé-Padullés et al., 2009); (2) distal structure-function relationships, where atrophy of region A impacts function of region B (Brassen et al., 2009); and (3) regional/local structure-function relationships where structural integrity of a given region accounts for its functional capacity (Johnson et al., 2000; Shafto et al., 2010; Thomsen et al., 2004). For example, Johnson et al. (2000) collected functional and structural magnetic resonance imaging (MRI) data (semantic categorization task) from healthy subjects and Alzheimer's disease patients. They limited their investigation to 2 broad regions of the brain (left superior temporal gyrus and inferior frontal gyrus) from which they derived a mean atrophy index and mean functional activity. No significant structure-function links were found in the healthy older group, but a significant relationship was seen in the Alzheimer group such as more atrophy of the inferior frontal region was related to increased activity in the same region. In another study, Thomsen et al. (2004) used a dichotic listening paradigm and showed that in older individuals less activity was found in the left middle PFC, a region that also showed atrophy. However, no statistics were performed between structural and functional data. Finally, Shafto et al. (2010) studied the tip-of-the-tongue states in aging and found an association between gray matter density and activity in the insula. In addition to the fact that these studies did not investigate episodic memory, the statistical methods used lacked specificity and sensitivity. Indeed, mean structural and functional indexes were derived from wide regions of interest, whereas age effects may be more localized. Indeed, meta-analyses showed very distinct functional age-related effects in different subregions of the PFC (Rajah and D'Esposito, 2005; Spreng et al., 2010). Also, nonuniform gray matter (GM) loss associated with aging has been shown in the PFC (Tisserand et al., 2004) and also in the MTL where different subfields may support different mechanisms and can be differentially impaired with advancing age (for example different subregions of the hippocampus or the parahippocampal gyrus, e.g., Daselaar et al., 2006; Kalpouzos et al., 2009; La Joie et al., 2010). Thus, structural effects on function may be underestimated when using a mean value representing a large cerebral region. Voxel-based structure-function approaches should overcome this shortcoming, but so far, only one study showed in a voxel-based manner that local gray matter may account for activity in the right inferior PFC. This relation was observed during a working memory task, but only within a group of older individuals and not in comparison with younger subjects (Bartrés-Faz et al., 2009).

Consequently, assessment of voxel-wise multimodal analyses in aging is warranted. Here we used the BPM toolbox (Biological Parametric Mapping; Casanova et al., 2007) in order to assess functional voxel-by-voxel comparisons during the encoding and retrieval phases of an episodic memory task between 16 younger and 20 older individuals while simultaneously considering individual local gray matter volume (GMv) information (in the following, the term "local" stands for voxel-based). We recently published the functional neuroimaging results of this experiment, with special focus on the hippocampus (Persson et al., 2010). In the previous study we found typical age-related underrecruitment of the occipital cortex and overrecruitment of the PFC (as well as lateral parietal cortex), as conceptualized in the Posterior-Anterior Shift in Aging (PASA) model (Davis et al., 2008) and integrated within the more general Scaffolding model of aging. Here we chose to use this dataset in combination with volumetric data in order to test whether local GMv loss accounts for functional differences in relation to aging.

Two main hypotheses can be extracted from current theories of the aging brain. First, it is reasonable to hypothesize that GM loss can account for age-related underrecruitment. Second, regarding age-related overrecruitment, 2 hypotheses can be formulated: (1) GM loss may not account for age-related functional differences, therefore overrecruitment could be a genuine functional compensation associated with strategic changes to cope with increasing cognitive demands; and (2) local GM loss could induce overactivation of the remaining neurons in a physiological compensatory attempt, exceeding the level of activity in young individuals. Finally, even though no cognitive performance differences were found between young and older subjects in the present study, investigation of individual differences in cognitive performance combined with functional and structural neuroimaging data allowed us to test the hypothesis that cognitive compensation was underpinned by brain modifications.

2. Methods

2.1. Study population

Sixteen young (8 females, mean age = 25; range: 21–39 years old) and 20 healthy older adults (20 females, mean age = 61.3; range: 52–69) were involved in this study. All participants except 1 older individual were right-handed and had normal or corrected-to-normal vision. The older subjects, who were examined by a physician, were healthy and had no known neurological problems that might cause dementia. Informed consent was obtained from all participants in accordance with the guidelines of the Swedish Council for Research in the Humanities and Social Sciences.

2.2. Episodic memory task and functional MRI

All subjects underwent blocks of encoding, retrieval, and control tasks. At encoding they had to associate and memorize pairs composed of a face and a name, both shown on a screen. At retrieval they had to select 1 letter among 3