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Age-related changes in brain activation during a delayed item recognition task

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Abstract

To test competing models of age-related changes in brain functioning (capacity limitation, neural efficiency, compensatory reorganization, and dedifferentiation), young ($n = 40$; mean age = 25.1 years) and elderly ($n = 18$; mean age = 74.4 years) subjects performed a delayed item recognition task for visually presented letters with three set sizes (1, 3, or 6 letters) while being scanned with BOLD fMRI. Spatial patterns of brain activity corresponding to either the slope or *y*-intercept of fMRI signal with respect to set size during memory set encoding, retention delay, or probe stimulus presentation trial phases were compared between elder and young populations. Age effects on fMRI slope during encoding and on fMRI *y*-intercept during retention delay were consistent with neural inefficiency; age effects on fMRI slope during retention delay were consistent with dedifferentiation. None of the other fMRI signal components showed any detectable age effects. These results suggest that, even within the same task, the nature of brain activation changes with aging can vary based on cognitive process engaged.

Keywords: Aging; Parietal cortex; Prefrontal cortex; Premotor cortex; Verbal working memory; Working memory; Articulatory loop; Memory load; Compensatory reorganization; Neural efficiency; Capacity limitation; Dedifferentiation; Canonical variates analysis

1. Introduction

Four extant hypotheses concerning changes in brain function with aging are compensatory reorganization, dedifferentiation, computational capacity limitation, and neural inefficiency. The purpose of the current paper is to test the ability of these hypotheses to predict age-related changes in brain function associated with various aspects of cognitive processing, including verbal working memory (WM) maintenance, engaged during performance of a delayed item recognition (DIR) task for letters.

1.1. Brain areas implicated in working memory maintenance in the young

WM is a psychological construct used to describe the maintenance and manipulation of information on a time scale of seconds [7]. WM seems to be divided into verbal, spatial, and object sub-systems [8,37,82,94]. Verbal WM is thought to be critical for language comprehension and reasoning [5]. Based on neuropsychological dissociations [95,98] and word length, phonemic similarity, irrelevant speech, and articulatory suppression effects [6,11,22,51], the maintenance of information in verbal WM has been modeled as an articulatory loop in which sub-vocal rehearsal refreshes a phonological store. Experimental variation of the amount of information to be stored in verbal WM (WM load) has yielded findings of increases in fMRI signal in premotor, parietal, inferior frontal, and middle frontal areas [55,72,73,76,96]. At least some aspects of articulatory loop neural processing vary in intensity with WM load [45,96,106].

1.2. Age-related changes in the brain mechanisms of verbal WM

Even in the absence of Alzheimer's disease (AD) and other recognized brain diseases, aging is associated with

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impairment in several different memory variables [78], including WM [9,17,23,49]. In particular, load-dependent deficits in WM processing have been observed with normal aging [2,23,26,62,64]. Age-related deficits in cognition are assumed to stem from age-related brain pathology [88]. Normal aging is associated with a decrease in neuropil and neuronal number in cortex [12,21,25] and in the subiculum region of the hippocampus [84,99], an increase in the number of infarcts in cortex, basal ganglia, and white matter [65], an increase in MRI white matter lesions [80], an increase in density of neurofibrillary tangles in the CA1 region of the hippocampus [81], and a global decrease in gray matter volume [31].

There is the broad question of whether the functional neural circuitry of the brain remains static in the face of this neuropathology. Though not exhaustive, four extant hypotheses concerning changes in brain function with normal aging are compensatory reorganization, dedifferentiation, computational capacity limitation, and neural inefficiency. The purpose of the current study is to test the ability of these hypotheses to predict age-related changes in brain function associated with load-dependent and load-independent aspects of encoding, storage/rehearsal, and recognition/response components of a DIR task for letters [90], which is thought to tap verbal WM maintenance. These four hypotheses will now be briefly described, in turn.

1.3. Models which predict changes in patterns of brain activation with aging

Some have put forward a hypothesis that the brain is constructed such that it can in some sense compensate for neuropathology (such as that associated with normal aging) via macro-reorganization of neural circuits [4,10,14,33,87,100]. The teleological argument is that the effect of this reorganization would be to reduce or potentially even eliminate any behavioral consequences of the neuropathology that would otherwise occur. Compensatory reorganization, occurring to varying degrees across individuals, could potentially explain how age-associated neuropathology exists even in certain proportions of the non-demented elderly [34,81,83,85], and why variability in cognitive functioning increases with age [18]. Consistent with a special version of the compensatory reorganization hypothesis referred to as HAROLD (hemispheric asymmetry reduction in older adults [15]), a more bilateral PFC fMRI activation pattern in older adults than younger adults has been reported in word encoding [60,71], source memory [14], retrieval [53], working memory [15,69], and visual attention task contexts [15].

The types of compensatory reorganization models that we consider here (subsuming, but not limited to, the HAROLD model) posit that higher performing elders are higher performing because of a change in brain reorganization relative to both young subjects and lower performing elders. Therefore, under this type of compensatory reorganization there would be a cross-sectional correlation within elders between the degree of brain reorganization and performance, such that the brain activation patterns of higher performing elders would be more dissimilar than those of lower performing elders to young subject activation patterns [14]. We refer to all such models as cross-sectional compensatory reorganization models, to distinguish them from other types of compensatory models which do not require such cross-sectional correlations [89]. The current work can only weakly test the latter type of models, so we focus on testing cross-sectional compensatory reorganization models.

Dedifferentiation is another hypothesis that predicts non-identical brain activity patterns between young and elder populations. But, unlike compensatory reorganization, this change is not beneficial for the behavior in question, and is thought to represent a general deterioration in the integrity of brain circuitry [15]. Dedifferentiation and compensatory reorganization can be distinguished as the two make opposite predictions concerning the cross-sectional relationship of age-related differences in activation patterns and performance.

A critical notion concerning both of these theories is that the spatial pattern of neuronal activity in a brain that has been reorganized or de-differentiated is not identical to within a scaling factor to the corresponding canonical pattern of brain activation (in our case, that of the healthy, young population). From here on, the phrase "identical patterns" implicitly means identical to within a scaling factor. In Section 1.5, we discuss the method used to test whether elder and young activation patterns are identical.

1.4. Models which predict no change in patterns of brain activation with aging

Another general hypothesis regarding the effect of neuropathology on brain function is a reduction in the capacity of information representation or throughput in a brain circuit. This might perhaps be caused by a limitation on the amount or quality of information entering a brain circuit due to impairment in sensory systems [35,47,50]. A simple reduction in computational capacity would predict, in the context of identical task stimuli and instructions, a decrease in both performance and neurophysiologic activity (i.e., less total ionic flux across neuronal membranes due to synaptic transmission, therefore less ATP utilization through ionic pumps, and presumably less cerebral blood flow), and so would arguably be associated with identical brain activity patterns in young and elders. Reductions in activation with aging have been reported in anterior frontal cortex [32,57,79], dorsolateral PFC [41,43,58,74,75], hippocampus [57,59], anterior cingulate [58], temporal [40], parietal [40,58] and occipital cortices [15,33,40,52,57]. Some of these reduced activations have been associated with age-related impairments in certain cognitive functions, such as resolution of competing response impetuses [43], memory scanning speed [74], and feature binding [59].