SPECIAL SECTION ON "COGNITION AND AGEING BRAIN"

RELATING MEDIAL TEMPORAL LOBE VOLUME TO FRONTAL fMRI ACTIVATION FOR MEMORY ENCODING IN OLDER ADULTS

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ABSTRACT

Neuroimaging research on the brain basis of memory decline in older adults typically has examined age-related changes either in structure or in function. Structural imaging studies have found that smaller medial temporal lobe (MTL) volumes are associated with lower memory performance. Functional imaging studies have found that older adults often exhibit bilateral frontal-lobe activation under conditions where young adults exhibit unilateral frontal activation. As yet, no one has examined whether these MTL structural and frontal-lobe functional findings are associated. In this study, we tested whether these findings were correlated in a population of healthy older adults in whom we previously demonstrated verbal memory performance was positively associated with left entorhinal cortex volume in the MTL (Rosen et al., 2003) and right frontal lobe activation during memory encoding (Rosen et al., 2002). Thirteen, non-demented, community-dwelling older adults participated both in a functional MRI (fMRI) study of verbal memory encoding and structural imaging. MRI-derived left entorhinal volume was measured on structural images and entered as a regressor against fMRI activation during verbal memory encoding. Right frontal activation (Brodmann's Area 47/insula) was positively correlated with left entorhinal cortex volume. These findings indicate a positive association between MTL volume and right frontal-lobe function that may underlie variability in memory performance among the elderly, and also suggest a two-stage model of memory decline in aging.

Key words: aging, fMRI, entorhinal cortex, memory

RELATING VOLUME AND fMRI ACTIVATION IN ELDERS

Two brain regions have been emphasized in the study of the neural substrates of age-related declines in declarative (Cohen and Squire, 1981), or consciously recollected, memory: the frontal lobes and the medial temporal lobes (MTL) (Della-Maggiore et al., 2002; Prull et al., 2000; Raz, 2000). Two major approaches to studying the alterations of the aging brain in living humans have been volumetric measurement and functional imaging. These two approaches have led to two major conclusions. First, smaller MTL volumes are associated with lower memory performance in nondemented older adults (deToledo-Morrell et al., 2000; Golomb et al., 1994; Hackert et al., 2002; Rosen et al., 2003). Second, functional imaging studies reveal that frontal lobe activation is less lateralized (i.e., less asymmetric) in older than in younger people for declarative memory and other cognitive tasks (for reviews see Cabeza, 2002; Reuter-Lorenz, 2002). There has not, however, been any examination of the relation of these two major findings in healthy elderly people. A single study has examined structure-function relations using functional MRI (fMRI) and volumetric measurement in demented and nondemented older adults (Johnson et al., 2000). That study reported a negative correlation in demented older adults between volume and fMRI activation in the same brain region, the left inferior frontal gyrus. To our knowledge, no one has yet attempted to relate in older adults variability in MTL volume and variability in frontal-lobe activation, as measured by fMRI, during a memory task.

MTL integrity is critical for declarative memory, (Rempel-Clower et al., 1996; Scoville and Milner, 1957), and MTL integrity often declines with increasing age (e.g., Geinisman et al., 1995; Small et al., 2000). The MTL is comprised of multiple structures, and volumes of the hippocampus and entorhinal cortex in particular have been related to age-associated memory decline. There is a positive relation between hippocampal volume and memory ability in nondemented older adults (de Leon et al., 1997; Golomb et al., 1994; Hackert et al., 2002). In humans, there is material-specific laterality in the MTL, with declines in verbal declarative memory being typically related to damage to left hippocampal regions (e.g., Milner, 1971, 1972). Correspondingly, memory for verbal material is more strongly associated with left hippocampal

volumes and nonverbal material is more strongly associated with right hippocampal volumes in patients with Alzheimer's Disease (AD; deToledo-Morrell et al., 2000).

Entorhinal cortex volume also correlates positively with memory ability among nondemented elderly. Left entorhinal cortical volume correlates more strongly than left hippocampal volume with immediate memory recall for verbal material in nondemented older adults (deToledo-Morrell et al., 2000; Rosen et al., 2003). Entorhinal cortex may be particularly sensitive to age-associated declines in memory because resting PET activation in that region predicts longitudinal memory decline in the healthy elderly (de Leon et al., 2001) and entorhinal cortex volumes better predict precipitous memory decline towards AD than hippocampal volume (deToledo-Morrell et al., 2000; Dickerson et al., 2001; Killiany et al., 2002; but see Xu et al., 2000). Thus, entorhinal function and structure may best predict memory decline among the elderly, both within the normal range and from normal to pathological performance.

Functional imaging studies of memory performance have revealed that older adults show patterns of prefrontal cortex activation that are less lateralized than in young adults (for reviews see Cabeza, 2002; Reuter-Lorenz, 2002). Decreased laterality in prefrontal activation typically refers to a reduction of the difference between activation in right and left prefrontal regions relative to young adults. Whether this age-associated reduced laterality reflects a decrease in the more intensely active hemisphere, or an increase in the less intensely activated hemisphere or both, may depend on the task or individuals selected for the study. In the current study, participants encoded words by making decisions based on meaning (semantic) or physical characteristics (non-semantic). Semantic relative to non-semantic processing enhances later memory recall (Craik and Lockhart, 1972) and yields activation in left prefrontal cortex in young (Gabrieli et al., 1996; Kapur et al., 1994; Wagner et al., 1998) and older adults (Logan et al, 2002; Rosen et al., 2002; Stebbins et al., 2002). Not only did older adults demonstrate less lateralized encoding-related frontal lobe activation than young adults, but older adults with high memory ability showed more intense right frontal activation than young adults (Rosen et al., 2002). Thus, activation of the hemisphere contralateral to the one most intensely active in young adults was associated with superior memory performance among older adults. There has been debate about how age-associated reduction in asymmetric activation is best interpreted (Buckner and Logan, 2002; Cabeza et al., 2002). One argument is that recruiting the contralateral hemisphere is an adaptive response to age-related declines in brain integrity, a useful form of compensation (Cabeza et al., 2002; Reuter-Lorenz, 2002). Alternatively, increased recruitment of the contralateral frontal lobe in older adults may reflect a maladaptive process such as dedifferentiation (a reduction in brain specialization) or disinhibition of the contralateral hemisphere (Buckner and Logan, 2002; Cabeza et al., 2002). One attempt to resolve this debate involves the investigation of individual differences. Presumably the brains of older adults with relatively good memory performance would reveal the pattern of brain activity that was most adaptive.

Two studies have compared groups of older adults psychometrically characterized as good or poor memory performers (Cabeza et al., 2002; Rosen et al., 2002). In a verbal encoding study, both low and high performing older adults recruited the left frontal lobes, but only high performing older adults exhibited activation in right inferior prefrontal cortex that was greater than that seen in young adults (Rosen et al., 2002). In a study of source memory retrieval, young, low, and high performing older adults recruited right frontal regions but only high performing older adults recruited the left frontal lobe (Cabeza et al., 2002). Further, whereas greater left prefrontal activation during the encoding of a word is correlated with the increased likelihood of subsequent memory for that word for young adults, (Wagner et al., 1998), this subsequent memory effect is less lateralized in older adults (Morcom et al., 2002). These studies indicate that greater recruitment of contralateral regions in older adults is associated with better memory abilities, i.e., that reduced activation asymmetry in older adults is compensatory.

Although there are multiple reports of relations between MTL volumes and memory among the elderly, and also of bilateral frontal activations in the elderly, it is currently unknown whether these phenomena are functionally related in older adults. A concurrent, longitudinal, structural MRI and SPECT study of AD by Matsuda et al. (2002) demonstrated that there was considerable discordance in changes across different brain regions in measures of atrophy and regional cerebral blood flow (rCBF). These results suggest that techniques based on hemodynamic response and volumetric data yielded different information about brain integrity. Primate studies have further demonstrated that lesioning specific MTL structures can result in hypometabolic changes in remote brain areas, including the frontal lobe (e.g., Millien et al., 2002). Relating structural and functional imaging studies in older adults thus may yield additional information about the relationships between different brain regions.

The goal of the present analysis was to discover if there is a relation between individual differences in MTL volumes and in frontal lobe activation within a single group of older adults. Both volumetric measurement of the MTL and fMRI of the frontal lobes during memory encoding were performed in older adults with a range of memory abilities (see Rosen et al., 2002, 2003 for further