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BRAIN RESEARCH

Research Report

Resting hippocampal blood flow, spatial memory and aging

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ABSTRACT

Aging is accompanied by a general deterioration of fluid cognitive processes and a reduction in resting cerebral blood flow (CBF). While the two phenomena have been observed independently, it is uncertain whether individual differences in cerebral blood flow are reliably associated with cognitive functioning in older adults. Furthermore, previous studies have concentrated primarily on gross measures of cognition and global gray matter CBF, leaving open the possibility that perfusion of specific brain regions may relate differentially to distinct cognitive domains. The present study sought to provide a more focused treatment of CBF and cognitive function in the context of aging by investigating the relationships among aging, spatial memory and resting hippocampal blood flow, both between and within younger and older adult groups. Blood flow was quantified using a novel Flow-Enhanced Signal Intensity (FENSI) technique which provides a localized, functionally relevant measure of volumetric flow across a given unit area. As expected, we found that aging was associated with poorer spatial memory and reduced resting CBF. Moreover, hippocampal blood flow was positively correlated with spatial memory performance in the older adult group, suggesting that increased blood flow to the hippocampus is associated with superior memory performance in older adults. These results demonstrate a region-specific CBF—cognition relationship and thereby offer new insight into the complex connection between the aging brain and behavior.

1. Introduction

Aging is associated with a general decline in cognitive performance and a pattern of diffuse neurophysiologic changes. Included among the changes in physiology is a significant decrease in resting gray matter cerebral blood flow (CBF) in older adults (Bentourkia et al., 2000; Leenders et al., 1990; Parkes et al., 2004; Slosman et al., 2001). Given the age-related deterioration of cognitive function and physiologic integrity, it is only natural to inquire after the relationship between these two reliable phenomena. That is, is resting cerebral blood flow associated with cognitive performance in aging? More precisely, is CBF differentially associated with certain cognitive domains in aging? Even more specifically, is *local* CBF differentially associated with particular cognitive domains in aging?

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In response to the first question, a handful of studies have interrogated the relationship between cognitive function and global gray matter perfusion in elderly adults. The results are conflicting. While some studies have reported positive correlations between cognition and resting CBF (Rabbitt et al., 2006), others have found negative associations (Bertsch et al., 2009) and still others have failed to find any relationship at all (Meyer et al., 1988; Poels et al., 2008).

With regard to the second question, Rabbitt et al. (2006) investigated the predictive power of carotid and basilar artery blood flow on performance on 10 different cognitive tasks assessing fluid intelligence (gf), information-processing speed, memory and executive function in older adults. They found that CBF negatively predicted scores on eight of the tests and accounted for up to 36% of the age-associated variance in the speed scores. Therefore, it was concluded that CBF is a sensitive marker for neurophysiologic changes underlying processing speed, but not for gf, memory or executive function.

In light of the results of the aforementioned studies, particularly that of Rabbitt et al., one may ask whether a physiologic index can be identified for distinct aspects of cognition. While global CBF has its largest influence on information processing speed, is it possible that local measures of blood flow could serve as a more powerful surrogate for other cognitive functions? To our knowledge, no study to date has explored associations between local blood flow and domain-specific cognitive performance within the context of nonpathologic aging. Therefore, one cannot exclude the possibility that blood flow to a particular brain structure may have differential effects on cognitive processes involving the structure.

Our study was designed precisely to address this gap in the literature. More pointedly, our fundamental question was: is resting hippocampal blood flow correlated with spatial memory performance in aging? Our objectives were threefold: (1) to confirm age-related differences in spatial memory, (2) to examine age-related differences in resting hippocampal blood flow, and (3) to explore the relationship between individual differences in resting hippocampal blood flow and spatial memory as a consequence of aging. Numerous studies have established the association between spatial memory and the hippocampus, both in structure and in function (Erickson et al., 2009; Glikmann-Johnston et al., 2008; Ross and Slotnick, 2008). We chose a spatial short-term memory paradigm with a parametric manipulation in which performance has been shown to vary with age and hippocampal integrity (Erickson et al., 2009; Greenwood et al., 2005).

In order to demonstrate the specificity of spatial memory as opposed to general cognitive slowing, we also incorporated a measure of information processing speed in our study, i.e., a choice reaction time task. Previous studies have revealed that age-related slowing of processing speed functionally determines declines in several cognitive abilities including memory (Rabbitt et al., 2007; Salthouse, 1996). Therefore, we included a choice reaction time paradigm without a memory component to which we could compare our spatial memory measures and also use as a covariate in our statistical analyses.

With regard to blood flow, we targeted the hippocampus as our region of interest and selected the brainstem as a control area. Measurement of flow through the brainstem would be instrumental in establishing a selective association between hippocampal blood flow and spatial memory. We chose the brainstem as a control region because its involvement in cognitive processes does not overlap with that of the hippocampus, thereby, providing an unbiased measurement of blood flow. Furthermore, the brainstem was clearly visible on the imaging slice and comparable in size to that of the hippocampus (see Fig. 3), thus, avoiding uncertainty and error associated with the localization of smaller brain structures.

To calculate blood flow through the regions of interest, we utilized a novel measurement technique: the Flow-Enhanced Signal Intensity (FENSI) method (Sutton et al., 2007). The FENSI technique computes volumetric flux (Q), i.e., the rate of volume flow across a unit area, in units of mL/min/cm^2. An imaging slice is oriented in the brain to maximize the field of view of the area of interest, and movement of blood perpendicular to the slice is tracked over time to yield a value that represents highly-localized blood flow. The FENSI method was particularly advantageous to our study as it is noninvasive, is able to assess flow through a full axial cross-section of the hippocampus, and makes no assumptions about the transit time or path of blood; it is thus well-suited for aging studies (see D'Esposito et al., 2003 for a list of cerebrovascular alterations accompanying aging).

In view of the preexisting literature, we predicted significant age-related differences in spatial memory performance between the younger and older adult groups, with older adults performing more poorly on the task. We also expected a negative correlation between age and our measure of memory in elderly adults. Regarding aging and hippocampal blood flow, we hypothesized that elderly adults would exhibit reduced blood flow through the hippocampus and brainstem compared to younger adults and that within both age groups, age and blood flow would be negatively correlated through the two brain regions, thus, confirming a global decrease in CBF (Parkes et al., 2004; Slosman et al., 2001). Finally, we predicted that within the older adult group, hippocampal blood flow, but not flow through the brainstem, would be positively associated with spatial memory performance. Such a finding would establish specificity in the relationship between local blood flow and a selective aspect of cognition in nonpathologic aging.

2. Results

2.1. *Cognitive performance and aging*

2.1.1. *Age-group differences in choice reaction time*

The mean reaction times (RTs) and accuracy percentages for the younger and older adult groups in the choice reaction time task are displayed in Table 1. An independent-samples *t* test revealed a main effect of age group on reaction time, $t(46) = -5.64$, $p < 0.001$, with older adults responding more slowly than younger adults.

2.1.2. *Age-group differences in spatial memory*

The mean reaction times and accuracy scores for the 1-, 2-, and 3-item conditions of the spatial memory task are presented in Table 1. Overall, the younger adults responded more quickly and more accurately on all conditions of the task (see Fig. 1A). A repeated measures analysis of variance (ANOVA) confirmed