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Hippocampus-dependent spatial learning is associated with higher global cognition among healthy older adults

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ABSTRACT

Cognitive deficits in normal aging have been associated with atrophy of the hippocampus. As such, methods to detect early dysfunction of the hippocampus have become valuable, if not indispensable, to early intervention. The hippocampus is critical for spatial memory and is among the first structures to atrophy with aging. Despite the presence of navigation deficits in aging, few studies have looked at the association between wayfinding ability, navigation strategies, general cognitive function, and hippocampal volume. In the current study we investigated whether better general cognitive function is associated with the use of hippocampal-dependent spatial strategies, better spatial memory, and increased hippocampal volume. We also investigated, within older adults, the effects of aging on spatial memory. Healthy older adults (N = 107) were tested on a virtual wayfinding task and a dual-solution navigation task that can be solved using either a hippocampal-dependent spatial strategy or a caudate nucleus-dependent response strategy. Participants were also administered the Montreal Cognitive Assessment (MoCA), a test that measures general cognition and is sensitive to dementia. A structural MRI was administered to a sub-set of participants (n = 49) and hippocampal volume was calculated using a Multiple Automatically Generated Templates (MAGeT) Brain algorithm. We found that age was negatively associated with wayfinding ability and hippocampal volume. On the wayfinding task, participants with higher MoCA scores found more target locations and travelled shorter distances. We also found a significant association between higher MoCA scores and spatial strategy use. MoCA scores, spatial memory ability, and spatial strategy use all positively correlated with a larger hippocampal volume. These results confirm that with age there is a decrease in spatial memory, which is consistent with decreased volume in the hippocampus with aging. Furthermore, better general cognitive function is associated with better wayfinding ability and increased use of hippocampal-dependent spatial strategies.

1. Introduction

There is high variability in the aging process, with some individuals only experiencing minor cognitive changes while others experience substantial memory decline. Cognitive impairment in normal aging can be a risk factor for more serious disorders such as mild cognitive impairment (MCI) and Alzheimer's disease (AD). As such, early detection of cognitive impairment is imperative for identifying those who may be at risk of MCI and AD.

Various criteria have been used to measure global cognition, diagnose MCI, and predict conversion to AD (Gauthier et al., 2006; Julayanont et al., 2014; Petersen et al., 1999). In particular, the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) is a screening tool which has shown efficacy in identifying patients with MCI. The MoCA has high sensitivity and specificity in distinguishing between patients with MCI (90% sensitivity, 87% specificity), patients with mild Alzheimer's disease (100% sensitivity, 100% specificity), and healthy controls (Nasreddine et al., 2005). Furthermore, a recent study by Julayanont et al. (2014) showed that patients with MCI with low MoCA scores were significantly more likely to convert to AD. Therefore, low MoCA scores may reflect the early stages in the development of cognitive impairments and predict future conversion to AD.

Longitudinal studies have shown that people with lower hippocampal volumes are also more likely to develop cognitive impairment and AD (Jack et al., 1999; Karas et al., 2008). The hippocampus plays a critical role in spatial memory processing. In rodent and human studies,

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spatial memory tasks are often used to assess the effects of lesions to the hippocampus; therefore it is no coincidence that spatial memory deficits are among the first symptoms of MCI and AD (Klein et al., 1999; Laczo et al., 2010; Vlcek and Laczo, 2014). In support of this, with normal aging, we observe atrophy in the hippocampus which corresponds with poor wayfinding performance (Head and Isom, 2010). Age has been shown to impair both the formation and retrieval of cognitive maps (Iaria et al., 2009) and in real-life and virtual reality navigation tasks, older adults have difficulty recalling routes travelled (Wilkniss et al., 1997), learning the location of landmarks (Driscoll et al., 2003; Kirasic, 1991), and finding target locations (Driscoll et al., 2003; Newman and Kaszniak, 2000). However, as with any aging effects, there is variability in spatial memory ability in older adults and this may be reflective of hippocampal atrophy and risk of developing cognitive impairment.

Although human and non-human animals with hippocampal lesions exhibit spatial memory impairments, certain navigation tasks can still be accomplished through the adoption of alternative strategies that rely upon other brain regions (Bohbot et al., 1998; Packard and McGaugh, 1996). When navigating in an environment, people can spontaneously adopt different strategies that can be used to guide behavior from a start location to a goal (Iaria et al., 2003; McDonald and White, 1994; Packard and McGaugh, 1996). The “spatial strategy”, dependent on the hippocampus, involves learning the relationships between different landmarks in an environment (Bohbot et al., 2007; Iaria et al., 2003; Packard et al., 1989; Packard and McGaugh, 1996). Knowledge of the relationships between landmarks is evidenced by flexible recombination of the information accumulated during learning, which can be tested by probing whether subjects can derive novel shortcuts to a target destination (O'Keefe and Nadel, 1978). In both younger and older adults, the spatial strategy is associated with increased grey matter and fMRI BOLD activity in the hippocampus (Bohbot et al., 2007; Dahmani and Bohbot, 2015; Iaria et al., 2003; Konishi and Bohbot, 2013; Konishi et al., 2013). The other distinct navigation strategy, the “response” strategy” involves learning a series of behavioural actions from specific points in the environment that act as stimuli and depends not on the hippocampus, but on the caudate nucleus of the striatum (Packard et al., 1989; Packard and McGaugh, 1996; White and McDonald, 2002). This strategy is inflexible in the sense that it does not allow deriving novel paths to target locations (O'Keefe and Nadel, 1978). The response strategy is associated with increased grey matter and fMRI BOLD activity in the caudate nucleus of the striatum (Bohbot et al., 2007; Iaria et al., 2003). Therefore, there are multiple strategies that one can use to navigate in an environment and these strategies depend on separate memory systems, namely the hippocampus and caudate nucleus.

Single-solution navigation tasks such as the standard Morris water maze in rodents and the wayfinding task in humans are designed to assess spatial learning. In contrast, on dual-solution navigation tasks, such as the plus maze or T-maze for rodents (Barnes et al., 1980; McIntyre et al., 2003; Packard and McGaugh, 1996), spatial and response strategies can be used to learn the task. In humans, the 4-on-8 virtual maze and the Concurrent Spatial Discrimination Learning Task developed by Bohbot and colleagues (Etchamendy et al., 2012; Iaria et al., 2003) and the virtual Y-maze developed by Moffat and colleagues (Rodgers et al., 2012) are examples of a dual-solution navigation task. One issue that arises with single-solution navigation tasks is that if strategy use is not controlled for (i.e. the task ensures that response strategies cannot be used) then non-hippocampal dependent memory systems can be used to solve the task. In effect, under certain conditions, response strategies are found to be just as efficient, if not more, than spatial strategies to find target destinations (Iaria et al., 2003). As such, tasks that dissociate navigation strategies may be more sensitive to hippocampal dysfunctions by revealing the decreased use of hippocampal-dependent memory systems.

Several studies have examined the effects of aging on navigation strategy use using dual-solution navigation tasks (Bohbot et al., 2012; Etchamendy et al., 2012; Konishi and Bohbot, 2013; Konishi et al., 2013; Rodgers et al., 2012). With aging, there is a shift in strategy use with older adults using response strategies significantly more than young adults. This shift in strategy use with aging corresponds with decreased fMRI BOLD activity in the hippocampus and increased fMRI BOLD activity in the caudate nucleus (Iaria et al., 2003). Furthermore, the use of response strategies is associated with decreased grey matter in the hippocampus (Bohbot et al., 2007). In the current study, we investigated in healthy older adults the relationship between aging, spatial memory, general cognitive function, and hippocampal volume. We also investigated whether response strategies are associated with lower general cognitive function and hippocampal volume, and thus potentially increased risk of cognitive impairment. We hypothesized that aging would be associated with decreased spatial memory ability and decreased hippocampal volume. Furthermore, we hypothesized that spatial memory impairments and the use of response strategies would be related to lower general cognitive function, assessed with the MoCA, and lower hippocampal volume.

2. Methods

2.1. Participants

107 healthy older adults (women: n = 59, men: n = 48; mean age: 65.07 ± 4.88; age range: 55–80; mean years of education: 16.11 ± 3.09) were tested on the wayfinding task. Of the 107 participants, 93 (women: n = 50, men: n = 43) were also tested on Concurrent Spatial Discrimination Learning Task (CSDLT). All participants were right-handed and had no history of neurological or psychiatric disorders or alcohol or drug abuse as assessed with a prescreening questionnaire. Participants reporting any diagnosis of MCI or AD were excluded from the study and any participants scoring below 27/30 on the Mini Mental State Examination (MMSE) (Folstein et al., 1975) were also excluded from the study. The MMSE is a commonly used test to assess general cognitive function (Folstein et al., 1975). Participants were recruited from the community via newspaper advertisements. A subsample of participants (n = 49; women: n = 29, men: n = 20; mean age: 66.04 ± 4.41; mean years of education: 16.59 ± 3.55) underwent a structural MRI scan. Of the 49 participants, two did not perform the CSDLT. There were no differences in demographics or performance on the CSDLT and Wayfinding between the whole sample and the sub-sample that underwent an MRI (Table 1). Informed consent was obtained in a manner approved by the local ethics committee. The study was approved by the Research Ethics Board at the Douglas Mental Health University Institute.

2.2. Montreal cognitive assessment

All participants were administered the Montreal Cognitive Assessment (MoCA) by a trained experimenter. The MoCA is a standard neuropsychological test (maximum score = 30) that measures general cognition and is sensitive to cognitive impairment in older adults (Nasreddine et al., 2005). The test examines various cognitive domains and is divided into the following sections: visuospatial/executive function, naming, attention, language, abstraction, delayed recall, and orientation.

2.3. Virtual wayfinding task

Before the task, participants navigated in a practice virtual environment to familiarize themselves with the keys (forward, left, and right) that allowed them to move around. The practice environment was a virtual castle and they were instructed to navigate down hallways, around corners, and up and down stairs. In order to best simulate real-world navigation, participants were instructed to not use the backward key. In the Virtual Wayfinding Task, participants were placed