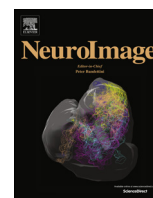




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A virtual water maze revisited: Two-year changes in navigation performance and their neural correlates in healthy adults

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ABSTRACT

Age-related declines in spatial navigation are associated with deficits in procedural and episodic memory and deterioration of their neural substrates. For the lack of longitudinal evidence, the pace and magnitude of these declines and their neural mediators remain unclear. Here we examined virtual navigation in healthy adults (N=213, age 18–77 years) tested twice, two years apart, with complementary indices of navigation performance (path length and complexity) measured over six learning trials at each occasion. Slopes of skill acquisition curves and longitudinal change therein were estimated in structural equation modeling, together with change in regional brain volumes and iron content (R2* relaxometry). Although performance on the first trial did not differ between occasions separated by two years, the slope of path length improvement over trials was shallower and end-of-session performance worse at follow-up. Advanced age, higher pulse pressure, smaller cerebellar and caudate volumes, and greater caudate iron content were associated with longer search paths, i.e. poorer navigation performance. In contrast, path complexity diminished faster over trials at follow-up, albeit less so in older adults. Improvement in path complexity after two years was predicted by lower baseline hippocampal iron content and larger parahippocampal volume. Thus, navigation path length behaves as an index of perceptual-motor skill that is vulnerable to age-related decline, whereas path complexity may reflect cognitive mapping in episodic memory that improves with repeated testing, although not enough to overcome age-related deficits.

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1. Introduction

Spatial navigation is a complex skill that requires maintaining cognitive representations in memory and updating them in real time, evaluating and implementing navigation strategies and deploying perceptual-motor skills—all of which demand substantial computational effort (Wolbers and Hegarty, 2010) and show significant age-related declines (Moffat, 2009). The study of age-related differences in navigation skill and neural correlates has been aided, in particular, by use of the Morris water maze (MWM; Morris, 1981) as an experimental method for investigating animal

Abbreviations: BS 95% CI, bias-corrected bootstrapped 95% confidence intervals; Cb, cerebellum; Cd, caudate nucleus; CFI, comparative fit index; FD, fractal dimension (path complexity); FIML, full information maximum likelihood; Hc, hippocampus; ICV, intracranial volume; LPFC, lateral prefrontal cortex; PHG, parahippocampal gyrus; RMSEA, root mean square error of approximation; SRMR, standardized root mean square residual; SWI, susceptibility weighted imaging; vMWM, virtual Morris water maze; WRMR, weighted root mean square residual

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navigation, and its virtual analog (vMWM, Astur et al., 1998) designed to study human behavior in a comparable framework. The task requires use of cues to navigate towards a hidden platform, often repeatedly to test learning a hidden goal location and stability of this knowledge. It is assumed that, to successfully reach the goal, the individual performing the task engages several cognitive processes, including procedural and episodic memory.

Given the differential vulnerability of these memory functions to decline in normal aging (Horn and Donaldson, 1980; Lindenberger et al., 1993; Park, 2000), understanding their contributions to navigation may elucidate the mechanisms of its decline. The magnitude of age-related differences in perceptual-motor skill acquisition depends on the task (Seidler, 2006), yet several studies have replicated poorer performance in older adults compared to their younger counterparts (Wright and Payne, 1985; Raz et al., 2000; Smith et al., 2005), with the differences appearing most robust when performance approaches asymptote (Ghisletta et al., 2010). Notably, whereas perceptual-motor skills decline with time (e.g., Rodrigue et al., 2005), episodic memory improves with repeated testing, even after long delays, albeit without overcoming the initial deficit observed among older adults (Bender et al., 2015;

Daugherty et al., 2015b; Persson et al., 2016). Based upon extant studies of canonical procedural and episodic memory tasks, we can expect age deficits in navigation in general, but perhaps differential declines related to memory function and perceptual-motor skill acquisition. Indeed, compared to younger counterparts, older adults take longer time to reach the vMWM platform, cover greater virtual distance (Moffat and Resnick, 2002; Driscoll et al., 2003, 2005), travel more complex paths (Daugherty et al., 2015a, 2015c), commit more heading errors (Moffat and Resnick, 2002), and evidence greater asymmetry in turning behavior (Yuan et al., 2013). Declines in general cognitive ability, perceptual-motor skill, memory (see Moffat (2009) for a review) and cognitive mapping function (O'Keefe, 1990; Daugherty et al., 2015a, 2015c) are hypothesized to underlie this age-related decline in navigation, but the relative contributions of various cognitive processes and skills and their vulnerability to decline in a navigation context are unclear. Thus, the use of varied, complementary indices of behavior is essential for understanding the nature of navigation skill and age-related changes therein.

Although indices of navigation performance are not entirely independent, their differential neural correlates and distinct patterns of age differences suggest a degree of specificity. Thus, multiple indices of performance complement each other and yield a richer understanding of human navigation skill than is obtained from examining single measures. In the context of vMWM, such complementary assessment is exemplified by using measures of traveled distance and time from the start to goal in conjunction with quantifying the degree of meandering along the search path via its fractal dimensionality (Daugherty et al., 2015a). Although all these measures characterize efficiency of the vMWM navigation and are correlated to some extent, they show different patterns of skill acquisition and age deficits therein (Daugherty et al., 2015a, 2015c). These differences highlight a critical feature of human navigation skill: optimal navigation is fast, short and does not meander, but successful navigation paths with low complexity can be either short or long. Consistently high correlations between traveled time and distance are noted across repeated vMWM trials, whereas path complexity becomes associated with these only when performance approaches asymptote (Daugherty et al., 2015a, 2015c).

Different indices of navigation appear to vary with respect to their structural brain substrates. Persistently complex paths during acquisition are associated with smaller hippocampal and parahippocampal gyrus volumes (Daugherty et al., 2015a, 2015c), more specifically the subiculum and entorhinal cortex (a part of the parahippocampal gyrus). These medial temporal lobe structures are putative neural substrates of cognitive mapping in episodic memory (O'Keefe and Nadel, 1978; O'Keefe, 1990, 1991; see Maguire et al. (1999) for a review) and more complex paths in the vMWM suggest an impoverished cognitive map (Kirasic et al., 1992; Moffat and Resnick, 2002; Daugherty et al., 2015a). Hippocampal and parahippocampal cortex volumes also correlate with navigation time and distance, but unlike path complexity, the neural substrates of those navigation indices include in addition striatum, prefrontal cortex, and cerebellum (Rondi-Reig and Burguiere, 2005; Moffat et al., 2007; Moffat, 2009; Daugherty et al., 2015a; Korthauer et al., 2015). Spatial navigation skill relies on more than cognitive mapping, and based upon the known functional specialization of these regions, it appears that distance and time of search in part reflect decision and perceptual-motor skill components.

In late adulthood, the relationship between regional brain volumes and navigation performance can be affected by the burden of age-related vascular and metabolic risk factors (see Raz and Rodrigue (2006) and Jagust (2013) for reviews) that in turn may be related to dysfunctional cellular processes. Declining cardiovascular

health, even in otherwise healthy adults, is associated with impaired cognitive spatial learning (Barak et al., 2015) and cardiovascular risk factors, such as increased pulse pressure (Waldstein et al., 2005; Bender and Raz, 2012), have been linked to age-related deficits in episodic memory and executive functions. The impact of vascular risk is considered to reflect multifarious molecular changes brought by oxidative stress (Dröge and Schipper, 2007) and chronic neuroinflammation (Finch et al., 1969; Finch and Crimmins, 2004; Grammas, 2011). These processes are difficult to assess directly in human brains, but their proxies, such as age-related increase in brain iron content, can be measured via MRI techniques—e.g., R2* relaxometry (Daugherty and Raz, 2015). Although the literature on longitudinal changes in brain iron is sparse, at least two studies showed that increase in striatal iron content predicts its shrinkage in healthy adults after two (Daugherty et al., 2015b) and up to seven years (Daugherty and Raz, 2016). Moreover, caudate iron accumulation, not shrinkage, over two years explained poorer cognitive performance in older adults (Daugherty et al., 2015b). Of note, hippocampal and caudate iron content is greater in older adults who display elevated vascular (Rodrigue et al., 2011) and metabolic risk factors (Daugherty et al., 2015b). Yet, the combined effects of iron accumulation and cardiovascular health on navigation skill are unknown. To date, iron accumulation as a correlate of declining navigation ability has been explored only in animal models (Maaroufi et al., 2009), although age-related deficits in other cognitive and perceptual motor abilities have been linked to greater iron content in the hippocampus (Rodrigue et al., 2012) and striatum (Adamo et al., 2014) in healthy humans. Thus, indices of regional brain iron content and pulse pressure may contribute to elucidating mechanisms of age-related deficit in navigation performance.

To the best of our knowledge, there are no longitudinal studies of navigation skill acquisition, trial-by-trial and therefore the pattern and magnitude of change during aging in that domain is unknown. However, two recent studies reported change in aggregate mean performance. One examined average time of navigation in vMWM at two occasions eight years apart and found no evidence of change while it replicated commonly reported cross-sectional age differences in travel time and its correlations with hippocampal and prefrontal cortical volumes (Korthauer et al., 2015). Another longitudinal study that included virtual navigation training accompanied by treadmill walking reported greater improvement in finding target locations by older adults compared to their younger counterparts, in spite of better performance by the latter (Lövdén et al., 2012). However, without analysis of acquisition curves in these small-sample studies, the possible longitudinal stability of navigation behavior and the source of age-related differences are difficult to assess. The above-mentioned evidence notwithstanding, the current reliance on cross-sectional designs precludes assessing age-related change in navigation skill and, in particular, evaluating its potential neural mediators (Maxwell and Cole, 2007; Lindenberger et al., 2011; Raz and Lindenberger, 2011).

To address the outlined shortcomings, we examined changes in two aspects of navigation skill acquisition (path length and complexity) across repeated trials within a baseline session and at a two-years follow-up in a sizeable lifespan sample of healthy adults. Based upon the existing literature, we hypothesized that volume and iron content of several brain regions that were previously identified as substrates of spatial navigation will be associated with change in navigation skill. The selected regions were caudate nucleus (Cd), cerebellum (Cb), hippocampus (Hc), parahippocampal gyrus (PHG), and the lateral prefrontal cortex (LPFC), all showing robust shrinkage in normal aging (Raz et al., 2005; Fjell et al., 2009; Tamnes et al., 2013; Persson et al., 2014; see Kennedy and Raz (2015) for a review) and partially accounting for change in perceptual-motor skill and memory functions (Rodrigue

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