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Age-related white-matter correlates of motor sequence learning and consolidation

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ABSTRACT

Older adults show impaired consolidation in motor sequence learning (MSL) tasks, failing to demonstrate the sleep-dependent performance gains usually seen in young individuals. To date, few studies have investigated the white-matter substrates of MSL in healthy aging, and none have addressed how fiber pathways differences may contribute to the age-related consolidation deficit. Accordingly, we used diffusion-weighted magnetic resonance imaging to explore how white-matter characteristics relate to performance using an explicit MSL task in young and older participants. Analysis revealed that initial learning scores were correlated to white-matter microstructure in the corticospinal tract and within the corpus callosum regardless of age. Furthermore, sleep-dependent consolidation scores, in young adults only, were related to white-matter tract organization in a frontal area where several major fiber bundles cross each other. These findings further our understanding of the neural correlates of MSL in healthy aging and provide the first evidence that age-related white-matter differences in tract configuration may underlie the age-related motor memory consolidation deficit.

1. Introduction

The ability to learn and maintain new motor skills is essential for the performance of everyday activities throughout the lifespan, and as the average age of the world's population continues to rise, a comprehensive understanding of the relationship between aging and motor learning is imperative. Yet, the effects of aging on motor memory acquisition and consolidation remain rather poorly understood. To study these mnemonic processes, investigators have often used motor sequence learning (MSL) paradigms (Doyon et al., 2009a). The motor skill learned through practice of such tasks has been shown to follow distinct acquisition phases: a first fast-learning stage in which considerable improvement in performance takes place within a single training session, a second slower stage in which further gains can be observed across several sessions, and finally, a consolidation phase during which savings from the initial training session, and even spontaneous gains in performance, can be observed between periods of practice (Doyon and Benali, 2005; Doyon et al., 2009a; Karni, 1996; Walker, 2005). Accumulated evidence has revealed that the newly formed motor memory trace is transformed into an enduring, resilient long-term memory during the later stage (Doyon et al., 2009b; Karni et al., 1995; Walker, 2005; Walker and Stickgold, 2004) and that sleep facilitates this consolidation process, especially for sequences of movements that are explicitly known to participants (Debas et al., 2010; Doyon et al., 2009b; Maquet, 2001; Robertson et al., 2004; Walker et al., 2002).

Work investigating the neural substrates mediating the different phases of MSL in young participants has repeatedly shown that both corticocerebellar and corticostriatal networks, as well as the hippocampus, contribute to the initial (fast) learning stage of a motor sequence, while consolidation and long-term storage are believed to be mostly dependent on a distributed corticostriatal circuit (Albouy et al., 2008, 2013; Debas et al., 2010; Doyon and Benali, 2005; Doyon et al., 2009a; Penhune and Steele, 2012; Seidler et al., 2002; Ungerleider et al., 2002). Although much less

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is known regarding the effects of aging on motor sequence learning and consolidation, results from behavioral studies have shown that performance in the initial learning phase is relatively spared in older healthy participants (Brown et al., 2009; Howard and Howard, 1989; Spencer et al., 2007). Yet, recent work has also revealed that older participants tend to demonstrate impairments in the consolidation of learned motor sequences, notably by failing to produce the expected gains in performance usually observed in young adults following a retention period that includes sleep (Fogel et al., 2014; Nemeth and Janacsek, 2011; Spencer et al., 2007; Wilson et al., 2012).

The age-related changes in neural substrates and plasticity underlying older adults' ability to learn and consolidate motor sequence memory traces have yet to be fully understood, but evidence from functional and structural imaging studies suggests that deficits could be mainly related to a degradation in the frontal cortex and striatum (i.e., the corticostriatal system) with age (Rieckmann and Bäckman, 2009; Rieckmann et al., 2010, see King et al., 2013 for a review). For instance, contrary to young participants, older adults are showing an increase in hippocampal activity as a function of practice during the initial learning phase, a finding that has been interpreted as a compensatory mechanism used to maintain similar initial learning rates despite the decline in structure and function of the striatum normally observed with aging (Rieckmann and Bäckman, 2009; Rieckmann et al., 2010). Second, a recent functional magnetic resonance imaging (MRI) study carried out in our laboratory investigating the role of sleep in MSL consolidation has revealed that the impairment in motor sequence consolidation in older participants is related to an interaction between altered sleep architecture and a decrease of activity in parts of the corticostriatal system (i.e., in the putamen) (Fogel et al., 2014). In addition to functional changes, substantial structural alterations in regions known to contribute to MSL, including volume reductions in the frontal cortex, striatum, and hippocampus (Gunning-Dixon et al., 1998; Kaasinen and Rinne, 2002; Raz et al., 2005; Rieckmann et al., 2010), have also been found to explain part of the deficits in motor sequence learning and consolidation in the older population.

The latter results are particularly significant, as there is evidence that the structural integrity and underlying configuration of white matter connecting these brain regions plays a significant role in MSL (Engel et al., 2014; Song et al., 2012; Steele et al., 2012). While the majority of structural studies investigating the white-matter correlates of motor memory in young healthy individuals have found that better performance is associated with higher fractional anisotropy (FA; a widely used measure obtained from diffusion tensor imaging) (Della-Maggiore et al., 2009; Engel et al., 2014; Scholz et al., 2009; Song et al., 2012; Tomassini et al., 2011), others have also reported an association with reduced FA values (Huang et al., 2015; Steele et al., 2012; Taubert et al., 2010). The reason for such discrepant findings is still conjectural, but evidence gathered so far suggests that the latter results may be due to the fact that FA is a composite metric that reflects not only white microstructural integrity, as usually reported, but the local fiber tract architecture as well (Behrens et al., 2007). Indeed, it is now widely recognized that FA is a complex measure influenced not only by myelination, axon size, and axon density, but also by the relative strength of other fiber populations within the same region (Beaulieu, 2002; Jbabdi et al., 2010). However, to this day, only a handful of studies have taken into account the underlying fiber tract configuration when interpreting differences in FA. Furthermore, the latter have only approximated tract organization through the concomitant interpretation of other nonspecific tensor-derived metrics such as axonal (AD), radial (RD), and mean diffusivity (MD). Yet in recent years, a simple, effective way of appraising the complexity of white-matter organization in the human brain has been proposed (Dell'Acqua et al., 2009; Jeurissen and Leemans, 2010). This new method consists of quantifying the number of fiber orientations (NuFOs) in each voxel through a constrained spherical deconvolution technique (Tournier et al., 2004), but this innovative measure remains relatively unknown outside the realm of methodological literature. NuFOs are estimated as the number of local maxima of the fiber orientation distribution profile in each voxel and can be visualized as maps where the gray scale intensity of each voxel corresponds to the number of fibers it contains. As such, NuFO may contribute substantially to a more precise interpretation of associations between FA and behavior.

To our knowledge, only 2 studies have investigated age differences in the white-matter correlates of MSL. First, Bennett and collaborators found that the integrity of the tracts linking both the caudate and hippocampus to the dorsolateral prefrontal cortex was related to motor sequence learning and that this relationship did not differ between young and older adults (Bennett et al., 2011). Second, Schulz et al., 2014 reconstructed 28 intrahemispheric and interhemispheric pathways connecting primary and secondary motor areas in young and older participants and found that tract-related integrity correlated with training gains on an explicit motor sequence task in older participants only. Yet, no study so far has explored the extent to which altered tract-related characteristics could contribute to the deficit observed with age on motor sequence consolidation. Furthermore, previous studies have either focused on single tracts of interest or used FA as a reflection of white-matter integrity without assessing the contribution of crossing fibers, which can obfuscate the outcome and interpretation of white-matter analysis techniques.

In response to this knowledge gap, the present study set 2 aims (1) to characterize the white-matter correlates of motor sequence learning and sleep-dependent consolidation in healthy young and older adults across the whole brain, while taking into account fiber tract configuration; and (2) to determine the extent to which these structure-behavior relationships are affected by age differences. The latter sets to understand the structural changes that occur with age and that might explain why sleep does not afford the benefit to memory consolidation in the older population. To achieve these goals, we used diffusion-weighted magnetic resonance imaging (DWI) to characterize structural properties of white-matter pathways in groups of young and older participants who were trained on a finger MSL task and retested after an afternoon nap or an equivalent period of rest. We expected to find significant associations between behavioral performance and various diffusion measures in white matter connecting cortical and subcortical motor-related regions known to contribute to the acquisition and consolidation of motor sequence memories (Dayan and Cohen, 2011; Doyon et al., 2009a). In addition, we hypothesized that older adults would show altered tract-related white-matter characteristics and fewer offline gains in performance (i.e., behavioral changes that reflect consolidation) compared to younger adults.

2. Material and methods

2.1. Participants

Groups of young healthy volunteers (n = 28, 17 women) between 20 and 35 years of age (mean [M] = 24.5, standard deviation = 4.0), and older healthy individuals (n = 29, 20 women) between the age of 55 and 75 years (M = 62.8, standard deviation = 4.0) participated in the study. Participants were included if they were right handed, nonsmokers, and free from medication known to interfere with sleep. To be included, participants were required to have a normal body mass index ($\leq$28), no history of neurological,