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White-matter integrity as a marker for cognitive plasticity in aging

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ABSTRACT

Age-related differences in white-matter (WM) integrity are substantial, but it is unknown whether between-subject variability in WM integrity influences the capacity for cognitive improvement. We investigated the effects of memory training related to active and passive control conditions in older adults and tested whether WM integrity at baseline was predictive of training benefits. We hypothesized that (1) memory improvement would be restricted to the training group, (2) widespread areas would show greater mean diffusivity (MD) and lower fractional anisotropy in older adults relative to young adults, and (3) within these areas, variability in WM microstructure in the older group would be predictive of training gains. The results showed that only the group receiving training improved their memory. Significant age differences in MD and fractional anisotropy were found in widespread areas. Within these areas, voxelwise analyses showed a negative relationship between MD and memory improvement in 3 clusters, indicating that WM integrity could serve as a marker for the ability to adapt in response to cognitive challenges in aging.

1. Introduction

Brain functions can be modified in response to changing environments and demands throughout the life span (Bavelier et al., 2012; Dahlin et al., 2008; Lovden et al., 2010). However, the potential for cognitive improvements varies substantially among older individuals (Bherer, 2015; West et al., 2002), and we do not know which brain characteristics can account for this. The aim of this study was to directly address this question, by testing whether individual variability in white-matter (WM) microstructure at baseline could predict cognitive plasticity, here defined as the extent of behavioral benefit after a memory-training intervention. We hypothesized that individual variability within WM regions vulnerable to age differences would be particularly predictive of cognitive benefit in the older group, and that reduced WM integrity would be associated with lower training gains.

A number of studies indicate that age-related variance in cognitive functioning is related to individual variability in the WM microstructure (Madden et al., 2012). The predominant findings from diffusion tensor imaging studies are increased mean diffusivity (MD) and decreased fractional anisotropy (FA) with aging, albeit accompanied by substantial individual variability (Bennett and Madden, 2014; Salami et al., 2012; Sexton et al., 2014; Westlye et al., 2010). MD represents the mean molecular motion independent of tissue directionality and is suggested to relate to cellular properties such as size and integrity (Basser, 1995; Pierpaoli et al., 1996). Evidence suggests that FA is related to restricted molecular motion caused by directionally oriented microstructures such as myelin sheaths and axonal cell membranes (Beaulieu, 2002; Pierpaoli et al., 1996). WM integrity can be further characterized by axial diffusivity (AD) and radial diffusivity (RD), which represent the rate of diffusion along the primary and secondary axes of the diffusion ellipsoid, respectively (Bennett and Madden, 2014).

Although the exact neurobiological underpinnings of diffusion metrics are unclear, MD and FA are, to some extent, reflective of WM integrity (Zatorre et al., 2012). While we recognize the uncertainties regarding the specific mechanisms underlying diffusion metrics, we will, for simplicity, refer to WM integrity when discussing overall diffusion metrics.

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The deterioration in WM microstructure observed in aging has been suggested to follow a posterior to anterior gradient with a greater magnitude of change in frontal regions (Bennett et al., 2010; Burzynska et al., 2010; Davis et al., 2009). The notion that frontal areas are particularly vulnerable to age-related changes has been linked to evidence showing stronger relationships between cognition and WM integrity in frontal regions (Madden et al., 2012). However, the general evidence for relationships between cognition and specific regions of WM is, thus far, unconvincing (Salthouse, 2011), and the regional characteristics of age-related changes in WM microstructure are still unclear (Barrick et al., 2010; Davis et al., 2009; Sexton et al., 2014; Westlye et al., 2010).

Recent years have been marked by a considerable interest in the effects of physical and cognitive training on both cognition and the brain. Studies involving cognitive training paradigms have shown positive training effects in both young and older samples (Burki et al., 2014; Jones et al., 2006; Li et al., 2008; Lovden et al., 2010), where the interindividual variability in training outcome tends to be larger in older groups (Bherer et al., 2006; West et al., 2002). Plotted data often reveal substantial individual variability in cognitive improvement in older adults (Engvig et al., 2012; Hofstetter et al., 2013; Lovden et al., 2012), which emphasize the need to investigate factors underlying the variation in potential for cognitive improvement. The neurological underpinnings of cognitive plasticity are commonly examined in the view of an interactive process between brain and cognition, associating cognitive improvement with change in structural and functional brain measures. Some studies have demonstrated relationships between altered WM microstructure and cognitive improvement after various training programs (Engvig et al., 2012; Hofstetter et al., 2013; Mackey et al., 2012; Nordvik et al., 2012; Schlegel et al., 2012; Scholz et al., 2009). However, individual variation in WM integrity is largely unexplored as a marker for cognitive plasticity.

Here, we aimed to study the effects of a memory-training intervention in older adults relative to active and passive control groups. Training gain was measured using standardized residuals, that is, training effects independent of baseline scores. The training group received 10 weeks of memory training aimed at improving serial verbal recollection memory by implementing the mnemonic technique method of loci (MoL) (Bower, 1970). This method is shown to improve serial recall substantially in older adults (Engvig et al., 2012; Kliegl et al., 1990). The active control group followed an identical schedule as the memory-training group but focused on popular scientific themes as opposed to specific memory training. Areas of significant age differences in MD and FA at baseline were identified in 104 older adults distributed across the different conditions (memory training, passive, and active control) relative to 52 young adults. A conjunction mask based on the areas showing age differences in both MD and FA was used as a region of interest (ROI) for further analyses. We then investigated whether interindividual variation in WM microstructure in areas showing significant age differences was predictive of benefit from cognitive training in the older group. The anchoring of analyses in brain age differences was chosen to investigate markers of cognitive plasticity in aging specifically. It was hypothesized that (1) only the training group would show significant improvement in memory performance after 10 weeks of memory training, (2) widespread areas would show age differences in terms of increased MD and decreased FA with advancing age, and (3) within these areas of age differences, rather than in areas not showing age differences, interindividual variability in WM microstructure in the older group would be predictive of cognitive gains after training, especially in frontal areas hypothesized to show the most prominent age differences.

2. Methods and materials

2.1. Sample

The sample was drawn from the ongoing project Neurocognitive Plasticity at the Research Group for Lifespan Changes in Brain and Cognition, Department of Psychology, University of Oslo. All procedures were approved by the regional ethical committee of Southern Norway, and written consent was obtained from all participants. Participants were recruited through newspaper and webpage adverts and were screened with a health interview. Participants were required to be either young or older (in or around their 20s or 70s, respectively) healthy adults, right handed, fluent Norwegian speakers, and have normal or corrected to normal vision and hearing. Exclusion criteria were history of injury or disease known to affect central nervous system function, including neurological or psychiatric illness or serious head trauma, being under psychiatric treatment, use of psychoactive drugs known to affect central nervous system functioning, and magnetic resonance imaging (MRI) contraindications. Moreover, for inclusion in the present study, participants were required to score $\geq$26 on the Mini-Mental State Examination (Folstein et al., 1975) and have scores within normal range ($\pm$2 standard deviations [SDs] from mean) for age and sex on the 5-minute delayed recall subtest of the California Verbal Learning Test II (Delis et al., 2000). Three persons in the older group were excluded based on these criteria. All participants further had to achieve an IQ above 85 on the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999). All scans were evaluated by a neuroradiologist and deemed to be free of significant injuries or conditions. Only participants who completed MRI scanning in addition to 2-assessment sessions were included in the current analyses. Ten of the older participants dropped out after 1 scan, 9 in the training group, 0 in the active control group, and 1 in the passive control group. These participants dropped out either because the particular time frame for assessment was inconvenient for them or because the participation was too time consuming. At the time of the present study, 52 younger and 104 older adults—a total of 156 participants—fulfilled the inclusion criteria. Sample demographics are listed in Table 1. The group of older participants who dropped out performed lower on the California Verbal Learning Test 5-minute recall (mean = 7.67.1, SD = 4.33; independent samples *t* test, t = 2.32, $p = 0.03$) and had lower education compared to the rest of the older sample (mean = 12.22, SD = 3.99, independent samples *t* test, t = 2.79, $p = 0.006$). Lower education and cognitive performance among dropouts is commonly observed in longitudinal studies, resulting in a selection effect toward higher functioning older adults (Salthouse, 2014).

2.2. Design and memory training program

The participants were assigned to 1 of 3 groups depending on registration date. Some participants started with 10 weeks of memory training (n = 36), some started with 10 weeks participation in the active control group (n = 19), and some started with 10 weeks as passive controls (n = 49). The passive control group also completed 10 weeks of memory training *after* the initial 10 weeks as passive controls, and was included in a larger training group for statistical analyses including their MRI scan and cognitive performance at time point 3. Thus, some participants were included both as controls (the first 10 weeks) and a part of the training group (the last 10 weeks) in the analyses. All participants were examined using MRI and cognitive testing, with a 10-week interval between each assessment. The training group received 10 weeks of memory training including a single group session each week led by a research fellow. The first group session included a presentation of