The Effects of Memory Training on Behavioral and Microstructural Plasticity in Young and Older Adults

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Abstract

Age differences in human brain plasticity are assumed, but have not been systematically investigated. In this longitudinal study, we investigated changes in white matter (WM) microstructure in response to memory training relative to passive and active control conditions in 184 young and older adults. We hypothesized that I) only the training group would show improved memory performance and microstructural alterations, II) the young adults would show larger memory improvement and a higher degree of microstructural alterations as compared to the older adults, and III) change in memory performance would relate to microstructural alterations. The results showed that memory improvement was specific to the training group, and that both the young and older participants improved their performance. The young group improved their memory to a larger extent compared to the older group. In the older sample, the training group showed less age-related decline in WM microstructure compared to the control groups, in areas overlapping the corpus callosum, the cortico-spinal tract, the cingulum bundle, the superior longitudinal fasciculus and the anterior thalamic radiation. Less microstructural decline was related to a higher degree of memory improvement. Despite individual adaptation securing sufficient task-difficulty, no training-related group differences in microstructure were found in the young adults. The observed divergence of behavioral and microstructural responses to memory training with age is discussed within a supply-demand framework. The results demonstrate that plasticity is preserved into older age, and that microstructural alterations may be part of a neurobiological substrate for behavioral improvements in older adults.

1. Introduction

The potential for human brain plasticity throughout the lifespan is not yet fully understood (Johansen-Berg and Duzel, 2016; Walhovd, et al., 2015). As a species, we rely on accumulated experience across decades, suggesting that major neural replacements in the adult brain are not feasible (Rakic, 1985; Walhovd, et al., 2015). Hence, there is wear and tear, and one might expect older adults to exhibit even lower capacity for structural brain change than young adults. Possibly counteracting this is how the accumulating brain changes must make the mismatch between functional capacity and environmental demands higher for older adults, as structural plasticity is believed to take place only when demands exceed capacity (Lovden, et al., 2010a). This paradox, with structural brain differences in ageing both constraining plasticity and potentially driving it, calls for a systematic investigation of brain plasticity across age. Thus, the aim of this study was to investigate changes in white matter (WM) microstructure in response to memory training in young and older adults.

Although evidence suggests that plasticity is preserved into older age (Burki, et al., 2014; Lovden, et al., 2010b; Lustig, et al., 2009), young adults tend to show larger training gains relative to older adults (Baltes, et al., 1992; Burki, et al., 2014; Dahlin, et al., 2008). This is consistent with animal models, where increasing age is associated with a lower magnitude of neuroplastic changes (Blumenfeld-Katzir, et al., 2011; van Praag, et al., 2005). However, studies focusing on human age differences show mixed findings. While one cognitive training study (Lovden, et al., 2010b) reported similar magnitudes of WM microstructural plasticity in young and older adults, another found that spatial navigation training yielded cortical changes in young adults only (Wenger, et al., 2012). Juggling exercise has been reported to affect grey matter in both young and older adults, although to a smaller extent in older

adults (Boyke, et al., 2008). Little is known about age differences in response to training of episodic memory, a cognitive function known as particularly challenging in older age (Nyberg, et al., 2012).

Further complicating conclusions are the possible effects of factors related to participation, such as general cognitive activity (Gallucci, et al., 2009). As modest cognitive improvement has been observed in active control groups (Legault, et al., 2011), the inclusion of such groups is necessary to determine the specific effects of training (Hart, et al., 2008; Law, et al., 2014). Some, but relatively few training studies include active control groups (Barnes, et al., 2013; Fabre, et al., 2002; Legault, et al., 2011; Oswald, et al., 2006; Schwenk, et al., 2010; Suzuki, et al., 2012; Zelinski, et al., 2011), and in particular this appears to be lacking in studies comparing young and older adults.

Some evidence suggests that the magnitude of structural alterations after training interventions can be linked to the degree of cognitive improvement (Engvig, et al., 2010; Hofstetter, et al., 2013; Mackey, et al., 2012b; Scholz, et al., 2009). Conversely, other studies report a lack of associations between cognitive and structural changes (Lovden, et al., 2010b; Lovden, et al., 2012b; Lovden, et al., 2013), and it has thus been suggested that the amount of time spent on training may have a larger impact on brain plasticity than improvements in performance (Scholz, et al., 2009). Evidently, there is a need to clarify plastic potential in young versus older adults, and how structural alterations relate to cognitive improvement.

In this study, microstructural changes related to memory training were measured using diffusion tensor imaging (DTI), from which mean diffusivity (MD), fractional anisotropy (FA), radial diffusivity (RD) and axial diffusivity (AD) were derived. DTI measurements reflect the restriction of the water molecules, which can

be imposed by microstructure such as myelin, microtubules and cell membranes (Beaulieu, 2002). 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). AD and RD 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 cannot be directly inferred (Wheeler-Kingshott and Cercignani, 2009), these measures reflect MRI signal changes that may be influenced by alteration in cellular properties (Zatorre, et al., 2012).

Memory improvement and changes in DTI metrics were measured across young and older trainers, passive and active controls. The training group received ten weeks of memory strategy training aimed at improving serial verbal recollection memory by implementing the mnemonic technique Method of loci (MoL) (Bower, 1970). The active control group program involved popular scientific topics. The intervention programs were matched to involve similar amounts of cognitive and social engagement. As individual adaptation of task difficulty is considered crucial to evoke plastic responses (Jones, et al., 2006; Lovden, et al., 2012a), the memory training was individually adapted for both young and older participants, in order to continuously place demands above each individual's present level performance. The following hypotheses were tested:

I. Only the training group will show improved memory performance and alterations in WM microstructure after ten weeks of memory training.

II. The young adults will show larger memory improvement and a higher degree of WM microstructural alterations relative to the older adults.

III. Improvement in memory performance will relate to changes in WM microstructure.

2. Methods and materials

2.1 Sample

The sample was drawn from the project *Neurocognitive Plasticity* at the Research Group for Lifespan Changes in Brain and Cognition (LCBC), 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 multiple newspaper and webpage adverts, which ran between one and seven days. All participants 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 (CNS) function, including neurological or psychiatric illness or serious head trauma, being under psychiatric treatment, use of psychoactive drugs known to affect CNS functioning, and magnetic resonance imaging (MRI) contraindications. Moreover, for inclusion in the present study, participants were required to score above 25 on the Mini Mental State Examination (MMSE) (Folstein, et al., 1975) and less than 2 standard deviations (SD) below mean on the five minutes delayed recall subtest of the California Verbal Learning Test II (CVLT II) (Delis, et al., 2000). Three individuals 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 (WASI; (Wechsler, 1999)). All scans were evaluated by a neuroradiologist and deemed to be free of significant injuries or conditions. Only participants who completed MR scanning at both baseline and follow up in addition to two assessment sessions were included in the current analyses. 15 of the older participants dropped out after the first

scanning session (13 in the training group, 1 in the active control group and 1 in the passive control group). 19 of the younger participants dropped out (12 in the training group, 5 in the active control group and 2 in the passive control group). The reasons included that the participation was too time consuming or that the particular time frame for assessment was inconvenient. At the time of the present study, 73 young and 111 older adults - a total of 184 participants - fulfilled the inclusion criteria. Sample demographics for the subjects included are listed in Table 1.

The young participants who dropped out performed lower than the rest of the young sample in terms of IQ (mean±SD for the drop outs = 107.0±10, for the included sample = 113.0±8.7; $t(71) = 2.3$, $p = 0.02$). The group of older participants who dropped out performed lower than the rest of the older sample in terms of IQ (mean±SD for the drop outs = 114.4±10.5, for the included sample = 120.5±10.2; $t(109) = 2.2$, $p = 0.03$) and CVLT 5 minutes recall (mean±SD for the drop outs = 8.3±3.7, for the included sample = 10.2±3.2; $t(109) = 2.1$, $p = 0.04$), and showed a trend towards lower MMS score (mean±SD for the drop outs = 27.7±1.4, for the included sample = 28.7±1.3; $t(109) = 2.0$, $p = 0.06$), and

Lower cognitive performance among dropouts is commonly observed in longitudinal studies, resulting in a selection bias effect towards higher functioning individuals (Salthouse, 2014). To control for selection bias, we performed a repeated measures analysis of covariance (ANCOVA) to test whether a group of included participants, who matched the participants who dropped out, differed from the rest of the sample in terms of memory improvement. Age and sex were used as covariates. 12 young participants were matched with the young trainers who dropped out on IQ (mean ± SD for the drop outs = 107.2±9.5, for the matched group =107.0±9.0). 13 older participants were matched with the older trainers who dropped out on IQ (mean

± SD for the drop outs = 112.3±9.6, for the matched group = 112.8±9.3). The results showed that the matched groups did not differ from the rest of the training group in terms of memory improvement ($F(1,28) = 0.38$, $p = 0.5$ for the young adults and $F(1,40) = 0.14$, $p = 0.7$ for the older adults).

[Insert Table I]

2.2 Design and memory training program

The participants were assigned to one of three intervention groups at registration. Pools of around 20 participants were recruited at a time, with continuous data collection for all three conditions simultaneously. Some participants received ten weeks of memory training (older adults: N = 44, young adults: N = 32), some received ten weeks of the active control intervention (older adults: N = 18, young adults: N = 13) and some were scanned and tested before and after ten weeks as passive controls (older adults: N = 49, young adults: N = 28). Some participants received ten weeks of memory training after an initial period as passive controls. These participants were included in a larger training sample used to analyze the statistical relationships between WM microstructural change and memory improvement. The design is illustrated in Figure 1. All participants were examined with MRI and cognitive testing, with a ten-week interval between each assessment. The training intervention included practicing the mnemonic technique Method of loci (MoL) (Bower, 1970). MoL has been shown to improve serial recall substantially in both young and older adults (Engvig, et al., 2012; Kliegl, et al., 1990; Nyberg, et al., 2003). The training program included a single course session each week and eight

weekly home assignments involving memorizing word lists. The home assignments were completed online and registered to a database. The number of total tasks completed was on average 73.7% in the older training group and 44.6% in the young training group. The level of difficulty was increased each week to ensure a continuous challenge. However, the participants were instructed to individually adjust the difficulty level, with the aim of achieving a challenging but manageable training level across all participants. Individual adjustment involved increasing/decreasing the number of words on the weekly tasks, performing the tasks within individual time limits and recollection of the word lists in reverse order. The active control group program involved attending popular scientific lectures and completing home assignments. None of the tasks or lectures in the active control program involved any specific form of memory training. Contact with staff, group meetings and the number of tasks were matched between the training group and the active control group, controlling for the possible effect of these factors on memory performance and WM microstructure. The number of total tasks completed in the active control group was on average 70% for the older adults and 38.5% for the younger adults. Independent samples t-tests showed that the number of tasks completed did not differ between the training groups and the active control groups (mean±SD = 32.7±20.1 for the young training group, 30.8±19.7 for the young active control group, $t(43) = -0.29$ $p = 0.8$, and mean±SD = 57.6±15.1 for the older training group, 55.5±21.1 for the older active control group, $t(60) = -0.45$ $p = 0.7$). Test sessions and time intervals were held identical for all participants, in order to ensure that test-retest effects would not differ across the groups.

[Insert Figure 1]

2.3. Image acquisition and analyses

A Siemens Skyra 3T MRI scanner with a 24-channel head-coil was used (Siemens Medical Solutions; Erlangen, Germany). For the current analysis, a diffusion-weighted echo-planar imaging (EPI) sequence was applied for each subject (FOV_{xy} = 252x256 mm, dimensions = 128x130x70, voxel size = 1.9626 x 1.9626 mm, slice thickness = 2 mm, repetition time = 9300 ms, echo time = 87 ms). Sixty-four unique diffusion weighted volumes were collected at b-value = 1000 s mm^{-2} in addition to two non-diffusion-weighted (b-value = 0 s mm^{-2}) volumes, one acquired with an opposite k-space traversal direction for the purpose of correcting susceptibility artefacts.

All scan-sets were manually checked for gross motion artefacts. The susceptibility-induced field was estimated using the FSL tool topup (Andersson, et al., 2003) and corrected for along with subject motion and eddy current-induced fields using the eddy tool (Andersson, et al., 2012). Signal dropout caused by subject motion during the diffusion encoding was also detected and corrected (Andersson and Sotiropoulos, 2014). Each acquired slice was compared with a model free prediction, and if the observed signal was statistically different (three SD) from the prediction, it was replaced by the latter. An average of 0.45, 0.42 and 0.45 slices per volume across subjects were replaced in the training group, the passive control group and the active control group, respectively. The number of slices replaced did not differ between groups ($F(2, 467) = 0.48$ $p = 0.62$). Non-brain tissue (skull etc.) was removed using Brain Extraction Tool (Smith, 2002), employing a mask based on the non-diffusion-weighted volume. Fractional anisotropy (FA) images were created by fitting a tensor model to the pre-processed diffusion data using FMRIB's Diffusion Toolbox (FDT) (Behrens, et al., 2003).

All participants' FA data were processed with the FSL software package *Tract-based spatial statistics* (TBSS) (Smith et al., 2006). The subjects FA images were aligned into a common space using the nonlinear registration tool FNIRT (Andersson, et al., 2010), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). Next, the mean FA image was calculated and thinned to create a mean FA skeleton, which represents the centers of all tracts common to the group. The threshold for the mean FA skeleton was set at 0.2, resulting in a mask of 137,832 voxels. Each participant's aligned FA data were then projected onto this skeleton. The nonlinear warps and skeleton projection stages were repeated using the mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) measures. TBSS is documented to be relatively robust to potential partial volume effects (PVE), as it assesses diffusion indices only in the estimated centers of white matter tracts (Berlot, et al., 2014; Smith, et al., 2006).

2.4 Test of memory performance

Memory performance was measured using a supervised word list test. Participants were given five minutes to learn as many words as possible in the correct list order, and ten minutes to recall the words immediately after the learning trial. The test enabled the MoL to be applied, such that the measure of memory performance was closely related to the utilized technique. To avoid potential ceiling effects, the word list consisted of 100 words. The words in the list differed between time points. All words in the lists were matched on criteria of frequency, complexity and how easy/difficult they were assumed to transfer to visual imagery.

2.5 Statistical analyses

2.5.1 Memory improvement

The total number of words recalled from the word list test was used as the outcome variable for training effects. We have recently shown specific training effects on memory improvement in a group of older adults drawn from the same sample (de Lange, et al., 2016) To examine the group differences in memory improvement for both young and older adults, repeated measures ANCOVA was conducted on the memory scores (number of words correctly memorized) at baseline and follow up, using age, sex and baseline memory performance as covariates. Greenhouse-Geisser corrections for violation of sphericity were used. Additional repeated measures ANCOVAs were run for the training group, active control group and passive control group separately, testing the change in memory performance from baseline to follow up. An independent samples t-test was performed to compare the number of tasks completed in the training group and the active control group.

2.5.2 Group differences in microstructural changes

To investigate group differences in mean WM change, we performed general linear model (GLM) analyses on the mean of the skeletonized tensor-derived values, using age, sex, motion and baseline WM values as covariates. Motion was estimated as the mean of the average root mean square displacement value across each diffusion-weighted volume derived from the eddy procedure (Andersson and Sotiropoulos, 2015).

We then performed voxel-wise GLMs using the values from follow up as the dependent variable, and the values from baseline as a per-voxel regressor, testing the differences between the intervention groups within the young and the older sample,

respectively. Permutation-based statistics with threshold-free cluster enhancement (Smith and Nichols, 2009) were performed with 5000 permutations (Nichols and Holmes, 2002), correcting for multiple comparisons across space, as implemented in *randomise*, part of FSL (Winkler, et al., 2014). The significance threshold was set at $p < 0.05$, as for all subsequent analyses.

2.5.3 Relationships between memory improvement and microstructural changes

To investigate relationships between change in WM microstructure and change in memory performance, all participants who completed the training program were included (N = 126 participants, 43 young adults and 83 older adults), as illustrated in Figure 1. Voxel-wise GLMs were performed on the full skeleton using the values from the MRI assessment after training as the dependent variable, and the values from the assessment before training as a per-voxel regressor. Permutation-based statistics were performed with 5000 permutations, as implemented in *randomise*. Age, sex and motion were used as covariates. Improvement in memory performance was measured by standardized residuals. This measure determines whether changes from baseline to follow up are large with respect to the group mean and SD. Standardized residuals were calculated from a linear regression analysis, using memory performance at baseline as the dependent variable and memory performance at follow up as the independent variable.

3. Results

3.1 Memory improvement

Memory improvement is shown in Figure 2, which includes the present results on group differences in the young sample in addition to group differences within the older sample, as previously published in (de Lange, et al., 2016). The analysis showed an interaction between group (training, active control, passive control) and time (baseline and follow up) when including both young and older adults ($F(2,175) = 56.4$, $p = 1.2 \times 10^{-19}$). Pairwise comparisons (bonferroni corrected) showed that the group receiving memory training improved more than the control groups (training group versus active control group: mean difference = 6.0, $p = 1.9 \times 10^{-10}$, training group versus passive control group: mean difference = 6.5, $p = 2.3 \times 10^{-18}$). No differences were found between the active and passive control groups (mean difference = 0.5, $p = 1.0$). The same analysis revealed an interaction between age and change ($F(1,177) = 58.3$, $p = 1.3 \times 10^{-12}$). Independent samples t-tests using the difference in memory performance (follow up minus baseline) showed that the young training group improved more that the older training group ($t(74) = 5.8$, $p = 1.3 \times 10^{-7}$). Separate analyses confirmed significant group interactions within each age group (older adults: $F(2,102) = 22.4$, $p = 8.1 \times 10^{-9}$; young adults: $F(2,64) = 36.2$, $p = 2.2 \times 10^{-11}$). Repeated measures tests of within subjects effects showed that the group who received memory training improved from baseline to follow up ($F(1,71) = 75.5$, $p = 7.9 \times 10^{-13}$). None of the control groups increased significantly from baseline to follow up. To control for a possible lack of power in the control groups due to smaller sample sizes, we performed a power analysis using G*Power (Faul, et al., 2007). The effects size measured within the training group was $f = 0.7701$, corresponding to a

power of 0.96, with 9 subjects required to detect an effect given the f-value. Thus, the lack of training effects in the control groups, consisting of 77 and 31 participants, respectively, was unlikely to be caused by a power issue.

As this paper focuses on training effects on white matter microstructure, the active and the passive control groups were merged into one larger control group on the basis of showing no improvement in memory after ten weeks. This merged control group was used in further statistical analyses.

[Insert Figure 2]

3.2 Group differences in microstructural changes

The group differences in mean WM change are shown in Figure 3. When including both young and older adults, the analysis of group differences in mean WM change showed an interaction between group (training, control) and time (baseline and follow up) in MD ($F(1,176) = 6.8$, $p = 0.01$), RD ($F(1,176) = 6.7$, $p = 0.01$) and AD ($F(1,176) = 6.4$, $p = 0.01$); The control group increased more in MD, RD and AD relative to the training group. No group difference was found in FA change. The same analysis revealed an interaction between age and change in MD, RD and AD ($F(1,176) = 19.3$, $p = 1.9 \times 10^{-5}$, $F(1,176) = 15.2$, $p = 1.4 \times 10^{-4}$ and $F(1,176) = 6.3$, $p = 0.01$, respectively).

To control for possible effects that might be related to WM lesions, which is known to increase in frequency with older age (Leritz, et al., 2014), we performed follow up analyses using repeated measures ANCOVA controlling for WM

hypointensities as well as age, sex, motion, baseline WM values. WM hypointensities were derived for each subject using the FreeSurfer (http://surfer.nmr.mgh.harvard.edu/) probabilistic procedure (Fischl, et al., 2002; Fischl, et al., 2004a; Fischl, et al., 2004b). This procedure has demonstrated sensitivity in measurements of WM lesions in older adults (Leritz, et al., 2014; Salat, et al., 2010). The results showed that WM hypointensities did not affect the results of the group analyses reported above when included as a covariate. No interactions were found between hypointensities and change in MD, RD and AD ($F(1,175) = 0.4$, $p = 0.6$, $F(1,175) = 1.1$, $p = 0.3$ and $F(1,175) = 0.1$, $p = 0.7$, respectively).

[*Insert Figure 3]*

Separate voxel wise analyses on the older groups showed that the control group decreased more than the training group in FA in 1.6% of the voxels (peak p-value = 0.02) and increased more in MD, RD and AD from baseline to follow up relative to the training group in 8.7%, 14.6% and 6.8% of the voxels, respectively ($p < 0.05$, peak p-value = 0.02, 0.02 and 0.02), in areas overlapping the corpus callosum, the cortico-spinal tract, the cingulum bundle, the superior longitudinal fasciculus (temporal part) and the anterior thalamic radiation.

As a follow up analysis, GLMs were performed on the difference maps of FA, MD, RD and AD, using difference scores in memory performance (follow up minus baseline). Age, sex and motion were used as covariates. The results showed that the control group decreased more than the training group in FA in 9% of the voxels (peak p-value = 0.02) and increased more in MD, RD and AD from baseline to follow up relative to the training group in 19.8%, 21.1% and 15.5% of the voxels, respectively

($p < 0.05$, peak p-value = 7.6×10^{-3}, 7.4×10^{-3} and 0.02), in areas overlapping those of the analyses using standardized residuals.

No differences were found between the training and control groups in the young sample. The group differences in WM change in the older adults are shown in Figure 4.

[*Insert Figure 4]*

3.3 Relationship between memory improvement and microstructural changes

A positive relationship was found between change in FA and memory improvement in the older adults in 12.87% of the voxels (peak p-value = 7.0×10^{-3}). Changes in MD, RD and AD correlated negatively with memory improvement in 25.6%, 24.1% and 24.1% of the voxels, respectively ($p < 0.05$, peak p-value = 1.5×10^{-3}, 1.8×10^{-3} and 1.5×10^{-3}). Changes in RD and AD occurred in areas overlapping those of MD. The relationships between memory improvement and change in FA and MD are shown in Figure 5. As a follow up analysis, GLMs were performed on memory improvement and FA and MD change using difference scores (follow up minus baseline). Age, sex and motion were used as covariates. The results showed a tendency for a positive correlation between difference in memory performance and FA change (peak p-value = 0.06), while no relationship was found between difference in memory performance and MD change (peak p-value = 0.14).

No relationships were found between microstructural changes and memory change in the older control group. In the younger adults, no relationships were found between change in WM microstructure and memory improvement.

[Insert Figure 5]

3.4 Relationships between number of tasks, memory improvement and microstructural changes

As a follow up analysis, we tested whether number of tasks completed during the training period was related to a) memory improvement and b) changes in WM microstructure. Memory improvement, age and sex were used as covariates. An independent samples t-test showed that the older participants completed more tasks (mean±SD = 57.41±14.13) during the training period relative to the young group (mean±SD = 34.67±18.60, $t(74) = 7.66$, $p = 1.0 \times 10^{-3}$). However, Pearson correlation analyses showed that the number of tasks completed during the training period did not correlate with either memory improvement or changes in WM microstructure in any of the age groups.

4. Discussion

This study aimed to investigate change in WM microstructure in response to ten weeks of memory strategy training in young and older adults. Overall, the results demonstrated that only the group that received the memory training intervention, rather than either the active or the passive control condition, showed significant improvement in memory performance. In the older adults, the training group showed less degree of age-related decline in WM microstructure in comparison to the control group, indicating that episodic memory training can have positive effects on microstructure in older age. The degree of cognitive improvement was related to the degree of microstructural changes, demonstrating a relationship between behavioral and microstructural plasticity. No group differences or relationships between memory and WM microstructure were found in the young sample, indicating that microstructural plasticity in response to memory training is not necessarily larger in young adults. Plastic responses may depend on whether the nature of the training exceeds the pre-existing range of processing capacity (Lovden, et al., 2010a) or induces a considerable change in environment. Thus, in this study, the training may have imposed a larger environmental change and challenge for the older adults relative to the young adults.

4.1. Memory improvement

We have recently shown specific training effects on memory improvement in older adults (de Lange, et al., 2016). The present results showed that within the respective age groups, both the young and the older training groups improved their memory to a larger extent than the active and passive controls. Thus, specificity of memory

improvement was found across age. In the current study, the number of tasks, group meetings and contact with staff was matched between the training group and the active control group, controlling for the possible effect of these factors on memory performance. Furthermore, test sessions and time intervals were held identical for all participants in order to ensure that test-retest effects would not differ across groups. The inclusion of an active control group in the current study strengthens the validity by allowing comparison of effects related to general components of the participation, and effects related to the specific components of the memory training (Hart, et al., 2008; Law, et al., 2014).

In accordance with previous studies, both the young and the older training groups improved their memory performance considerably in response to the training (Nyberg, et al., 2003). As commonly observed in training studies, the young adults improved their memory to a larger extent than the older adults (Baltes, et al., 1992; Brehmer, et al., 2012; Burki, et al., 2014; Dahlin, et al., 2008).

4.2. Group differences in change in WM microstructure

In accordance with previous studies showing positive effects of cognitive training on WM microstructure in older adults (Bennett, et al., 2011; Engvig, et al., 2012; Lovden, et al., 2010b), the older training group showed less decrease in FA and a smaller increase in MD, RD and AD compared to the control groups, indicating that the training had a positive impact on microstructural decline.

The predominant findings from cross-sectional and longitudinal aging studies are decreased FA accompanied by increased MD, RD and AD with older age

(Barrick, et al., 2010; Bender, et al., 2015; Bennett, et al., 2010; Burzynska, et al., 2010; Charlton, et al., 2010; Davis, et al., 2009; Salami, et al., 2012; Salat, et al., 2005; Sexton, et al., 2014; Westlye, et al., 2010). As the group differences were partly driven by the age-related decline in the control group, it is likely that the memory training may serve as a maintaining factor for WM microstructure in older age (Engvig, et al., 2012).

Changes in both FA and RD have been associated with myelination in animal studies (Blumenfeld-Katzir, et al., 2011; Song, et al., 2005). Thus, the group differences observed on these metrics could be driven by differential changes in myelination. Increased immunofluorescence staining of myelin basic protein (MBP), which is indicative of myelination, has been observed in animals in co-occurrence with increased FA after training (Blumenfeld-Katzir, et al., 2011; Sampaio-Baptista, et al., 2013). However, as axonal membranes also contribute to anisotropic diffusion (Beaulieu, 2002), the observed differences in FA change may have been influenced by the condition of axonal membranes. The group differences in general diffusivity reflected by MD may indicate differential changes in relatively isotropic structures such as astrocytes. Animal studies have shown changes in the activation of astrocytes as an effect of spatial memory training (Blumenfeld-Katzir, et al., 2011; Sagi, et al., 2012), which may underlie reductions in MD through intra/extracellular ratio alterations or cellular tissue swelling (Le Bihan, et al., 2001; Theodosis, et al., 2008). However, myelination of axons in crossing fiber regions may also influence MD (Mackey, et al., 2012a), thus, the interpretation of the underlying changes in DTI metrics depends upon the local fiber architecture.

Although evidence suggests that DTI may be sensitive to underlying cellular changes with sufficient volumetric contribution (Fields, 2015; Sagi, et al., 2012), the

signal changes require careful interpretation as the neurobiological underpinnings cannot be directly inferred (Wheeler-Kingshott and Cercignani, 2009; Zatorre, et al., 2012). Although the signal may be modulated by cellular properties and myelination, it is also influenced by how axons are laid out within the voxel, as the gradient is applied along a given axis (Jones, et al., 2013).

The group differences in WM microstructure were found in areas overlapping the corpus callosum, the cortico-spinal tract, the cingulum bundle, the superior longitudinal fasciculus and the anterior thalamic radiation. The cognitive processes involved in mnemonic strategy training are likely to rely on multiple brain areas. Thus, the highlighted areas may represent regions of importance for efficient information transfer that is beneficial for cognitive gains after this type of training. However, although individual studies have shown relationships between cognitive processes and WM properties in highly specific regions (Kerchner, et al., 2012; Zhu, et al., 2015), the overall evidence does not demonstrate a high degree of regional specificity in the relationship between WM microstructure and cognition (de Lange, et al., 2016; Madden, et al., 2009; Salthouse, 2011).

The training affected WM microstructure in the older adults only. Although this was unexpected, the finding supports other studies showing that plastic responses to cognitive training are not necessarily larger in young adults relative to older adults (Kempermann, et al., 2002; Lovden, et al., 2010b). In a theoretical framework suggested by Lövdén and colleagues (2010a), plastic alterations in brain and behavior are thought to take place when there is a mismatch between the functional capacity and the environmental demands. The capacity for variations in behavior that do not require structural brain changes is referred to as flexibility. Flexibility can generate improvements in performance, but does not require changes in intrinsic capacity as

opposed to plasticity (Noack, et al., 2009). Thus, flexibility depends on the pre-existing range of processing capacity, while plasticity takes place only when the demands placed exceed the existing capacity. In view of this theory, the results may indicate that the memory training more substantially exceeded the functional capacity of the older adults, thus resulting in microstructural alterations solely in this group. Although the training posed increasing demands and the individuals could adjust the tasks to their own level, the intervention itself may not have provided demands as substantially exceeding the functional capacity in young adults, which is considered to be crucial for the initiation of plastic responses (Lovden, et al., 2010a).

It should be emphasized, however, that there was a cognitive change x age interaction, showing that the younger adults still managed to improve their memory performance more than the older adults. Hence, the observed divergence of behavioral and brain responses to training with age may be interpreted within a supply-demand framework. The improvement of performance in response to environmental demands may have been within the functional capacity of the young adults, while the demands may have exceeded the functional capacity of the older adults, thus, even more modest improvements would require brain changes. This is in line with the nature of the training being likely to have imposed a larger overall change in environment for the older adults. Indeed, the younger adults were in a phase where memory training may be more intrinsic to their everyday life, with studies and new work tasks typically posing continuous demands. The training was thus more likely to represent a considerable environmental change for the group of older adults, of which the majority of the individuals were retired. Thus, microstructural plasticity in response to memory training may depend on whether the level of the training exceeds the pre-

existing range of processing capacity (Lovden, et al., 2010a), and whether the nature of the training induces a considerable change in the environment.

4.3 Relationship between memory improvement and microstructural changes

Only few studies have documented relationships between cognitive improvement and altered WM microstructure in older adults (Bennett, et al., 2011; Engvig, et al., 2012). Our results showed that the degree of cognitive benefit from memory training was related to the degree of change in WM microstructure in the older adults. Thus, the older participants who improved their memory performance to the largest extent showed a decrease in MD, RD and AD, and an increase in FA, suggesting that these microstructural changes may be part of a neurobiological substrate for the behavioral improvements. However, the follow up analyses suggested that these relationships varied depending on how training gain was measured, i.e. difference scores or standardized residuals. Difference scores are commonly used as a measure of training outcome (Engvig et al., 2010; Lovden et al., 2010), as is absolute scores, i.e. performance after training (Draganski et al., 2004) and proportional gain such as percentage scores (Engvig et al., 2014). Absolute scores and difference scores may be suitable as a way of measuring change, but do not take into account differences in relative improvement across individuals. Thus, difference scores do not account for the influence of baseline variance in analyses. For instance, two individuals, one with a low (5 points) and one with a high baseline score (10 points), may both exhibit the same training gain (2 points). In a difference analysis they are treated equivalently, even though their gains relative to baseline (40% and 20%, respectively) are not equal. Standardized residuals, however, provide a measure of training gain where baseline performance is accounted for.

The lack of relationships between memory improvement and change in WM microstructure in the young adults may indicate that memory improvement in this group did not require microstructural plastic alterations. The young adults completed a lower number of tasks during the training period relative to the older adults. However, in correspondence with other studies that have failed to observe an association between the amount of time spent on the training and plastic responses (Boyke, et al., 2008; Driemeyer, et al., 2008), the results showed that number of tasks completed did not relate to either memory improvement or microstructural plasticity.

4.4 Conclusions

This study provides evidence of relationships between microstructural alterations and cognitive improvement after memory training in older relative to younger adults, and demonstrates that both cognitive and microstructural plasticity is preserved into older age. The somewhat counter-intuitive lack of microstructural changes in the young group may imply that the demands of the memory training, despite being dynamically adapted to performance levels, did not exceed their existing range of processing capacity, and thus did not require microstructural plasticity (Lovden, et al., 2010a). Hence, a matched training program adapted to individual performance level for young and older adults may promote specific cognitive improvements for all, yet fail to promote structural plastic alterations in both age groups, due to age-related differences in flexibility, or perhaps the greater overall changes in experience and environment for older adults. Further investigations are required to determine whether this also applies to other brain characteristics and how the changes develop over extended time periods.

Acknowledgements

This research was funded by the European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013) / ERC grant agreement n° 313440 to K.B.W.

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Legends

Figure 1

Illustration of the design. N represents the number of participants in each group.

Figure 2

Memory improvement measured by the word list consisting of 100 words is shown for the young and older intervention groups. Memory scores are shown on the Y-axis.

Figure 3

Group differences in microstructural changes are plotted separately for young and older adults. The means of the skeletonized diffusion metrics are shown on the Y-axis. The axis ranges are of equal size for young and older adults, but the values vary due to age differences in diffusion metrics.

Figure 4

Areas showing group differences in microstructural changes in the older sample. Sagittal and coronal views of Talairach coordinates x = 105, y = 110, z = 112 for FA and x = 110, y = 117, z = 112 for MD, overlaid on the mean FA skeleton (green) and the standard MNI152 T_1 1 mm^3 brain template. The results are thresholded at $p < 0.05$ and corrected for multiple comparisons. The plots show the mean values within the respective areas of group differences in MD and FA.

Figure 5

Areas showing relationships between memory improvement and microstructural changes in the older sample. Sagittal and coronal views of Talairach coordinates x =

74, y = 120, z = 85, overlaid on the mean FA skeleton (green) and the standard MNI152 T_1 1 mm^3 brain template. The results are thresholded at $p < 0.05$ and corrected for multiple comparisons. The plots show the relationships between MD and FA change and memory improvement measured by standardized residuals.