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Effects of Cognitive Training on Gray Matter Volumes in Memory Clinic Patients with Subjective Memory Impairment

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Abstract. Subjective memory impairment (SMI) is a common risk factor for Alzheimer's disease, with few established options for treatment. Here we investigate the effects of two months episodic memory training on regional brain atrophy in 19 memory clinic patients with SMI. We used a sensitive longitudinal magnetic resonance imaging protocol and compared the patients with 42 matched healthy volunteers randomly assigned to a group performing the same training, or a no-training control group. Following intervention, the SMI sample exhibited structural gray matter volume increases in brain regions encompassing the episodic memory network, with cortical volume expansion of comparable extent as healthy training participants. Further, we found significant hippocampal volume increases in the healthy training group but not in the SMI group. Still, individual differences in left hippocampal volume change in the patient group were related to verbal recall improvement following training. The present results reinforce earlier studies indicating intact brain plasticity in aging, and further suggest that training-related brain changes can be evident also in the earliest form of cognitive impairment.

Keywords: Aged, cognition disorders, episodic memory, hippocampus, intervention studies, longitudinal studies, magnetic resonance imaging, neuronal plasticity, training

INTRODUCTION

Subjective memory impairment (SMI) is common in the elderly [1]. In the memory clinic, a diagnosis of SMI is used for patients who feel that their cognitive capacity is reduced, but for whom neuropsychological tests are within normal range [2]. SMI patients are at increased risk of depression [3] and dementia [4–7]; the finding of an increased risk of Alzheimer's disease (AD) is likely independent of depressive symptoms [8].

Multi-modal neuroimaging indicates early AD pathology in SMI (for a recent review, see [9]). Erk

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and colleagues assessed memory clinic outpatients with SMI on functional magnetic resonance imaging (MRI)-estimates of neuronal activity during episodic memory retrieval [10]. Despite similar recall performance, the SMI subjects showed reduced activation in the hippocampus and right dorsolateral prefrontal over-activation, compared with adults without memory problems. SMI-subjects are further prone to accelerated hippocampal atrophy [11–14] (also see [15]).

Interestingly, physical and navigation training have recently been shown to reduce hippocampal atrophy [16, 17], and memory training has been associated with increased cortical thickness in healthy elderly [18]. These findings indicate potential for training-related structural remediation, at least in healthy elderly, in a manner that contrasts the reductions associated with SMI and early-AD like pathology.

Cognitive intervention is emerging as a putative prevention technique for individuals at increased risk of AD [19], and memory clinic attendees with SMI [20], as well as mild cognitive impairment (MCI) [21] show cognitive test-improvements following memory training. SMI-subjects represent a very interesting group for treatment in this regard: These individuals are probably more responsive to cognitive interventions compared with patients with more severe cognitive impairment and established dementia where neurodegenerative processes are far more advanced.

In two previous publications, we documented effects on cognitive test-performance and brain macro- and microstructure of an eight-week episodic memory-training program for healthy older adults [18, 22], and also characteristics predictive of cognitive training effects in patients with memory complaints [23]. However, longitudinal training effects on brain characteristics in SMI have not been studied. The extent to which structural plasticity in response to memory training previously reported in healthy adults generalizes to clinical samples is unknown. Increased knowledge about the capacity for structural change in the brains of at-risk individuals is essential for evaluating therapeutic potential.

Therefore, the main objective of the present study was to investigate whether memory training in SMI patients is accompanied by gray matter alterations using structural MRI. To this end, we scanned a group of 19 SMI patients, as well as a matched healthy control sample before and after participation in an intensive eight-week memory-training scheme. We estimated regional gray matter volume changes within the brain by means of a highly sensitive registration algorithm (Quarc) [24, 25].

First, we hypothesized that SMI-subjects would exhibit regional increases in cortical gray matter volume following training, in a manner comparable to healthy subjects undergoing the same training regimen. We tested training-related gray matter volume change across the cortical surface, providing an unbiased estimate of cortical changes across the mantle. The two intervention groups were compared with no-contact controls, allowing us to model the effects of group on change.

The hippocampi are not included in the presently employed surface models (c.fr. http://surfer.nmr.mgh.harvard.edu/). Thus, we tested the hypothesis that memory training impacts structural changes in the hippocampus by using a region of interest (ROI) analysis.

As discussed above, some SMI subjects are prone to both reduced hippocampal volumes and activity. Yet, it is not known whether SMI selectively targets structural plasticity in the hippocampus. Thus, we finally tested the hypothesis that memory training has a differential impact on neocortical gray matter changes as compared with hippocampal change in SMI.

MATERIALS AND METHODS

Participants

The sample included 19 subjects with SMI undergoing memory training (SMI-training), and 42 healthy controls (HC) without memory complaints. HC were randomly divided into one group receiving the same training program as those with SMI (HC training), and one group serving as a no-contact controls (HC no-training). Table 1 describes baseline characteristics of the three groups. Of note, the present study includes novel analyses on two previously published datasets, combining the participants in SMI [23] and HC [18] to directly address possible differences in neuroplastic potential.

Briefly, HC were recruited from newspaper ads and were not experiencing any memory worsening or concerns. Subjects with SMI were recruited from two Oslo-area memory clinics. SMI-subjects were referred to the memory clinic by their general practitioner or a specialist in neurology for assessment of suspected memory impairment. The subjective memory problems were in most cases confirmed by close relatives or spouses, whom are invited to the clinic as part of the routine exam. Onset of perceived memory impairment was less than 10 years prior to inclusion. The examining memory clinic physician screened all SMI-subjects for dementia based on ICD-10 criteria before

Table 1
Clinical characteristics of subjects with SMI and healthy controls (HC), mean (SD)

	SMI, training	HC, training	HC, no training
Age	60.9 (10.4)	61.3 (9.4)	60.3 (9.1)
Gender	9F/10M	12F/10M	11F/9M
Education	15.0 (2.4)	15.1 (1.9)	15.6 (1.8)
IQ	119.3 (10.7)	118.0 (8.9)	118.8 (9.2)
MMSE	29.1 (0.9)	29.0 (1.0)	29.1 (0.9)
Rey-O, recall	22.2 (7.7)	19.1 (6.7)	21.1 (5.7)
CVLT, 5-min delay recall	11.0 (2.7)	11.5 (3.1)	11.7 (2.6)
CVLT, 20-min delay recall	11.3 (3.1)	12.1 (2.2)	12.4 (3.0)
Re-test interval	65.5 (10.3)	65.3 (6.7)	65.3 (9.5)
EMQ*	100.8 (35.9)	69.7 (24.2)	57.2 (18.6)
GDS*	9.2 (6.2)	1.8 (2.0)	1.5 (2.2)
SF-36, Mental health*	70.3 (19.4)	88.0 (8.2)	85.0 (10.6)

*$p < 0.05$, significant main effect of group. IQ, intelligence quotient derived from Wechsler Abbreviated Scale of Intelligence (WASI) matrices and vocabulary sub tests; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale, higher score indicates more depressive symptoms; SF-36, Mental health the five-item mental health inventory of the Short-form 36 form, higher score indicates less depressive symptoms; Rey-O, 30 minutes delayed recall score of the Rey-Osterreith complex figure test; CVLT, 5- and 20-minute delay recall, raw scores from the free recall trials of the California Verbal Learning Test II; Re-test interval denotes days between 1st and 2nd MRI scanning session. Missing data: One subject lacked IQ and Rey-O data.

entering the study. We employed the following exclusion criteria based on neuropsychological test results: Mini-Mental State Examination (MMSE) [26] score <26; pre-training scores lower than 1.5 standard deviations (SD) below age- and sex-standardized population norms on California Verbal Learning Test (CVLT-II) short and long-delay free recall [27]; and intelligent quotient (IQ) scores <85, estimated from the vocabulary and matrices sub-tests in the Wechsler Abbreviated Scale of Intelligence (WASI) [28]. We did not set any upper-limit on any of the test results. One healthy participant was excluded on the basis of the CVLT-scores immediately following screening; one patient discontinued the intervention during the second week of the program. The CVLT scores obtained at screening were also used as pre-training scores to evaluate training efficacy (see the Cognitive outcome measure section). Finally, we used the Rey Complex Figure Test (RCFT; see Table 1) [29] to provide a measure of pre-training visual memory function without specifying any cut-off criterion for exclusion. The Eastern Norway ethical committee for medical research, and the Data protection official for research at Oslo university hospital, Ullevål approved the study. Informed consent was obtained from all subjects.

Quantitative assessment of subjective memory and depressive symptoms

We quantified subjective memory problems and depressive symptoms according to the Everyday Memory Questionnaire (EMQ) [30] and the Geriatric Depression Scale (GDS) [31], respectively. In addition, the Short-Form 36 Mental Health Inventory [32] was used for screening of depression. Two participants in the SMI-group scored above validated cut-offs for clinical depression. Since both subjects denied chronic depression or any anti-depressant use they were not excluded from the study. We tested for effects of depressive symptoms (GDS) and subjective memory load (EMQ) on brain volume changes by means of analysis of covariance (See Statistical analyses).

Memory training

Memory training was administered during eight weekly class-sessions of about 90 minutes each. In addition to the class sessions supervised by a trained instructor, participants were given five weekly homework assignments to complete on five of the six subsequent weekdays throughout the program. The program has been shown to improve memory in subjects with SMI and healthy older adults [18, 23]. SMI-subjects spent 27.3 minutes (SD = 9.6) on each of the 32 homework assignments while the HC subjects spent 25.0 minutes (SD = 10.1); this group difference was not significant (independent samples *t*-test, $t = 0.75$, $p = 0.46$).

For a more comprehensive description of the program, see [18, 23]. The main aim of the program was to improve verbal recall memory by method of loci (MoL) training [33]. MoL is a mental framework that facilitates verbal recall; the technique enables the participant to associate to-be-remembered material with visuospatial routes from long-term memory.

We used the exact same training content, including program curriculum and practice material, for both HC and SMI. For motivational purposes, however, the instructor kept the overall focus of the sessions for the SMI group more toward remediation and support. The training program provided SMI-participants experiencing memory problems tools and knowledge for improving episodic memory and at the same time offered an arena to meet and discuss with others experiencing similar memory concerns.

Cognitive outcome measure

We assessed verbal memory performance using CVLT-II approximately one week before and after training [27]. The pre-training CVLT scores were both used as part of the outcome measure and for screening prior to inclusion. We used scores on the 5- and 20-minutes delayed free recall trials from the original and alternate versions of the test as cognitive outcome measures.

MR data acquisition

MRI data were collected at two time-points, on average 65 days apart (SD = 8.7), using a 12 channel head coil on a 1.5 Tesla Siemens Avanto scanner (Siemens Medical Solutions, Erlangen, Germany) at Oslo University Hospital. We used the same scanner software and software version at both time-points. The pulse sequence was a 3D T1-weighted MP-RAGE with the following parameters: TR/TE/TI/FA = 2400 ms/3.61 ms/1000 ms/8°, matrix 192×192, field of view = 240, 160 sagittal slices, voxel size $1.25 \times 1.25 \times 1.20$ mm. The sequence was repeated twice in each session and the two acquisitions were averaged during processing to increase the signal-to-noise ratio (SNR). Each scan took 7 minutes and 42 seconds.

In addition, a T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence was used to aid neuroradiological examination. A senior neuroradiologist (P.D.T.) evaluated all MRI scans for any significant injuries or conditions (e.g., signs of brain tumors or stroke). None of the participants were excluded on the basis of this.

Processing and data analysis

FreeSurfer version 5.1 (http://surfer.nmr.mgh.harvard.edu) was used to segment baseline cortical and subcortical gray matter structures [34–39]. We used baseline FreeSurfer-generated cerebral cortical surfaces and estimated hippocampal formation volumes to evaluate any group differences before training. We quantified rates of volumetric gray matter change using Quarc [24, 25, 40]. Methodological bias in image registration can artifactually elevate effect sizes, constituting a concern in neuroimaging studies [41]. Quarc uses an explicit inverse-consistent approach [24] that essentially eliminates potential bias by combining forward and reverse image registrations and has been favorably compared with other methods [25].

Briefly, for each participant, dual 3-D follow-up structural scans were rigid-body aligned, averaged, and affine aligned to the participant's baseline. A deformation field was calculated from a nonlinear registration [24]. The images are heavily blurred (smoothed), making them almost identical, and a merit or potential function was calculated. This merit function expresses the intensity difference between the images at each voxel and depends on the displacement field for the voxel centers of the image being transformed. The merit function by design will have a minimum when the displacement field induces a good match between the images. Having found a displacement field for the heavily blurred pair of images, the blurring is reduced and the procedure is repeated, thus iteratively building up a better displacement field. The final displacement field is added to the image being transformed and the resultant image nonlinearly registered to the same target and finally traced back through the displacement field thus calculated to find the net displacement field. This enables very precise registration, even at small spatial scales with low boundary contrast. Nonphysical deformations are precluded because, at each level of blurring, the image undergoing deformation is restricted to conform to the target. The resulting deformation field was used to align scans at the subvoxel level.

The aligned change image for each participant underwent skull stripping and hippocampal segmentation with labels applied from the FreeSurfer-processed baseline scan. Also, voxel-wise estimates of longitudinal volumetric gray matter change were mapped onto individual brain surfaces generated using FreeSurfer, yielding a continuous mapping of volumetric change along the cortical surface. Volumetric gray matter change was sampled at a relative distance of 35% from the white boundary into the gray matter. Individual cortical gray matter change surfaces were resampled, mapped to a common surface, smoothed with 176 iterations and submitted to statistical analyses.

Statistical analyses

In the present study we compare two intervention groups and a HC no-training group. Note that a 2 x 2 design including also a SMI no-training group would have been more ideal, but we were not able to recruit enough patients to allow two reasonably sized SMI groups. The present design thus allows comparing effects of intervention across groups of patients and healthy elderly, but precludes direct testing of whether the intervention could have, e.g., atrophy-reducing effects in the patient group compared to no-training patients.

We analyzed volumetric group-differences before training and longitudinal regional gray matter changes across the cortical surface using general linear models (GLM) within the FreeSurfer suite. We used IBM SPSS Statistics 20 (IBM Corp.) for other analyses.

We performed paired samples *t*-tests to estimate recall improvements (post-training – pre-training) within each group. We reported effect sizes for recall change as following: First, we reported t-values of paired samples *t*-test in Table 2. Second, we calculated improvement in raw recall scores as percent change ((time-point2 – time-point1)/time-point1) for each group (Table 2). Third, we estimated Cohen's *d* as a standardized effect size measure by comparing the mean differences in recall scores of HC-training and SMI-training with the HC no-training group. We used analysis of variance (ANOVA) to test group differences in both the demographic and cognitive data.

To assess regional volumetric differences between any of the groups at baseline, we ran one-way ANOVAs with each surface vertex as dependent variables, modeling effects of group on baseline cortical volume. For longitudinal analysis of gray matter changes we first assessed whether average change in the two training groups differed from change in no-training HC, modeling effects of group at each vertex. All surface models were corrected for multiple comparisons across the surface by means of Monte Carlo simulations: Data were tested against an empirical null distribution of maximum cluster size across 10,000 iterations using Z Monte Carlo simulations synthesized with a cluster-forming threshold of $p < 0.05$ (two-sided) as implemented in FreeSurfer [42, 43]. Corrected *p*-value maps were thresholded at $p < 0.05$. To model effects of individual differences in baseline regional brain volumes, subjective memory score and depressive symptoms, we extracted average change data from significant clusters and tested for these variables by means of analysis of co-variance (ANCOVA).

The hippocampal formation is not included in the FreeSurfer-based cortical surface models. Thus, we first extracted average left and right hippocampal volumes from the FreeSurfer-generated subcortical segmentations at baseline. Then, we tested for any group differences in the hippocampus by including the left and right hippocampal baseline volumes as dependent variables in separate ANCOVAs with group as fixed factor and total brain volume as a covariate to account for differences in head size and global atrophy. Next, to test the hypothesis that memory training impacts hippocampal volume change, we extracted average Quarc-estimated change within FreeSurfer segmentations of the left and right hippocampi. Finally, we introduced these hippocampal change estimates in ANCOVAs to model effects of group on hippocampal change, and to test for effects of baseline hippocampal volumes, subjective memory, and depressive symptoms. We applied *post-hoc* tests to assess differences in volume change between the three groups.

Next, we assessed whether differential effects of memory training across groups (HC training, SMI training) would occur in cortical as compared with hippocampal ROIs. We extracted change estimates from the cortical cluster showing the strongest training effect as well as from the hippocampus, and entered the data in an ANOVA with two training groups (HC training, SMI training) and two ROIs (cortical, hippocampal).

We examined relationships between brain and cognitive change measures using partial correlations. We included the relevant baseline brain volume and pre-training cognitive performance, as well age as covariates. For partial correlation analyses with cortical surface volumes, we used average baseline and change data from within each significant cluster resulting from the surface analysis reported above and controlled for baseline volumes, performance, and age.

RESULTS

Clinical and cognitive results

Table 1 summarizes demographical and clinical characteristics. A significant main effect of group on EMQ ($F = 14.7$, $p < 0.0001$) and GDS ($F = 25.0$, $p < 0.0001$) indicated poorer subjective memory and more depressive symptoms in SMI subjects. The remainder of the variables in Table 1 was of comparable magnitude (ANOVA, between-group F's<1.1, p's>0.33).

Table 2 shows verbal recall performance for the three groups at baseline and follow-up. A two groups × two

Table 2
CVLT-II, delayed free verbal recall performance at baseline and follow-up, mean (SD)

	SMI, training				HC, training				HC, no training			
	Baseline	Follow-up	*t*-value	%-change	Baseline	Follow-up	*t*-value	%-change	Baseline	Follow-up	*t*-value	%-change
Recall, 5-min delay	10.95 (2.74)	14.05 (2.86)	5.5	32 (28)	11.68 (2.56)	14.36 (2.34)	4.2	29 (36)	11.45 (3.14)	13.05 (2.34)	3.7	21 (28)
Recall, 20-min delay	11.32 (3.07)	14.11 (2.62)	5.0	37 (57)	12.09 (2.20)	14.36 (2.30)	4.3	22 (26)	12.35 (3.03)	13.37 (2.31)	3.4	13 (20)

Missing CVLT-II data at follow-up for one HC no-training subject. Effect sizes are *t*-values from paired samples *t*-tests and percent change (SD) for each group for each test; all test results were significant at $p < 0.01$, indicating that each group performed better at re-test for both short- and long delayed recall.

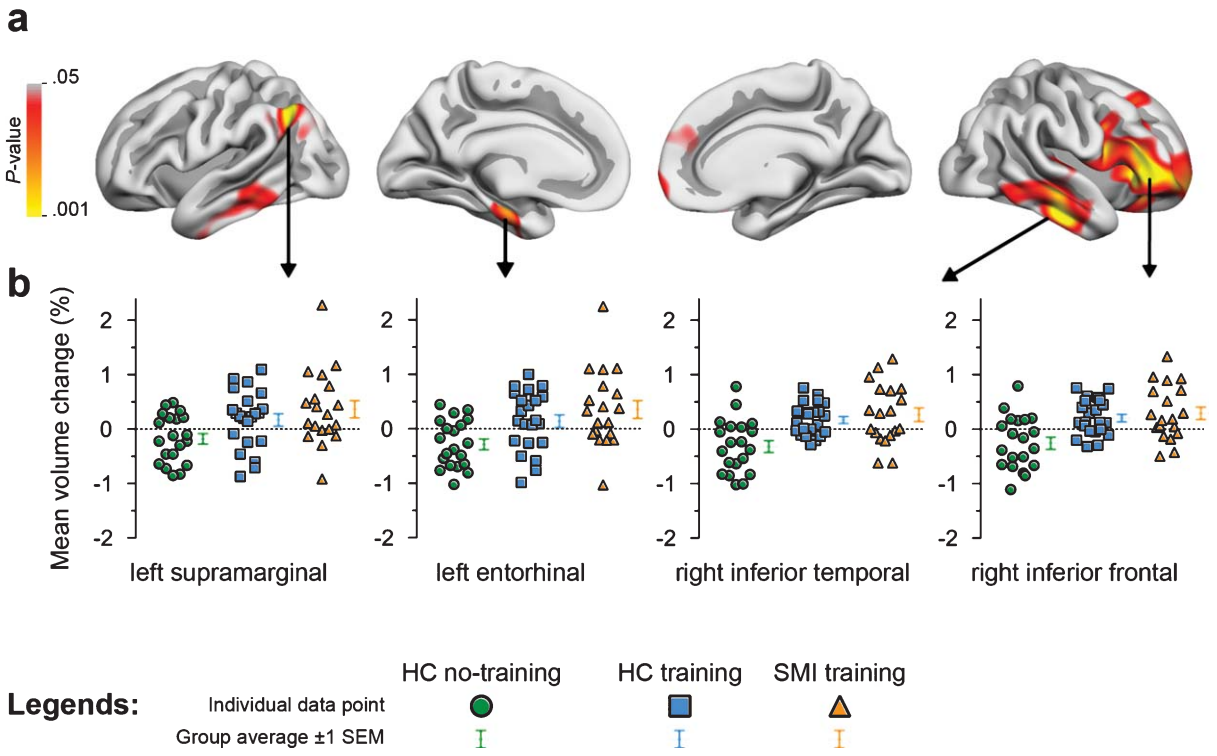

Fig. 1. a) Longitudinal increases in cortical volume in SMI- and HC-training groups following training. The GLM-analysis yielded four significant clusters, two in each hemisphere (cluster-wise $p<0.05$, two-tailed, fully corrected for multiple comparisons across space). p-value maps from the GLM-analysis are color-coded in red-yellow gradient and overlaid template cortical surfaces for visualization purposes. Average volume change within each cluster is plotted for each participant together with group means (±1 standard error of the mean; c.fr. lower row figure legend in b).

delayed recall intervals (5-minute, 20-minute) × two time-points (baseline, follow-up) ANOVA revealed a significant group (training; no-training) × time interaction ($F=4.7$, $p=0.034$), indicating greater recall increases in the two training groups as compared with no-training HC.

We proceeded to compare the differences between the two training groups using a two groups (HC-training, SMI training) × two recall intervals × two time-points ANOVA. The results revealed a significant main effect of time ($F=57.2$, $p<0.0001$), as both training groups (SMI- and HC-training) improved their recall performance at follow-up (see Table 2). There was no significant recall interval × time interaction effect, suggesting that the improvements in 5-minute and 20-minute delayed recall were comparable between the two training groups. Notably, there was no significant training group × time interaction, suggesting that the two training groups did not differ significantly in improvements in recall performance. Although the two training groups did not differ significantly in recall improvements, effect size calculations nevertheless indicate numerically greater increases in the SMI-group: Cohen's d, comparing change in HC-training with HC no-training, was 0.37 and 0.54 and for 5-minute and 20-minute delayed recall, respectively. Cohen's d for SMI-training compared with HC no-training, was 0.61 and 0.81 for 5-minute and 20-minute delayed recall, respectively.

Training-related regional change in cortical volume

We found no significant group differences in regional cortical baseline volume, using a corrected p-value threshold of <0.05. Fig. 1a shows the results from vertex-wise GLMs testing differences in longitudinal cortical gray matter change between the two training groups and HC no-training. The results suggest volume increases in the two training groups compared with controls. The significant clusters encompassed the lateral temporal lobes bilaterally, the supramarginal and entorhinal gyri of the left hemisphere, and the inferior frontal and lateral orbitofrontal cortices of the right. Group averages as well as individual change estimates from the analysis in Fig. 1a

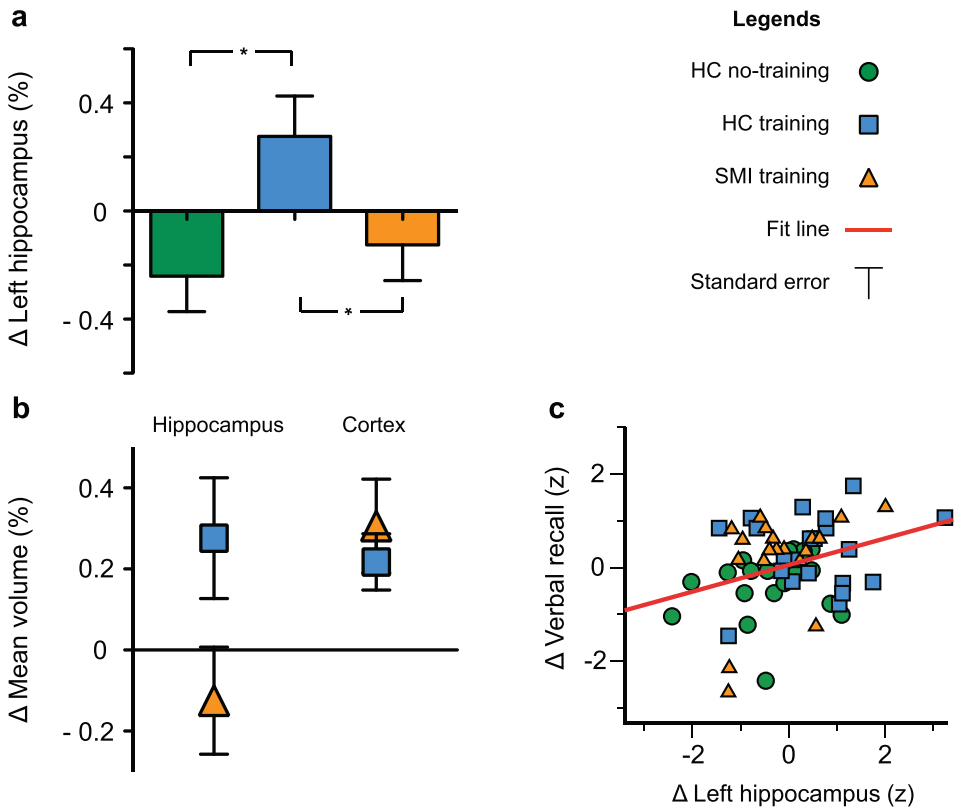

Fig. 2. a) Memory training is associated with increased hippocampal volume in HC-training group. The bar plot shows group averages (±1 standard error of the mean (SE)) of left hippocampal volume change. b) Differential effects of memory training on frontal cortical and hippocampal plasticity in SMI (two-way ANOVA; ROI × training group interaction indicating comparable cortical plasticity, but significantly lower hippocampal plasticity in SMI compared with HC-training, c.fr. Results). The plot shows average (±1 SE) gray matter volume change for HC (blue) and SMI-training (orange) groups in the left hippocampus and the right prefrontal cluster shown in (a). c) Hippocampal volume change correlates with verbal recall improvement across all participants. The scatterplot shows CVLT 5-minutes delay free recall change residuals corrected for baseline performance (Y-axis) and baseline-corrected left hippocampal volume change (X-axis). A linear fit line across groups is shown in red.

are plotted for each group in Fig. 1b. The strongest effects of training were found in the right prefrontal cortex (Fig. 1b, rightmost plot; Talaraich coordinates of max vertex: X = 43.1, Y = 36.1, Z = −0.7; Brodmann area 47). We found no significant differences in cortical gray matter changes between the SMI- and HC-training groups (independent samples *t*-tests, $df = 39$, $ts < 1.1$, p's>0.27), indicating that the increases were of comparable magnitude. We found no significant effects of baseline volumes, subjective memory score or depressive symptoms on volume change (ANCOVA, $F's < 2.7$. p's>0.11).

Training-related change in hippocampal volume

There were no effects of group on left ($F = 0.08$, $p = 0.9$) or right ($F = 0.6$, $p = 0.5$) hippocampal volumes at baseline, respectively. We found a significant group effect for left—but not right—hippocampal volume change (left: $F = 4.9$, $p = 0.011$; right: $F = 1.8$, $p = 0.17$). Student-Newman-Keuls corrected *post-hoc* tests suggested significant increases in left hippocampal volume in HC training compared with HC no-training (absolute change difference = 0.52%, $q = 3.8$, $p < 0.05$). HC training also exhibited more positive left hippocampal volume change compared with SMI training (absolute change difference = 0.40%, $q = 2.9$, $p < 0.05$). SMI showed slightly more positive relative change in left hippocampal volume compared with no-training HC, but this group difference failed to reach statistical significance ($q = 0.82$, n.s.). Figure 2a shows average left hippocampal volume change for each group. There was no effect of baseline hippocampal volume, subjective memory score, or depressive symptoms on left hippocampal change (F's<0.91, p's>0.34).

We compared hippocampal volume change with change in the cluster encompassing the right inferior frontal gyrus and lateral orbitofrontal cortex to assess training-group differences in change between cortical and hippocampal brain regions. A two ROIs × two groups ANOVA revealed a significant ROI (frontal cortex; hippocampus) by group (HC-training, SMI-training) interaction ($F(1,39) = 4.4$, $p < 0.05$), indicating comparable cortical, but not hippocampal plasticity between the training groups, as HC-training showed more positive change in the hippocampus. Figure 2b shows mean volume changes in the two brain regions for the SMI and HC-training samples.

Finally, we assessed relationships between brain and behavioral change using partial correlations with baseline volumes and performance, and age as covariates. For the whole sample, left hippocampal volume change correlated with 5-minute delay free recall change ($r = 0.28$, $p = 0.03$). When running the analyses for each group separately, we found a significant relationship for the SMI-training group only ($r = 0.52$, $p = 0.044$). Figure 2c shows a scatterplot of the verbal recall and hippocampal volume change residuals for all participants. No significant relationships between cortical and verbal recall change were found.

DISCUSSION

We found gray matter volume increases in cerebral association cortices in SMI patients following two-month episodic memory training. Training-related cortical increases were of similar extent as those of a healthy training group. The HC-training group further showed increased left hippocampal volume following training, compared with no-training controls. The SMI-training group showed no significant group change in the hippocampus, although individual differences in hippocampal change were related to greater memory improvement following training. Overall, the present study provides initial neuroanatomical support for the putative benefits of cognitive intervention in SMI [20, 44].

Cortical gray matter increases following training

The finding of increased cortical gray matter volume in two independent intervention groups (HC, SMI) supports the idea that training-related structural plasticity extends into middle- and old age [45]. The present results are among the first to suggest that structural plasticity may not be restricted to healthy aging, as memory clinic outpatients with SMI showed a similar structural response to memory training in the cortex. The pattern of increased gray matter volume following intervention is compatible with results reported in other studies of healthy older adults [16, 46–48].

The regional volume increases reported in the present study resemble our previous findings of training effects on cortical thickness in the healthy control group using different processing and analysis tools [18]. In the previous study, we found effects of training in the right anterior insular and orbitofrontal cortices, partly overlapping the present results, in addition to non-overlapping effects in the left orbitofrontal cortex and in the right fusiform gyrus. When correcting for multiple comparisons by means of Monte Carlo simulations, the present cortical volume changes were more widespread and stronger than our previously reported thickness results. Importantly, while we previously reported change in cortical thickness as a function of training, we now measure change in all directions relative to the reconstructed surface, and the change measure will thus be affected by changes in both thickness and area, i.e., effectively reflecting a measure of volumetric change. Also, a recent comparative MRI-study [25] indicated that the presently employed analysis stream, Quarc might be more sensitive to detect change in any direction as compared with the method used on cortical thickness change in our previous publication [18].

Mechanisms underlying cortical volume changes in response to training are poorly understood. Roughly, dendrites (30%), axon collaterals (29%), neuronal somas (7.8%), and synapses (6%) make up bulk gray volume composition (c.fr., [49]). Thus, these compartments represent candidates mediating training-related change in a manner detectable by macroscopic MR-estimates. Accordingly, work on animals has identified axonal remodeling, dendritic spine growth, and synapse turnover as structural mechanisms for experience-dependent plasticity in adult cortex [50].

The cortical volume changes reported in the present study did not correlate with verbal recall performance and could be due to non-specific neuronal responses to cognitive training. The current training program offered prolonged cognitive demands which could trigger changes in existing neuronal supplies [51], but not necessarily in a manner that co-vary significantly with change in clinical neuropsychological tests. In contrast to this hypothesis, however, is our finding of a correlation between free recall improvements and left hippocampal volume change. As discussed below, greater inter-individual differences in this structure

due to preclinical neurodegenerative process are not unlikely, and might explain the closer proximity to cognitive measures for this structure.

The strongest training effects on volume change were found in the right prefrontal cortex (peak voxel corresponding to Brodmann area 47). Right prefrontal cortex is activated during contextual monitoring and episodic memory retrieval [52]. Right prefrontal over-activation in SMI compared with controls during verbal recall has been interpreted in terms of neuronal compensation [10]. Whether compensatory mechanisms are mediating training-related structural adaption needs to be tested.

In no-training controls, we found volume reductions in agreement with previous longitudinal reports on brain structure in elderly samples; mean hippocampal volume change in the HC no-training group was -0.23% (SE = 0.14), corresponding to a six-month change of nearly -0.6%. Using the same technique, Fjell et al. [53] reported hippocampal volume change corresponding to -0.42% in six-months in healthy elderly (c.fr. also [54]). Whereas these latter studies support longitudinal volume loss in healthy adults, discrepancies in magnitude between studies may stem from differences in MR-scanners, sample populations, and recruitment criteria.

Training-related hippocampal plasticity and SMI

Increased hippocampal volume was found in healthy training subjects following intervention. The result is supported by other intervention studies indicating that both physical and mental exercise protect the hippocampus from age-related deterioration [16, 17]. The SMI-subjects showed numerically less decrease in hippocampal volume compared with no-training controls, but this finding failed to reach significance. Whether SMI is associated with disrupted hippocampal plasticity, or whether training halts otherwise accelerated hippocampal shrinkage in SMI [13] compared with no-training SMI-controls is not known. Functional imaging results of memory training in MCI by Belleville and colleagues [55], however, support a hypothesis of distrupted hippocampal plasticity: The authors showed that following 2-month of episodic memory-training, MCI patients exhibited increased activation in several cortical regions during encoding and retrieval, but not in the hippocampus. The hypothesis of disrupted structural hippocampal plasticity in SMI needs to be addressed in future studies including a SMI non-training control group, and ideally diagnostic follow-up examinations for years.

Hippocampus is the structure most vulnerable to early AD in terms of atrophy [56], and increased rate of decline is seen before clinical symptoms are manifest [57]. In a recent study of the SMI-training group only, we showed that individual differences in subregional volumes of the left hippocampal formation predicted cognitive improvements following training [23]. In the present study, we did not include analyses of hippocampal subregions, but tested whether total hippocampal baseline volumes in SMI differed from HC. We failed to find any significant group-differences in the hippocampus before training. However, rate of hippocampal change differed significantly between SMI- and HC-training groups, making us speculate that structural training-response or plasticity could be a more sensitive marker of early impairment than mere static baseline measures. It could be that some of the SMI participants experience very early AD-related atrophy explaining the present findings of subtle volume shrinkage despite memory training and also contribute to the correlation between functional gains and volumetric change. Of note, naturally occurring longitudinal hippocampal volume reductions have been shown to be related to memory change in healthy elderly [58–60], even those at very low risk of AD [61]. Thus, it is conceivable that memory intervention could impact memory function both through induction of hippocampal volume increase and through reduced atrophy, and it is not yet known how such processes may relate to early AD-related events.

Also of note, we found training-related increases in a cluster encompassing the left entorhinal cortex in the SMI group (Fig. 1a). The entorhinal cortex is often regarded as part of the hippocampal formation itself and is susceptible to AD-like neurodegeneration comparable to that of the hippocampus proper [62, 63]. The finding of increased entorhinal volume in SMI-subjects suggests that some of these individuals are not prone to reduced medial temporal lobe plasticity and is probably rooted in the heterogeneity among individuals included in the rather crude SMI entity.

Effects of memory training on cognitive measures

Cognitive effects of the current training program was documented for the HC-training sample previously [18], and similar programs have shown to be effective in SMI [20, 44], as well as for MCI [21, 55]. In the present study, both the training groups and the HC no-training control group showed significant increases in CVLT-II free verbal recall scores at follow-up, where the latter likely represents test-retest

effects [64]. Importantly, analysis of variance indicated greater recall increases in the two training groups compared with the control improvements, pointing to an effect of the present intervention itself. It should be stressed that the behavioral effects reported here are for cognitive test-performance only, as we did not include measures of transfer. A recent meta-analysis indicated that most studies to date have failed to show consistent transfer effects on, e.g., measures of activities of daily living [65].

Limitations

This study has limitations. First, we did not include a SMI no-training group, but instead compared SMI-subjects with healthy controls. The lack of an active control group prevents us from dissecting direct effects of memory training per se from additional, intervention-related factors, such as social interaction. Further, as SMI-controls might show greater hippocampal atrophy than do HC-controls [13], the lack of a SMI-control group could have masked a true effect of the present intervention in halting hippocampal atrophy; this hypothesis remain to be tested in future controlled trials.

Other limitations include the short observational period, which does not allow inference about long-term effects of training. Also, the present study did not include cerebrospinal fluid or genetic biomarkers. Assessment of genetic variation may broaden our understanding of plasticity in aging [66–68], and need to be applied to future SMI trials.

Increased depressive symptom load in SMI has been reported previously (e.g., [8, 10, 12]). SMI subjects in the present study reported more depressive symptoms compared with HC, but no subjects reported chronic depression or antidepressant use, and the symptoms are likely to be temporary. In the present training program, SMI subjects got some opportunity to express their memory concerns and meet peers with similar worries in the group-sessions. Yet, the psychosocial impact of the present training, particularly for the SMI-group, remains untested. In follow-up trials we will need to measure depressive symptoms longitudinally, and study how relevant mental health changes relate to the neurocognitive measures.

Conclusion

Implementing preventive interventions for individuals experiencing memory problems seems crucial in face of the aging population. Yet, neuroanatomical support for cognitive training effects has been lacking. In the present study, we report initial findings suggesting that training-related structural brain plasticity remains in the earliest form of cognitive impairment.

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