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ARTICLE

Changes in Brain Volume Resulting from Cognitive Intervention by Means of the Feuerstein Instrumental Enrichment Program in Older Adults with Mild Cognitive Impairment (MCI): A Pilot Study

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Abstract

There is increasing interest in identifying biological and imaging markers for the early detection of neurocognitive decline. In addition, non-pharmacological strategies including physical exercise and cognitive interventions may be beneficial for those developing cognitive impairment. The Feuerstein Instrumental Enrichment (FIE) Program is a cognitive intervention based on *Structural Cognitive Modifiability* and the *Mediated Learning Experience* (MLE) and aims to promote problem-solving strategies and metacognitive abilities. The FIE program uses a variety of instruments to enhance the cognitive capacity of the individual as a result of mediation. A specific version of the FIE program was developed for the cognitive enhancement of older adults, focusing on strengthening orientation skills, categorization skills, deductive reasoning and memory. We performed a prospective interventional pilot observational study on older subjects with MCI who participated in 30 mediated FIE sessions (two sessions weekly for 15 weeks). Of the 21 subjects who completed the study, there was a significant improvement in memory on the Neurotrax battery comparing pre- and post-intervention scores (pre: M=95.3, SD=12.2, post: M=101.2, SD=7.9, $p<.05$). Complete sets of anatomical MRI data for voxel-based morphometry, taken at the beginning and the end of the study, were obtained from 16 participants (mean age 83.5 years). Voxel-based morphometry showed an unexpected increase in grey matter (GM) in the anterolateral occipital border and the middle cingulate cortex. These initial findings of our pilot study support the design of randomized trials to evaluate the effect of cognitive training using the FIE Program on brain volumes and cognitive function.

Keywords

Brain morphometry • Magnetic Resonance Imaging • Cognition • Mild cognitive impairment • Feuerstein Instrumental Enrichment • Structural Cognitive Modifiability • Mediated Learning Experience

Declarations

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Conflicts of interest/Competing interests R. Feuerstein, S. Cohen, H. Devisheim and D. Tzuriel are employees of the Feuerstein Institute which developed the Feuerstein Instrumental Enrichment Program. The other authors report no conflicts of interest.

Ethics approval The study was approved by the Helsinki Committees of the Rambam Health Care Campus (0580-16-RMB) and the Maccabi Healthcare Services (0043-17-BBL). The study is registered at ClinicalTrials.gov (NCT03447236).

Availability of data and material All data are available on request in accordance with confidentiality limitations.

Code availability Not applicable

Authors' contributions All authors were involved in designing the concept of the study and in the preparation of the manuscript. TD submitted for Ethics Committee approval, and obtained informed consent from the subjects. SC supervised the study

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performance and intervention and acquired and analyzed the cognitive data. HD analyzed the cognitive data. DM performed the imaging analyses. MI evaluated the cognitive data.

MAIN TEXT

Introduction

Aging is often associated with physical and cognitive comorbidity. Deterioration in cognitive function may lead to Mild Cognitive Impairment (MCI) and subsequently to dementia. There is increasing evidence supporting the value of timely recognition and diagnosis of deteriorating cognitive function [1]. Research is now focusing on identifying biological and imaging markers for the early detection of subsequent neurocognitive decline. The discovery of reliable markers will allow for the initiation of pharmacologic and non-pharmacologic interventions that may hopefully delay the onset of cognitive symptoms [2].

MCI is a condition in which individuals develop cognitive impairment with minimal impairment of activities of daily living (IADL) [3]. MCI frequently constitutes a pre-dementia state, particularly for those with amnestic MCI, a condition that may predict the future development of Alzheimer's Disease [4]. The diagnosis of MCI is based on clinical criteria as determined by Consensus Conference guidelines [3]. The practice guidelines of the American Association of Neurology do not support the use of pharmacological agents for the treatment of MCI. However, non-pharmacological strategies such as physical exercise and cognitive interventions are recommended [5,6]. There is increasing interest on the effects of cognitive training on brain plasticity in MCI and early dementia [7].

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Feuerstein Instrumental Enrichment Program

The Feuerstein Instrumental Enrichment Program (FIE) is a cognitive intervention based on *Structural Cognitive Modifiability* and the *Mediated Learning Experience* (MLE) theory [8]. The FIE aims to promote problem-solving strategies and metacognitive abilities. It focuses on strengthening cognitive functions and on developing learning strategies.

MLE processes describe a special quality of interaction between a mediator and a learner. In the MLE interaction, learning is achieved with the active instruction of the mediatior who interposes him/herself between the learner and structured stimuli. MLE processes are gradually internalized and integrated by the learner, allowing for modifying cognitive function by means of self-mediation.

The FIE program uses a variety of instruments to enhance the cognitive capacity of the individual as a result of mediation. Each instrument consists of a set of tasks with increasing levels of difficulty, and in a process of active learning recommendations are provided in order to enable the learner to acquire general principles for domains and contexts beyond the original domains presented. The Feuerstein Institute developed a specific application of the classic FIE designed for cognitive enhancement of aging adults (Feuerstein Memory Program developed by the author RSF). Beyond contributing to the preservation and possible improvement in cognitive function, this program aims to promote feelings of competence, independence and benefits on the emotional state.

The classic FIE instruments include the following tasks: Organization of Dots, Comparisons, Spatial Orientation, Analytical Perception and Instructions. These tasks are designed to develop skills related to systematic information-gathering, reigning in impulsivity, analysis and planning. The tasks comprising the Feuerstein Memory

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Program that was used in our study are memory-focused and include the following: Processing and Memory, The Social Sphere, Everyday Functioning, Temporal Orientation and Figural Differences. Emphasis is placed on verbalization and outcome definition. Word fluency is addressed in every session. Strategies are taught to aid retrieval and memory, and focus is placed on strengthening the participants' orientation skills, categorization abilities, deductive reasoning and memory.

MRI and Cognitive function

Several MRI techniques are useful as biomarkers of aging and cognitive decline in research and clinical settings [9,10]. Connectivity among cortical regions, probably the most versatile of the MRI biomarkers, is based on functional MRI data. This biomarker has been implemented in studies of the aging human brain [11–14] as well as for investigating interventions aimed at delaying undesirable aging-related effects [15–17]. However, obtaining high-quality functional MRI data depends on the full cooperation of the participants. The requirement of lying still without falling asleep for quite long periods [18] presents a challenge to many older people. In addition, in a longitudinal study design such as ours a high level of cooperation in repeated imaging sessions over time is necessary.

The acquisition of structural MRI is less cumbersome to older participants, since the only requirement is that they adjust to the restrictive environment of the MRI machine and refrain from moving during the scans. Anatomical connectivity can be elegantly studied using diffusion-based MRI, which allows for identifying processes involved in brain aging and dementia [19,20]. There are as yet few reports describing longitudinal follow-up studies in older subjects [21,22]. A possible explanation for the lack of such studies may relate to the fact that reducing scanning-times to about five

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minutes, which is tolerable for the older population, requires advanced MRI technology that has only recently become routinely available [23]. Since our MRI system lacked this capability, we utilized morphometric data to measure and map changes in the amounts of brain grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF).

MRI morphometry is gaining acceptance as an adjunct biomarker for differentiating normal aging from the accelerated degeneration of brain tissue associated with various dementias [24–26]. Most clinical measurements target specific brain regions, focusing particularly on the hippocampus and entorhinal cortex which are directly implicated in the pathophysiology of common types of dementia [27,28]. Preliminary, comparative evidence shows that an even better correlation with the clinical signs of dementia may be achieved using global mapping of atrophy rates [29]. Research software for implementing global morphometric mapping is now readily available (for example https://www.fil.ion.ucl.ac.uk/spm).

Besides these practical considerations, there is also a major, substantial incentive to include morphometry in an intervention study. Gradual atrophy of brain tissue is the rule in adults, and this is even more so in the aging brain [10,28,30,31]. Thus, a finding of an increase in the amount of brain tissue would clearly be an exception to the rule, implying a beneficial role for the intervention under investigation.

Study Goals

This study aimed to examine the effect of the FIE program on the structure of the brain in older participants with MCI. Our goal was to find evidence for a change in brain morphometry that may imply beneficial effects of the intervention.

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Methods

Study description

We performed a prospective interventional pilot observational study of older subjects with MCI who participated in a period of cognitive training using the FIE program. Outcome measures included cerebral volumetric MRI and functional MRI imaging to determine the association between this form of cognitive training and changes in imaging metrics. While the functional data are still being processed and analyzed, we report the preliminary findings of the morphometric measurements of the brain over time in this interventional study.

Participants

All participants were residents of the same assisted living center. They were recruited following a lecture explaining the research study. Interested subjects provided written informed consent for inclusion in the study. Demographic and medical background data were collected. A MoCA test (www.mocatest.org) was administered for initial cognitive screening, and those who received a score of 18-26 (inclusive), which is compatible with a diagnosis of MCI [32], were included.

We excluded those subjects with a medical or functional condition that would not allow them to participate in the study, such as those with an unstable or symptomatic medical condition, depression, bipolar disorder, schizophrenia, or dementia. Subjects with other comorbidities, including cardiovascular disease, cerebrovascular disease or diabetes, were included if their condition was stable. Those with a MoCA test score of 17 and below or 27 and higher were excluded. Subjects who could not perform an MRI due to the presence of metallic or electronic implants were not included. Computerized cognitive assessment using the NeuroTrax battery were attained at pre-intervention, post-intervention, and follow-up assessments.

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Procedure

For the functional part of the study participants were divided into two groups. The first group (Group A) of 13 subjects underwent an initial MRI session before the intervention. Subsequent MRI sessions were performed post-intervention and at follow-up - one year after the first session (a total of 3 sessions). The second group (Group B) of 10 subjects, started the experiment 6 months after the first group and participated in 4 MRI sessions: at baseline (followed by a 15-week waiting period with no intervention), pre-intervention, post-intervention, and at follow-up - one year after the baseline session. Two sessions of high resolution volumetric MRI scans were planned for each participant, at baseline and after one year, at the end of the study. In these volumetric sessions the participant was in the scanner for less than 20 minutes. An expert radiologist provided an individual report based on these anatomical brain images.

Instruments

The Montreal Cognitive Assessment (MoCA)

The MoCA [32] was developed as cognitive screening tool for patients with MCI and is both sensitive and specific in differentiating mild cognitive decline from preserved cognitive function in older adults. This instrument has been translated and validated for use in Hebrew [33] which was the version used in this study. The test consists of eight sections with a maximum score of 30 points. A score in the range 18-26 is generally considered compatible with a diagnosis of MCI. Those with an educational level of 12 years or less are granted an extra point. The MoCA test is not normalized for age.

CogSym Metacognition Questionnaire

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The CogSym instrument comprises 10 questions regarding cognitive symptoms and daily instrumental functional abilities. Subjects are requested to rate their ability on a Likert scale from 1-5 (1 = asymptomatic; 5 = markedly symptomatic) [34]. The symptoms include forgetting names of people in general, forgetting names of close contacts, misplacing belongings, forgetting meetings or events, getting lost in familiar environments, getting confused with days or times, word-finding difficulties, difficulty performing household tasks, difficulty with taking medications, and difficulty with shopping or managing finances. A modified version of this instrument was found to be useful in screening for MCI [35].

Wellbeing Questionnaire

Developed by the World Health Organization this questionnaire comprises 5 items related to subjective wellbeing [36,37]. The subject is asked to refer to the previous two weeks and indicate for each of the five statements the frequency at which the response is correct on a 5-level scale (5 = all the time, 0 = never). The total raw score, ranging from 0 to 25, is multiplied by 4 to give the final score, with 0 representing the worst wellbeing and 100 representing the best imaginable wellbeing.

"NeuroTrax" Computerized Neuropsychological Assessment Battery

This computerized cognitive assessment battery was designed for widespread clinical and research use in evaluating cognitive function. Neurotrax can significantly discriminate between MCI and cognitively healthy older people across multiple cognitive domains (memory, executive function, visual-spatial skills, language and attention) and provides a comprehensive profile of cognitive function [38].

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Cognitive data analysis

The statistical analysis for the cognitive data was performed using a paired-samples t-test comparing pre- and post-intervention in the different cognitive domains scores of participants. A total of 23 participants were included in the analysis. We used the the IBM® SPSS® software to perform the data analysis for the cognitive data.

MRI data acquisition and processing

The experiment consisted of several MRI sessions as detailed in the "procedure" paragraph. Complete sets of anatomical MRI data for voxel-based morphometry, taken at the beginning and the end of the study, were obtained from 16 participants. All MRI sessions took place between 8:00 AM and 10:30 AM. The anatomical scans were performed on a 3T system (GE, MR-750) using a T1-weighted, 3D, inversion-prepared, gradient-echo, BRAVO sequence defined with parameters: sagittal-oblique orientation, voxel size 0.9 mm^3, inversion delay 450 ms, TR/TE 6.6/2.5 ms, acceleration factors in the phase/slice directions 1.75/1.25 for a total time of 3 minutes and 50 seconds. An eight-channel head coil was usually used, except for the end-of-the-year session of the first-round group, in which for technical reasons the head configuration of the clinical HNS coil was employed. To ameliorate the potential bias we added the group round as a covariate for the statistical model as detailed later.

Preprocessing using Statistical Parametric Mapping software (SPM12) adapting the optimized protocol described by Good et al. [39] consisted of an initial segmentation of all volumetric images to GM, WM, and CSF, then applying on each segment: 1) SPM old normalization utility for fitting the end-of-the-year scan to the beginning-of-the-year scan, keeping the *amounts* of the segments in the resulting images; 2) old

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normalization fitting the beginning-of-the-year to a matching standard MNI template segment, adding the normalized end-of-the-year segment to the written volumes, and keeping the *concentrations* of the segments in the resulting images; 3) smoothing with an 8 mm kernel. The output of this pipeline provided the voxelwise relative change of each tissue segment over the year.

Intervention

Specifically, for this study, the Feuerstein Instrumental Enrichment (FIE) Program comprised a combination of classic IE instruments as well as novel instruments. In each session both classic and novel IE instruments were included in the training program. In our study FIE was administered in group settings by instructors who were specifically trained to mediate based on the needs of the older population, including increased font sizes, larger spaces between the dots, and other adaptations. Subjects participated in 30 mediated FIE sessions (two sessions weekly for 15 weeks, each session continuing for an hour and a half). Attendance data were gathered throughout the intervention period.

Results

A total of 23 subjects participated in the interventional arm of the study (13 in Group A and 10 in Group B). The baseline characteristics of the study cohort are presented in Table 1.

Imaging results

Complete, two-session sets of volumetric MRI data for voxel-based morphometry were obtained from 16 participants, 5 men and 11 women. The mean age was 83.5 (S.D. 5.0) years. Ten of the participants were widowed, 5 were married and one was single.

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Voxel-based morphometry maps of the relative changes in brain tissues over one year in those who participated in cognitive training showed an increase in GM in two regions (figure 1A and table 2): 1) the anterolateral occipital lobe, bordering the parietal and temporal lobes of the left cerebral hemisphere. Surrounding CSF in this region was, correspondingly, decreased; 2) the middle cingulate cortex.

There was an increase in WM, abating the increased GM in the left occipital lobe. But unlike the limited increase in GM, the WM effect was broader, dispersing over the dorsal parts of both hemispheres. Expected, aging-related changes were also observed (figure 1B). A decrease in GM was observed bilaterally in frontal-basal regions, and diffusely over the right hemisphere. Increased CSF was noticeable in the lateral ventricles, as well as in the anterior longitudinal and the Sylvian fissures in both hemispheres.

Cognitive results

The global cognitive scores and the scores in specific cognitive domains, as assessed by the Neurotrax computerized tests performed before and after the Feuerstein Instrumental Enrichment (FIE) program were compared. Data were gathered from a total of 21 subjects, including 11 participants from the first group of subjects and 10 participants from the second group (who started the FIE after a 15-week waiting period).

In the global score, there were no significant differences between pre and post-intervention (pre: M=94.9, SD=9.5, post: M=97.2, SD=9.2; t (22)=1.51; p=0.15). A score of 100 in the Neurotrax computerized tests is the average score corrected for age and education, and a standard deviation of 15.

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In memory, there was a significant improvement between pre and post-intervention (pre: M=95.3, SD=12.2, post: M=101.2, SD=7.9; t (22)=2.47; p<.05). There was also a significant improvement between pre and post-intervention in immediate verbal memory (pre: M=95.5, SD=15.9, post: M=103.8, SD=12.5; t (22)=2.46; p<.05) and in delayed nonverbal memory (pre: M=92.6, SD=12.2, post: M=99.1, SD=13.3; t (22)=2.11; p<.05). There were no significant differences between pre and post-intervention in delayed verbal memory (t (22)=1.37; p=0.19), or in immediate nonverbal memory (t (22)=0.94; p=0.36).

There were no significant differences between pre and post intervention in **executive function** (pre: M=95.9, SD=11.7, post: M=96.3, SD=10.6; t (22)=0.15; p=0.88), **in attention** (pre: M=96.4, SD=16.8, post: M=100.7, SD=13.1; t (22)-1.69; p=0.11) and **in visual spatial abilities** (pre: M=92.1, SD=13.7, post: M=90.7, SD=15.4; t (22)=0.42; p=0.68).

No significant morphometric correlates to cognitive scores could be found.

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Discussion

Our results indicate that the FIE cognitive training practiced in the current study may induce a sustained, localized increase in GM and WM of older individuals with MCI. Research and clinical protocols routinely use MRI-based measurements to evaluate brain atrophy in older adults, demonstrating an association between accelerated brain tissue degeneration and cognitive decline. However, few reports describe an increase in GM over time in human adults.

A localized increase in GM has been observed, along with functional and anatomical modifications, after a period of practicing simultaneous translation [40]. GM and WM volume recovery was observed following abstinence from excessive habitual alcohol consumption [41,42]. The effects in these studies were unrelated to age. There are a couple of reports on increased GM in older adults, which followed months of intense computer games activity [43,44]. One of these studies included participants at risk for MCI [44]. This study measured volume in predefined regions, e.g. the anterior commissural and dorsolateral prefrontal cortices. Another study of patients with subjective memory impairment (SMI), which is considered a possible risk factor for Alzheimer's disease, showed structural GM volume increases in brain regions encompassing the episodic memory network, with cortical volume expansion of comparable extent as healthy training participants, after two months of episodic memory training. Hippocampal volume increases were detected in the healthy training group but not in the SMI group [45].

One of the first reports dealing with patients categorized as having MCI, who went through a physical and cognitive exercise plan, describes, along with other MRI biomarkers, an increase in GM in the cingulate cortex [46]. The location described in this paper is near one of the regions found in our study (Figure 1A, Table 2).

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Interestingly, most of the previous studies, involving the older population, included physical activities in their interventions [43,44,46,47]. A closer look at some of these papers gives the impression that the older population is not usually engaged in the types of activities that have been proven effective in improving cognition: dancing [47] or virtual reality gaming [43,44] versus standard sportive activity. The protocol of the current study did not have a physical activity element, but the cognitive approach that was implemented can be considered as a new experience for the participants. Likewise, a recent publication describes the use of computerized, multi-domain cognitive training [48], which reminds of our multi-faceted teaching approach. Their finding in amnestic MCI subjects was an increase in the GM in the right hemisphere's angular gyrus (Figure 1A, Table 2). Our findings include a GM increase in the left hemisphere's angular gyrus.

Our morphometric estimations also included the WM, which also increased following the cognitive training. This change was noticed near the foci of increased GM but extended to adjacent regions as well as to the right cerebral hemisphere (Figure 1A). Better characterization of the WM effect may be achieved with diffusion-based MRI measurements.

Behaviorally the FIE was associated with an improvement in verbal and non-verbal memory. However, an increase in the grey matter was detected in the middle cingulate cortex and not in the retrosplenial cortex -part of the posterior cingulate cortex which is considered to be involved in episodic memory. The midcingulate cortex (MCC_g) has been proposed to be engaged when predicting and monitoring the outcomes of decisions during social interactions. In particular, the MCC_g processes statistical information that tracks the extent to which the outcomes of decisions meet goals when interacting with others [49]. The FIE training took place in a group and was mediated

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by a trainer, and thus involved inter-personal interaction. This might explain the increase in the grey matter of the middle cingulate.

We must emphasize that there are a number of limitations to our study. Our imaging results are from a small treatment group of 16 participants. The statistical significance that we found in such a small sample must be regarded with caution, and it is difficult to reliably evaluate the effects of confounding variables such as age and gender. Nevertheless, other reported studies [43,44,47] based their findings on similar numbers of subjects in the main treatment group. Indeed, the statistical significance of our findings accord with those described previously in other studies. Another major limitation of our study is the lack of a proper control group. Taking this into account, there may be two possible explanations for our findings of a localized increase in brain tissue during the follow-up period. On the one hand, the training program may have indeed stimulated those regions of the brain described earlier, or alternatively the findings may represent a global relative reduction in brain tissue, with the atrophy being more pronounced in certain regions. Data from an adequately powered control group would allow for a better understanding of the observed signs of atrophy represented by a decrease in GM and an increase in CSF (Figure 1B) as compared to the effects of the cognitive intervention on brain volume.

Conclusion

In this pilot study we report the findings of a localized increase in both cerebral grey matter and white matter in subjects participating in a cognitive intervention program. These findings are in contrast to the expected age-related decrease in brain tissue over time. We also found a significant improvement in memory, particularly in immediate

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verbal memory and in delayed nonverbal memory. We believe that the results of this small pilot study support further investigation in larger randomized trials to evaluate the effect of cognitive training using the FIE Program on brain volumes and cognitive function.

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Table 1 Characteristics of the study cohort

	Group A (n = 13)	Group B (n = 10)	P values
Sex			
Female	76.9 %	80.0%	0.73
Age (years)	82.8	83.7	0.72
Education (years)	11.4	11.6	0.82
MoCA	20.9	22.7	0.06
CogSym	23.3	21.2	0.38
Wellbeing	18.1	18.6	0.75

Values are presented as means. Group A commenced the intervention following baseline assessments. Group B commenced the intervention following a 6-month post-baseline waiting period. *MoCA* Montreal Cognitive Assessment; *CogSym* CogSym Metacognition Questionnaire; *Wellbeing* Wellbeing Questionnaire

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Table 2 Increase in grey matter at one year post-baseline in MCI patients who participated in the FIE Program

Region	x,y,z (mm)[a]	Gyri	Cluster (mm^3)	Effect (%)	T value	p (FDR)[b]
1	-43,-50,+43	Lt. Angular Lt. Supramarginal Lt. Inferior Parietal	610	2.13	5.34	0.043
2	+2,-27,+40	Lt. Middle Cingulate Rt. Middle Cingulate	520	1.14	7.97	0.050
3	-45,-65,-7	Lt. Inferior Temporal Lt. Fusiform Lt. Inferior Occipital	2850	4.19	7.22	<0.001

[a] Position in the standard MNI (Montreal Neurological Institute) space of the maximum T value in voxel-clusters that survived a statistical threshold of uncorrected $p < 0.001$.

[b] The cluster p-values of the false detection rates (FDR) i.e. odds of discovering such clusters by chance.

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Figure 1

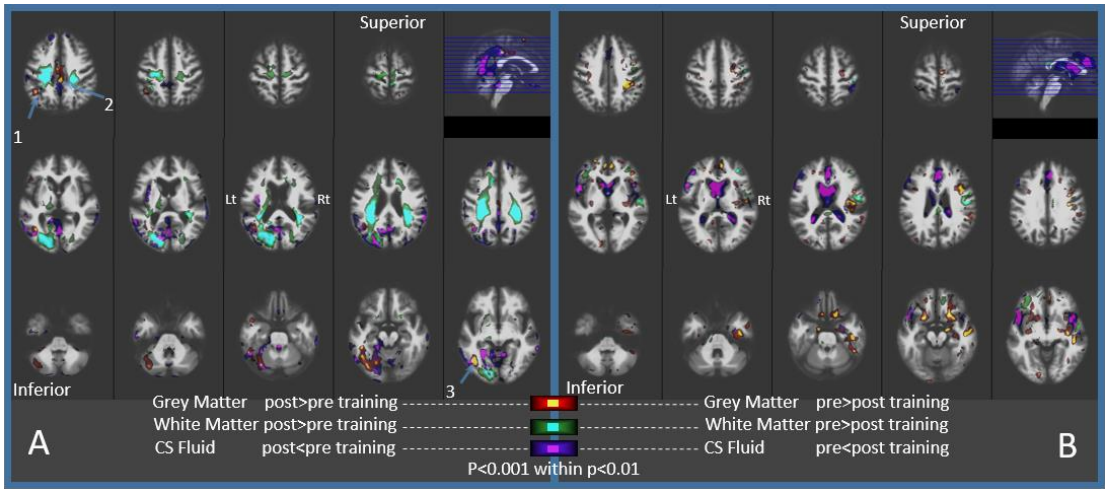

Figure 1. *Brain tissue changes over the year that included 15 weeks of the FIE cognitive training.* A. Increased GM concentrates in left posterior regions surrounded by decreased CSF. Increased WM extends to the dorsal parts of both hemispheres. Clusters of GM with a higher statistical significance, located on the anterior occipital-lobe border and cingulate cortex are listed in table 1 ($p<0.05$, FDR corrected, numbered 1-3). B. Decreased GM is prominent in bilaterally in fronto-basal and in right temporal regions. Increased CSF is prominent in the lateral ventricles and Sylvian fissures.

The locations of the axial slices are marked on a mid-sagittal section. Overlaid maps of two, uncorrected significance levels are color coded as indicated in the figure.