Functional and structural substrates of neural modulation in older adults after executive control training

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Abstract

The fronto-parietal control network (FPCN) and dorsal attention network (DAN) are critical for goal-directed cognition (GDC), which is known to decline with advancing age. Here, we investigated whether a strategy-based executive control training intervention (GOALS) would alter recruitment of the FPCN and DAN in healthy older adults. We also investigated whether functional brain changes would be associated with improvements in GDC and structural integrity of frontal-posterior white matter tracts. Thirteen participants were randomly assigned to the five-week long GOALS training and 12 were randomly assigned to a time and intensity matched control intervention group. Both groups were tested before and after intervention on a goal-directed cognitive task while undergoing fMRI scanning. We observed post-training increases in activation within the FPCN during a selective working memory task requiring GDC in the GOALS training group as compared to the control group, $p < .001$. These increases were positively correlated with the integrity of white matter pathways connecting frontal and posterior brain regions in the GOALS group, $p < .001$. In conclusion, this study is the first to our knowledge to report changes in functional neural networks known to subserve GDC in older adults after training and relate these changes to the integrity of underlying white matter tracts.

Dedications

This thesis is dedicated to my husband, Shafi, without whose support this thesis would not have been possible, and my parents who always told me to do what I loved.

Author Contributions

Areeba Adnan conceptualized and conducted the statistical analysis and prepared the manuscript under the supervision of Dr. Gary Turner. Participants were recruited and underwent the intervention at the University of California at Berkeley and were tested by Dr. Gary Turner and others under the research program of Dr. Mark D’Esposito.

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TABLE OF CONTENTS

List of Tables

List of Figures

List of Abbreviations

Abbreviation	Meaning
aIPL	Anterior inferior parietal lobe
ATR	Anterior thalamic radiations
Behav-PLS	Behavioural PLS
BET	Brain extraction tool
BHW	Brain health workshop
DAN	Dorsal attention network
DMN	Default mode network
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
FDT	FMRIB’s diffusion toolbox
FMRIB	Functional magnetic resonance imaging in the brain
FPCN	Fronto-parietal control network
FSL	FMRIB Software Library
GDC	Goal-directed cognition
GMT	Goal management training
GOALS	Goal-oriented attentional self-regulation training
IFOF	Inferior fronto-occipital fasciculus
LV	Latent variable
MFG	Middle frontal gyri
PFC	Prefrontal cortex
PLS	Partial least squares
PPA	Parahippocampal place area
ROI	Region of interest
SE	Standard error
SLF	Superior longitudinal fasciculus
TBSS	Tract-based spatial statistics

Introduction

Functioning in real world contexts requires us to engage in goal-directed cognition (GDC), which is dependent on our ability to attend to relevant stimuli while ignoring distracting stimuli. At the level of the brain, this phenomenon, known as top-down modulation, operates both by enhancing and suppressing the neural representations for the respective stimuli within the environment and allows us to engage flexibly with the range of sensory streams available in our everyday lives (Gazzaley et al., 2005). When presented with task-irrelevant, or distracting, visual stimuli, it is now well understood that neural representations for these stimuli are suppressed within the stimulus selective visual cortices (Gazzaley et al., 2005; Chadick & Gazzaley., 2011). Older adults, however demonstrate a compromised ability to attend to relevant stimuli in the presence of irrelevant stimuli (de Fockert et al., 2009; Haring et al., 2013; Mager et al., 2007; Schmitz et al., 2010), as measured behaviorally. Distractibility in older adults has been correlated with a selective inability to suppress the neural representations of distracting stimuli, although enhancement of relevant stimulus representations appears to be maintained (Gazzaley et al., 2005; Gazzaley et al., 2008).

This top down modulation of neural response, which allows us to engage in GDC, is known to emerge from dynamic patterns of regional co-activation and internetwork coupling (McIntosh, 2000). Top-down modulation of visual representations has been associated with activity in the dorsal attention network (DAN), consisting of the dorsolateral prefrontal cortex (PFC), frontal eye fields, inferior precentral sulcus, superior occipital gyrus, middle temporal motion complex and superior parietal lobule (Corbetta & Shulman, 2002; Fox et al., 2005), interacting closely with the sensory cortices (Corbetta and Shulman, 2002; Kastner and Ungerleider, 2000). In the presence of relevant stimuli, regions of the DAN exert a biasing influence on the sensory cortices to allow for enhancement of these task relevant stimuli representations (Gazzaley et al., 2005). The fronto-parietal control network (FPCN), comprising the lateral PFC, precuneus, anterior inferior parietal lobe, medial superior PFC and the anterior insula (Vincent et al., 2008), allows for flexible coupling between networks to facilitate successful GDC (Spreng et al., 2010, 2013). Specifically, the FPCN has been shown to be involved in dynamic functional coupling between the default mode network (DMN), involved in internally directed cognition, and the DAN. This dynamic networking coupling between networks has been associated with enhanced goal-directed cognition (Spreng et al., 2010, 2013). The FPCN has also been implicated in a wide range of cognitive control tasks and is closely linked to GDC (Niendam et al., 2012; Spreng et al., 2010, 2013; Vincent et al., 2008; Braver et al., 2009). Critically, both the DAN and FPCN have been shown to undergo changes across the adult lifespan; particularly, reductions in overall within-network functional connectivity (FPCN: e.g. Rieckmann et al., 2011; DAN: e.g. Andrews-Hanna et al., 2007).

Reduced efficiency in the DAN and FPCN in older adults can also arise due to a loss in integrity of the underlying structural architecture, specifically white matter tracts that provide pathways for efficient functional connectivity (Moseley et al., 2002). This disconnection of task-relevant cortical circuits as a result of decreased white matter integrity has been proposed as a general mechanism of age-related cognitive decline (for a detailed review see Bennett & Madden, 2013). Indeed, age has been shown to have the largest negative effect on association fibers that comprise cortical-cortical connections and provide long-range connectivity between regions to form functional networks compared to projection fibers that connect cortical and subcortical regions (e.g., corticospinal tract) and callosal fibers that connect the left and right hemispheres of the brain (Stadlbauer et al., 2008). The superior longitudinal fasciculus (SLF) is one such association fiber bundle and provides anatomical connections between the frontal, occipital, parietal and temporal lobes (Makris et al., 2005). Declines in the integrity of the SLF have been correlated with overall executive function declines in older adults (Sasson et al., 2012; Sasson et al., 2013). Another critical association fiber bundle connecting the frontal lobes with the posterior parietal and temporal lobes is the inferior fronto-occipital fasciculus (IFOF) (Kier et al., 2004). Structural integrity within this tract is related to complex visuospatial tasks in older adults (Voineskos et al., 2012). Tasks requiring spatial and visual attention coupled with executive functions appear to be mediated by the IFOF's connection to anterior frontal regions, which may allow for better organization and planning of these complex tasks (Voineskos et al., 2012). In addition to these aforementioned association fiber bundles that decline in integrity with age, thalamo-cortical projections have also been shown similar age-related losses (Hughes et al., 2012). Specifically, the anterior thalamic radiations (ATR), which play a critical role in the coordination of information flow from various sensory regions to frontal regions via the anterior thalamus, show greater age-related decline than other thalamic projections to other cortical regions (Hughes et al., 2012). The ATR, given their unique role in information flow, play a critical role in executive function and working memory (Charlton et al., 2010). Given the importance of white matter tracts in mediating effective executive function and giving rise to GDC, examining their structural integrity could provide a window into understanding the role of structural connectivity on network performance and, ultimately, shed further light on the neural mechanisms underlying age-related cognitive decline. However, while evidence supporting the role of integrity of white matter tracts in the general domain of executive function is abundant (Voineskos et al., 2012; Davis et al., 2009, Sepulcre et al., 2009, Nestor et al., 2007, Hamilton et al., 2008; Kantarci et al., 2011, Sasson et al., 2013), there is a dearth of literature examining this question with respect to GDC in older adults.

Given the impact of compromised GDC in everyday living, targeted interventions aimed at improving GDC by altering activity within large-scale brain networks represents a novel approach to enhancing complex cognition in older adulthood. Currently, evidence for effective behavioral interventions to enhance executive control in older adults is limited (Anguera et al., 2013, Milewski-Lopez et al., 2014, Nyberg et al., 2003, Ball et al., 2002), with most training protocols demonstrating poor efficacy and limited transfer to real-world functional outcomes. Goal Management Training (GMT) is one of the few published theory-driven approaches targeted at improving executive control (Turner & Levine, 2004). Specifically, GMT is aimed at improving cognitive control functions important for GDC with an emphasis on transfer to real-world functional improvements. Clinically, this intervention has been associated with improvements in GDC in older adults (Levine et al., 2007,VanHooren et al., 2007) and other populations including those with mixed etiologies and documented problem solving deficits (VonCramon et al., 1991), traumatic brain injury (Levine et al., 2000; Fish et al., 2007) and in case studies of patients with focal cerebellar damage (Schweizer et al., 2008) and encephalitis (Levine et al., 2000). A modification of the original GMT protocol (GOALS training), with an emphasis on mindfulness-based attention regulation strategies applied to daily life situations and complex functional tasks (described in detail in Novakovic-Agopian et al., 2011), has been demonstrated to increase GDC in individuals with acquired brain injury (Chen et al., 2012; Novakovic-Agopian et al., 2011). This evidence is promising for the use of GMT-related training approaches to improve GDC in older adults. However, training response is likely dependent on functional and structural integrity within frontally mediated brain networks such as the FPCN and DAN. In sum, declines in GDC are commonly observed in normal aging and these changes appear to be dependent on functional connectivity within FPCN and DAN. This suggests that interventions aimed at improving large-scale network engagement may offer a novel approach to enhancing GDC in older adults and for better understanding the neural mechanisms subserving training-related changes.

The overall objective of this study was to determine the underlying neural patterns of functional and structural connectivity that support training-related improvements in GDC in older adults. Specifically, we aimed to investigate these underlying neural patterns using a previously reported training intervention that has demonstrated efficacy for improving GDC in acquired brain injury (Novakovic-Agopian et al., 2011; Chen et al., 2011). We hypothesized that training aimed at improving GDC in older adults would lead to increased functional engagement within the FPCN and DAN. To test this hypothesis in the current study, healthy older adults underwent functional magnetic resonance imaging (fMRI) before and after the aforementioned intervention. Whole-brain patterns of functional connectivity were examined to investigate whether these changes occur in the DAN and FPCN, large-scale brain networks that have previously been implicated in GDC. Our second hypothesis was that patterns of change in neural networks observed after training would be associated with the integrity of underlying white matter structure, specifically long-range white matter tracts that provide structural connectivity between distant brain regions comprising these core networks. To test this hypothesis, we examined the relationship between functional connectivity changes post-training and the integrity of white matter within the SLF, IFOF and ATR using diffusion tensor imaging (DTI).

Methods

Participants

34 healthy older adults, ages 60-85 years, participated in this study after providing written informed consent in accordance with a protocol approved by the

University of California, Berkeley Committee for the Protection of Human Subjects. 30 of these participants (age range: 60-80 years, 18 females) completed the pre- and post- intervention assessments and were included in the current study. All participants were right handed and had normal, or corrected-to-normal, vision. Participants were prescreened for the presence of medical, neurological, or psychiatric illness, and the use of prescribed drugs with known effects on cognition. Al participants were neuropsychologically normal but had self-reported concentration problems and/or distractibility identified at in-take interview. Table 1 provides a summary of domain-specific neuropsychological performance; Table A1 in Appendix A provides a detailed summary of the domain specific scores

Table 1

Average z scores for domain specific scores based on standardized neuropsychological tests for goal-oriented attentional self-regulation training group (GOALS) and brain health workshop group (BHW). Z scores were calculated using normative data from standardized measures where accessible for each subtest. Domain z scores were calculated by averaging the z scores for component tests for each domain. The following neuropsychological tests were used to calculate each domain z score: Executive control domain included the Consonant Trigrams, Letter Number Sequencing, DKEFS Color Word Interference, DKEFS Design Fluency, DKEFS Verbal Fluency, Trail Making Test B, DKEFS Tower Test and Mazes Test; Learning and Memory domain includes Hooper Visual Learning Test and Brief Visuospatial Memory test; Speed of processing domain includes Digit Span and Trail Making Test A; Motor Functioning includes Grooved Pegboard Test.

Domain	GOALS	BHW
Executive Control Function	0.49	0.42
Learning and Memory	-0.24	-0.16
Speed of Processing	-0.11	0.16
Motor Functioning	0.08	0.005

Note: DKEFS = Delis-Kaplan Executive Function System

Interventions

Two intervention conditions were employed: (i) training in goal-oriented attentional self-regulation (GOALS training) and (ii) a comparison educational activity (brain health workshop – BHW, a psycho-educational program). The GOALS training protocol was based on a goal-management training intervention (Robertson, 1996; Levine et al., 2000, 2007), as well as principles highlighted in other attention, mindfulness and problem-solving interventions (D’Zurilla and Goldfried, 1971; Kabat-Zinn, 1990; VonCramon et al., 1991; Rath et al., 2003; Nezu et al., 2007). The GOALS training protocol involved 10 two-hour sessions of group-based training, three individual one-hour training sessions and 20 hours of home practice over five weeks. Training was conducted in a small group format with three to five patients and two instructors per group. To ensure consistency of administration, intervention manuals were written for instructors and participants. Experienced clinicians (occupational therapists, neuropsychologist) were trained in administering both interventions and were supervised by registered neuropsychologists.

Mindfulness-based attention regulation training was emphasized in the first half of the GOALS training intervention, and goal management strategies applied to participant-defined goals were emphasized in the second half. Thus, initial group sessions focused on incorporating strategies for reducing distractibility, emphasizing principles of applied mindfulness to redirect cognitive processes towards goal-relevant activities in the context of increasing levels of distraction. Strategies included identifying the primary goal, identifying information as either relevant or non-relevant, and working to selectively maintain relevant information while letting go of non-relevant information. Introductory training via in-class exercises began with a brief applied mindfulness exercise as a first step in refocusing on tasks at hand. This was applied to progressively more challenging situations including maintaining increasing amounts of information in mind during distractions. These exercises were supported by homework assignments including daily practice with mindfulness. Homework then progressively emphasized application of these skills to challenging situations in each individual’s daily life. To assist application in daily life situations, participants were trained in applying a single phrase meta-cognitive strategy (‘STOP-RELAX-REFOCUS’) to stop activity when distracted and/or overwhelmed, relax and then refocus attention on the current, primary goal.

The second phase of the goals training protocol emphasized learning strategies for accomplishing individually salient, self-generated complex goals. In order to emphasize active application of these strategies, participants were asked to identify feasible and realistic functional goals as individual projects (e.g. planning a meal, learning to use an organizer and follow a schedule) and group projects (e.g. planning a group outing or presentation), and were then trained to apply attention-regulation and goal-management strategies on the functional task(s) of their choice.

In the alternate, control intervention, brain health workshop *(*BHW*)*, a comparison educational activity was utilized for five weeks. This involved didactic educational instruction regarding brain changes in aging (causes, symptoms and effects). Sessions were administered in the same schedule and were of equivalent duration as GOALS and were administered in the same groups by the same trainers. BHW served as a control condition for the GOALS training (active intervention condition) and was carefully matched for overall training duration, time spent on training and therapist interaction.

Study Design

Participants were randomly assigned to either the goals training group (GOALS) or the alternate brain health educational workshop group (BHW). Both groups completed a baseline fMRI and structural MRI assessment before they began the intervention (pre) and at the end of the five-week training program (post). Of the 34 participants, 30 completed both pre- and post- intervention assessments and were eligible to be included in the current analysis. Of these, 15 participants were randomly assigned to the GOALS group, and 15 to the BHW group (Figure 1).

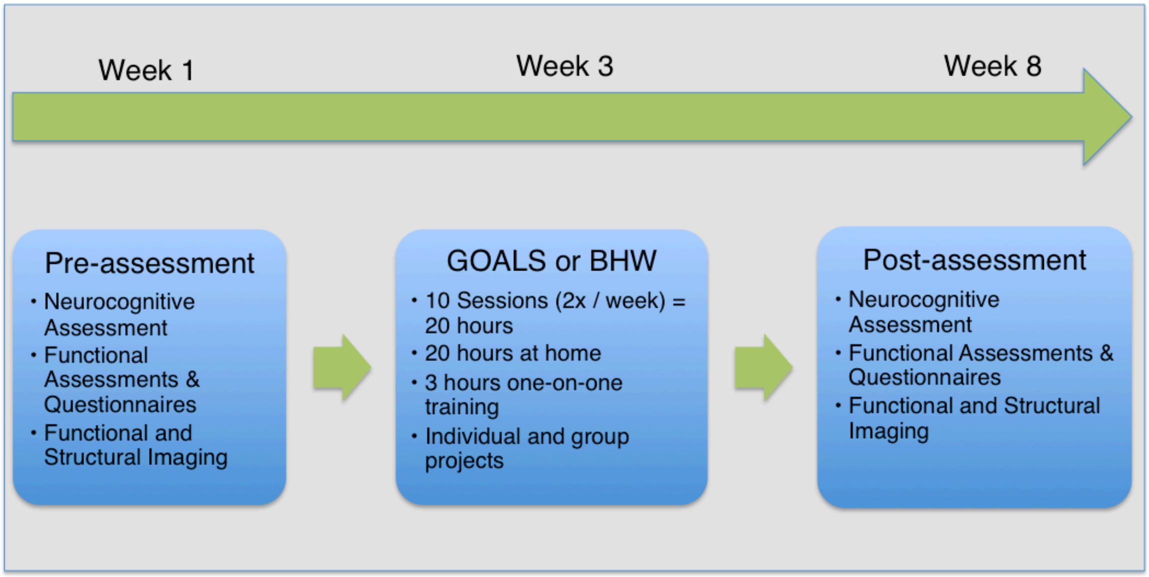

*Figure 1***.** A schematic representation of the employed study design (GOALS = goal-oriented attentional self-regulation training, BHW = brain health workshop).

Of these, 13 in the GOALS group (three males) and 12 in the BHW (six males) had artifact-free fMRI data. All five participants excluded from the two groups had artifacts (motion and scanner artifacts) upon visual inspection present during the fMRI acquisition that could not be resolved through our preprocessing methods. There were no significant differences between the two groups in age (GOALS mean = 65.9 years, SD = 5.20 years; BHW mean = 69.36 years, SD = 5.20 years), *t* (25) = -1.64, *p* = .72 and years of education (GOALS mean = 17.30 years, SD = 1.83 years; BHW mean = 17.09 years, SD = 2.34 years), *t* (25) = .23 *p* = .99

Functional MRI cognitive task design

In all task conditions, participants viewed a series of images composed of two categories (faces and scenes) interleaved in a pseudo-randomized order with jittered timing (three, five or seven seconds apart) (Figure. 2).

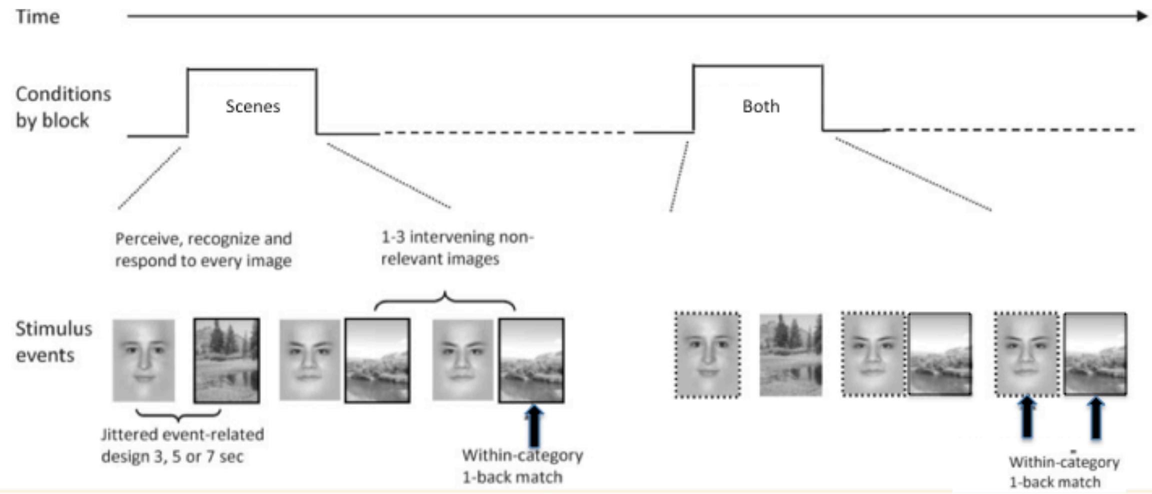

Figure 2. Selective attention task performed during fMRI acquisition. Participants viewed a series of images composed of two categories (faces and scenes). In two selective attention conditions (scenes, both) participants were instructed to selectively attend and hold images from one category. In the scenes condition, scenes were task relevant, while faces were task irrelevant. In the both condition, both scenes and faces were task relevant and had to be kept in mind simultaneously. Solid and dashed lines are used only for the purposes of illustrating task relevance, while only the grey-scale images were used in the actual task.

Perceptual information was matched, but task demands differed in four attention conditions. The first condition (Categorize) served as a control condition where the face and scene stimuli were presented and participants categorized the stimuli into faces or scenes. In the selective attention condition (Scenes) participants were instructed to selectively attend and hold in mind images from one category. Task performance required recognition of one-back matches within the relevant category, with button-press responses to every image indicating whether the image was a ‘match’ or ‘non-match’ to the preceding image from the relevant category. Therefore, in order to successfully complete the task, participants had to perceive and recognize all images but selectively maintain only relevant images in working memory in the face of potential distraction from non-relevant images. In the “Both” condition, participants were asked to attend and hold in mind the most recent image from both stimulus streams. For the purpose of our study, in our task-based analyses we only focused on comparing two conditions for both groups: Categorize and Scenes. For our secondary analyses we included all three conditions: Categorize, Scenes and Both.

In each block, 20 images (10 faces and 10 scenes) were presented sequentially. Jittering and image category orders were balanced across condition blocks and counterbalanced across participants. Five blocks of each experimental condition were presented during the session, resulting in a sample of 100 stimulus events per condition (total sample of 400 stimulus events). Condition orders within runs were counter-balanced over the course of the scanning session. Four alternate sets of stimuli were generated for use in multiple sessions, and set order was permuted across subjects.

Data acquisition and analysis

FMRI

Imaging was performed using a 3-T Siemens Magnetom Trio whole-body magnetic resonance scanner with a transmit-receive 12-channel quadrature birdcage head coil at the Berkeley Neuroimaging Centre. For each task block, 114 whole-brain T2-weighted echo planar images were acquired (slice thickness, 5mm; 0.5mm skip; 18 slices; repetition time = 1000 ms; echo time = 27 ms; flip angle = 62; matrix, 64 x 64 axial field of view). A T1-weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE) and a T2 –weighted fluid-attenuated inversion recovery (FLAIR) sequence was acquired for each subject for characterization of structural anatomy.

Functional data were preprocessed with Analysis of Functional Neuroimages (AFNI; Cox, 1996). Outliers were removed using L1 regression, corrected for slice timing differences, and head motion across the run by co-registering to the 8th TR of the first run in each session. The data was next co-registered into MNI space (Saad et al. 2009) and spatially smoothed within a whole-brain mask using a Gaussian kernel with a full width at half maximum of 6 mm and resampled to a voxel size of $3mm^3$. The pre- and post- runs were concatenated for both GOALS and BHW for each participant in preparation for a multivariate analysis, using Partial Least Squares (PLS; Krishnan et al., 2012).

Whole-brain fMRI analyses were conducted using PLS (Krishnan et al., 2012), a multivariate analysis technique that identifies whole-brain patterns of activity related to the experimental design (task-PLS). This method is similar to principal component analysis, in that it identifies a set of principal components or ‘latent variables’ (LVs) that optimally capture the covariance between two sets of measurements. In task-PLS, each LV identifies a pattern of brain regions that, as a whole, maximally relate to task contrasts also identified by that LV. Each brain voxel has a weight, known as a salience, which indicates how strongly that voxel contributes to the LV overall. The significance of each LV as a whole was determined using a permutation test (McIntosh et al., 1996), using 500 permutations. In addition, the reliability of each voxel’s contribution to a particular LV was tested by submitting all saliences to a bootstrap estimation of the standard errors (SEs; Efron, 1981), using 100 bootstraps. Peak voxels with a salience/SE ratio 3.0 ($p < .001$) were considered to be reliable. Clusters containing at least 10 reliable contiguous voxels were extracted, with a local maximum defined as the voxel with a salience/SE ratio higher than any other voxel in a 2 cm cube centered on that voxel (the minimum distance between peaks was 10 mm). A 10-voxel cluster-size threshold was selected as a conservative threshold without excluding, significant activations in smaller brain regions where the hemodynamic response is more variable across individuals (e.g., Garrett et al., 2011; Grady et al., 2010; Protzner & McIntosh, 2007). Coordinates of these locations are reported in MNI space. Finally, to obtain summary measures of each participant’s expression of each LV pattern, we calculated ‘brain scores’ by multiplying each voxel’s salience by the BOLD signal in the voxel, and summing over all brain voxels for each participant in each condition. These brain scores were then mean-centered (using the grand mean across all participants) and confidence intervals (95%) for the mean brain scores in each condition were calculated from the bootstrap. Significant differences in activity between conditions (within a group) and between groups (within a given condition) were determined by non-overlapping confidence intervals.

To examine the effects of intervention on GDC in older adults, block design task-PLS was performed on two task conditions (Scenes and Categorize) for the GOALS and BHW group. We were specifically interested in these two conditions as they are equivalent in their perceptual demand but differ only in task demands, where the Scenes condition required GDC with the goal of attending to scenes only, while ignoring face stimuli. This analysis identified a pattern of brain regions (LV1, see results, Table 3) with increased activation specific to the GOALS group in the Scenes condition.

DTI

DTI data were acquired for nine of 13 participants in the GOALS group and 11 of 12 participants in the BHW group along 30 non-collinear diffusion-encoding, directions, 50 slices, TR = 6400 ms, TE = 87 ms, FOV: 256 × 256 mm^2, 128 × 128 matrix, 2.2 × 2.2 mm^2 in-plane resolution, 2 mm thick axial slices.

The DTI data was preprocessed using the Functional Magnetic Resonance Imaging in the Brain (FMRIB) Software Library (FSL) (Smith et al., 2004; Woolrich et al., 2009). First, the Digital Imaging and Communications in Medicine files of each DTI acquisition were converted to a single multivolume 4D format in the MRIcron software (Rorden et al., 2007). Next, they were corrected for effect of head movement and eddy current distortion using the eddy correct tool in FMRIB's Diffusion Toolbox (FDT), a part of FSL. This tool conducts an affine registration of each individual volume to a specified b0 volume. Brain tissue was segmented using the Brain Extraction Tool (BET) (Smith, 2002), a part of FSL Smith et al., 2004; Woolrich et al., 2009) and a brain mask was created at a specified threshold. The FDT tool was then used in FSL to fit a diffusion tensor model at each voxel in the brain-extracted images created from the BET tool and created fractional anisotropy (FA) maps for each participants. Voxelwise statistical analysis of the FA data was carried out using Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006), part of FSL (Smith et al., 2004). Region of interest (ROI) masks for the SLF, IFOF and ATR were created using the JHU-ICBM-DTI-81 Atlas based on their previously discussed role in executive function (Mori et al., 2008) (Figure 3.).

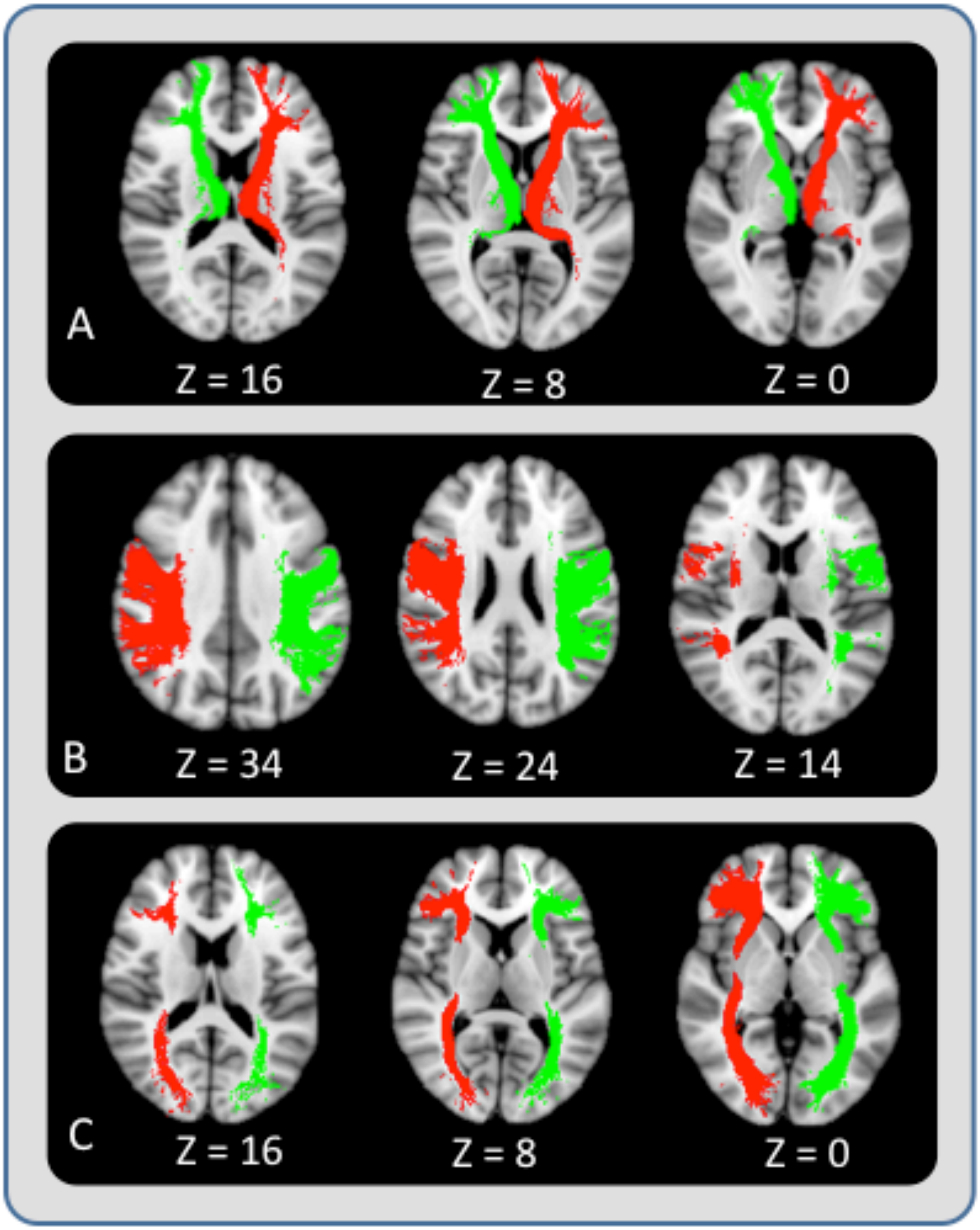

Figure 3. White matter tracts ROI's used to calculate overall FA for each tract. Panel A visualizes the left (red) and right (green) anterior thalamic radiations (ATR): panel B visualizes the left and right superior longitudinal fasciculus (SLF) and panel C visualizes the inferior fronto-occipital fasciculus (IFOF). These ROI masks were then used to extract FA values for each participant using the TBSS derived FA skeleton image. We averaged the FA values for the left and right tracts (ATR, SLF and IFOF) to give one FA value to represent the overall metric of structural integrity for that tract.

Using a behavioral PLS (behav-PLS) model, which allows us to look at the correlation between our behavior of interest and the functional covariance in brain regions, we were interested in examining the functional-structural relationships for the GOALS and BHW group pre- and post- intervention in the conditions of interest (Scenes and Categorize). Behav-PLS allows us to examine the relation between behavioral measures, specifically the FA for the ATR, SLF and IFOF, and the observed fMRI signal in these conditions.

The average FA values for each ROI were used as a behavioral measure, which we entered into a behav-PLS model. The method employed in behav-PLS is the same as task-PLS; however, the correlation between the behavioral measure (FA) and overall fMRI signal covariance is computed across all subjects, within each condition. The results are the within-condition brain-behavior correlations (McIntosh, Chau & Protzner, 2004). Using this model, we entered FA values for each ROI and examined the brain-behavior relationships for all conditions (Categorize, Scenes, Both) in both groups, pre- and post-intervention. Our hypothesis was that the underlying average structural integrity of these global white matter tracts, which are involved in selective and non-selective attention, would be positively correlated to neural network engagement across all conditions after GOALS training which require both selective and non selective attention; hence even though our task-PLS analysis was focused on looking at differences between the Categorize and Scenes conditions, for this analysis, all three conditions were included for all participants who had completed the task and had DTI data.

Conjunction Analysis

Finally, we were also interested in identifying whether the brain regions that showed changes in activation after the GOALS training overlap with those that show greatest positive correlation with the underlying integrity of the white matter tracts. To this end, we conducted a conjunction analysis that combined the significant LV results (LV 1 for both the task-PLS and behav-PLS) from both of the aforementioned multivariate analysis. We entered both of these LV's, thresholded at a bootstrap ratio of ±3, cluster uncorrected.

The conjunction was formulated as conjunction null hypothesis (Friston et al., 2005; Nichols et al., 2005), and should therefore yield activations that are significantly present in both original contrasts of the conjunction (also referred to as a minimum statistic). That is, a conjunction represents a logical "and" requiring both LV's to be separately significant for the conjunction to be significant.

Results

Behavioral Results

Mean reaction time (RT) for hits and overall percent accuracy for the Categorize, Scenes and Both condition were submitted to a mixed analysis of variance (ANOVA), with group (GOALS, BHW) as a between-subject factor and time (pre- and post-) as a within-subject factor. We also conducted post-hoc paired sample t-tests for both RT and accuracy where significant main effects were observed. Tables 2 and 3 provide mean and standard deviations for RT and accuracy. Figures 4 and 5 are a graphical representation of these and denote significant effects where found.

Categorize

There was no significant main effect of time (pre- to post- interventions), *F* (1, 22) = .65, *p* = .43, η_p^2 = .03 and group (GOALS and BHW), *F* (1,22) = .89, *p* = .36,η_p^2= .04 for mean RT. We also found no significant interaction between group and time for mean RT, *F* (1, 22) = .62, *p* = .44, η_p^2 = .03.

There was no significant main effect of time, *F* (1, 22) = .68, *p* = .42, η_p^2 = .03 and group, *F* (1,22) = .32, *p* = .58,η_p^2= .14 for mean accuracy. There was no significant interaction between group and time for mean accuracy, *F* (1, 22) = .21, *p* = .16, η_p^2 = .09.

Attend to Scenes (Scenes condition; Ignore faces)

There was no significant main effect of time, *F* (1, 22) = 2, *p* = .17, η_p^2 = .08 and group, *F* (1, 22) = .00, p = .998, η_p^2= .00 for mean RT. We also found no significant interaction between group and time for mean RT, *F* (1, 22) = .69, *p* = .41, η_p^2 = .03.

Similarly, for accuracy, no significant main effect of time, *F* (1, 22) = .22, *p* = .65, η_p^2 = .01 and group, *F* (1, 22) = 1.26, *p* = .27, η_p^2= .05 was observed. There was no significant interaction between group and time for mean accuracy, *F* (1, 22) = .41, *p* = .531, η_p^2 = .02.

Attend to Both Scenes and Faces

There was a significant main effect of time observed for mean RT, *F* (1, 22) = 19.52, *p* < .001, η_p^2 = .47. There was no significant main effect of group, *F*

(1, 22) = .81, p = .38, η_p^2 = .04 for mean RT and no significant interaction between group and time for mean RT, *F* (1, 22) = 1.06, *p* = .315, η_p^2 = .05.

For accuracy, we observed no significant main effect of time, *F* (1, 22) = .66, *p* = .43, η_p^2 = .01 and group, *F* (1, 22) = .03, *p* = .87, η_p^2 = .001. We also found no significant interaction between group and time for accuracy, *F* (1, 22) = 1.23, *p* = .27, η_p^2 = .06.

Further post-hoc paired sample t-tests for the GOALS group showed a significant reduction for average RT for the Both condition from pre- to post-intervention, *t* (12) = 3.50, *p* = .02. The BHW group also showed similar reductions in average RT for the Both condition from pre- to post- intervention, *t* (10) = 2.63, *p* = .006.

Table 2

Mean (SD) of mean reaction time on the task by condition for goal-oriented attentional self-regulation training group (GOALS) and brain health workshop group (BHW)].

	Categorize		**Select Scenes**		**Both**	
	Pre	Post	Pre	Post	Pre	Post
GOALS	641.67 (83.05)	641.83 (87.67)	735.22 (105.93)	699.55 (90.72)	958.17 (37.68)	904.16 (41.37)
BHW	604.70 (66.49)	621.92 (70.83)	722.10 (107.75)	712.85 (98.64)	1020.73 (134.36)	933.94 (95.14)

Table 3

Mean (SD) of accuracy on the task by condition for goal-oriented attentional self-regulation training group (GOALS) and brain health workshop group (BHW)].

	Categorize		**Select Scenes**		**Both**	
	Pre	Post	Pre	Post	Pre	Post
GOALS	97.77 (2.68)	96.77 (3.42)	94.08 (5.02)	94.92 (6.65)	86.46 (7.51)	85.77 (9.01)
BHW	97.63 (1.43)	97.91 (1.22)	95.27 (3.00)	95.45 (2.94)	83.55 (9.42)	87.73 (8.31)

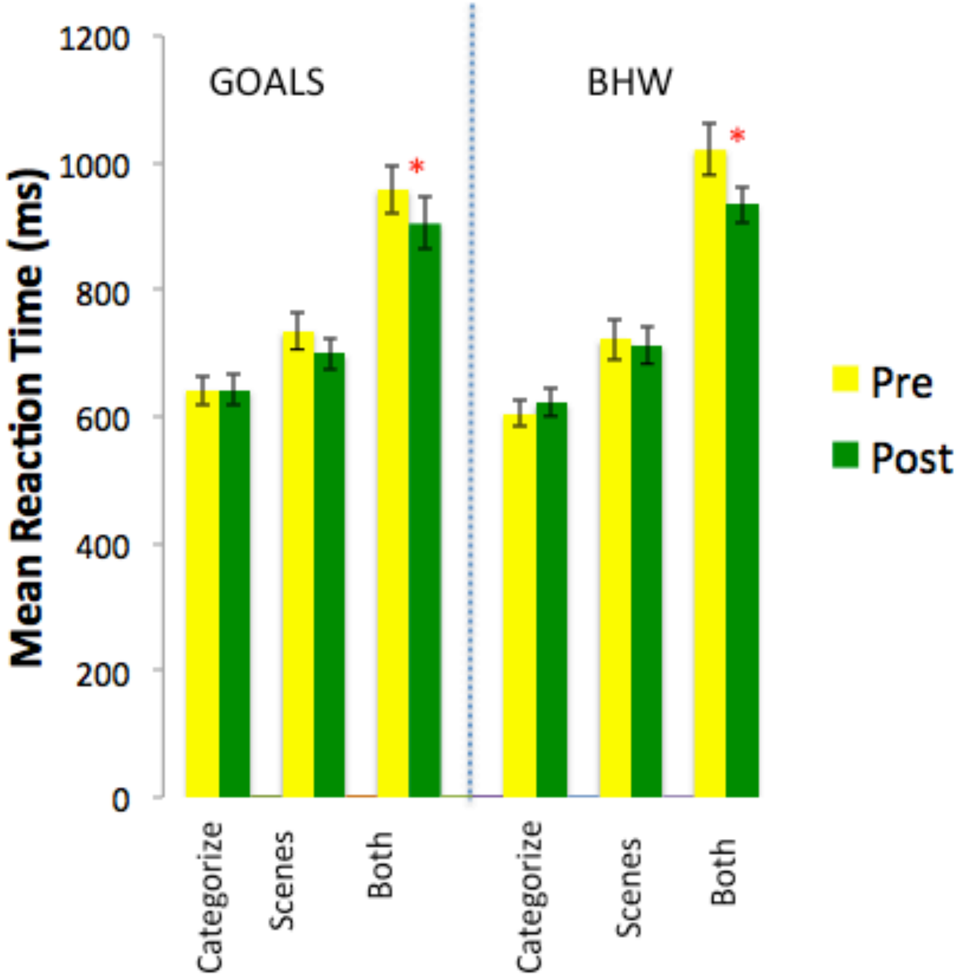

Figure 4. Mean reaction time as a function of condition and time displayed for each group [goal-oriented attentional self-regulation training group (GOALS) and brain health workshop group (BHW)]. Error bars represent the standard errors of the mean. Significant differences between pre- and post- intervention within group are denoted by asterisk.

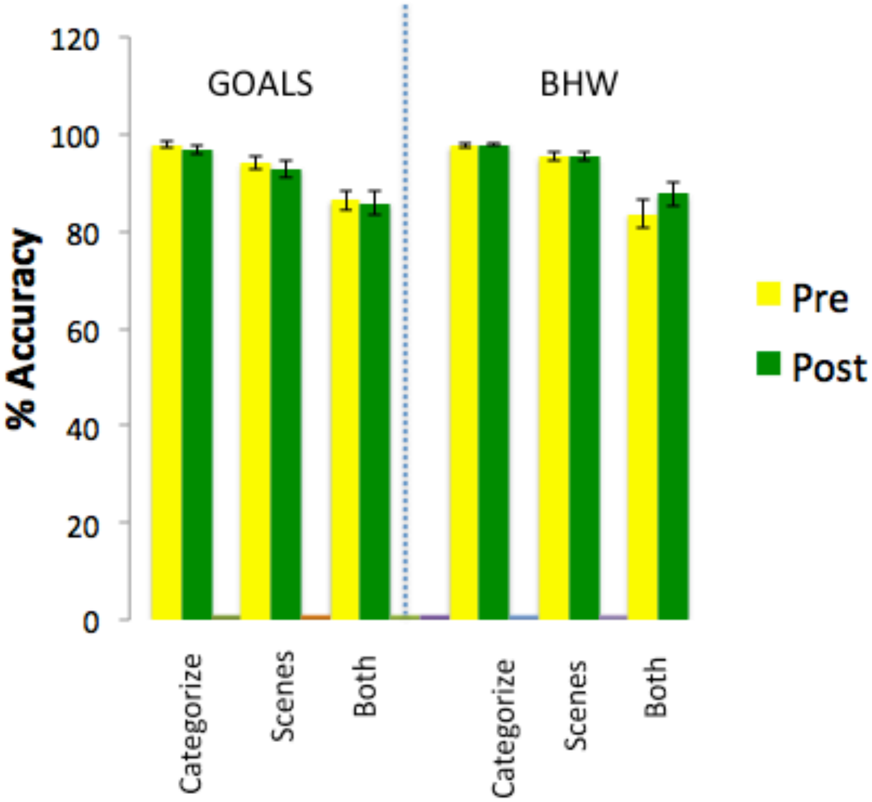

Figure 5. Percent accuracy as a function of condition and time displayed for each group [goal-oriented attentional self-regulation training group (GOALS) and brain health workshop group (BHW)]. Error bars represent the standard errors of the mean. Significant differences between pre- and post- intervention are denoted by asterisk.

fMRI: Whole-brain analyses

Task-based Analyses.

The first LV from the task-PLS analysis (p < .001) accounted for 35.53% of the covariance in the data and differentiated the Categorize and Scenes condition by pre- and post- intervention for both GOALS and BHW (Figure 6, Table 4).

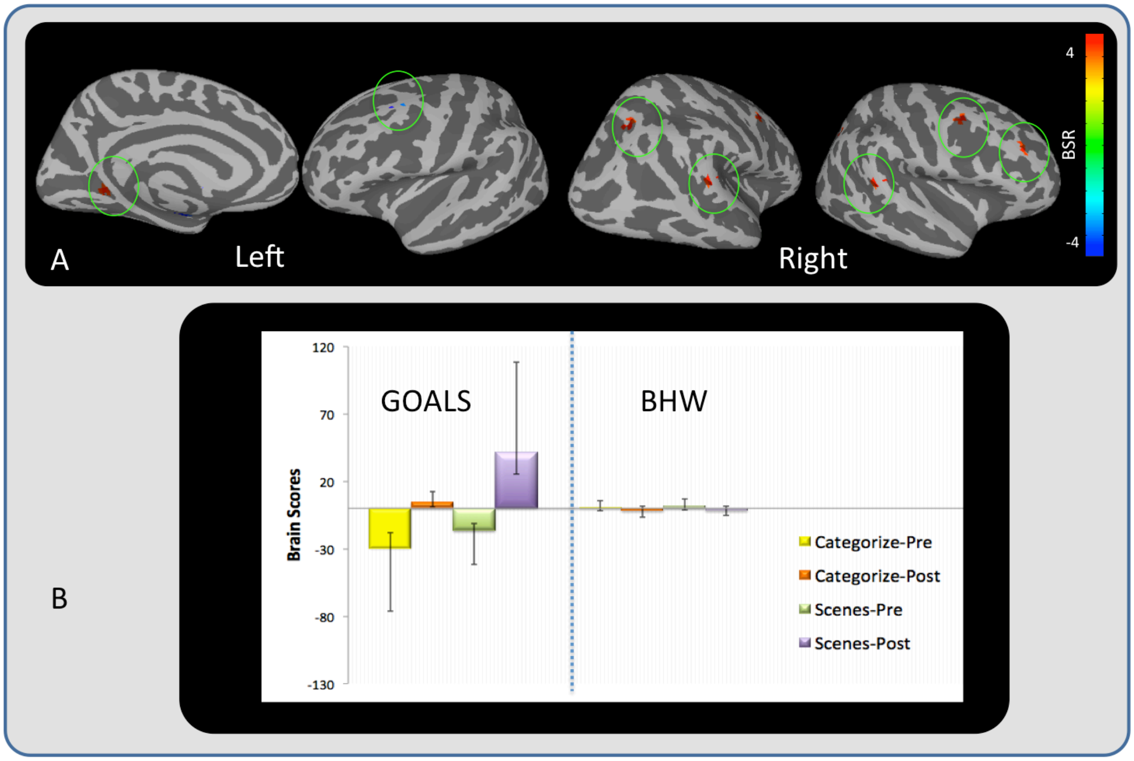

Figure 6. LV1 from the task-PS analysis contrasting modulations of activity across Categorize and Select Scenes in both groups pre- and post- intervention, shown on a cortical surface map. The pattern identified in the top panel shows area with greater activity for the goal-oriented attentional self-regulation training group (GOALS) specific to the select scenes condition post-intervention (shown in warm colors and associated with positive brain scores), cluster size *k*=10. No activation patterns related to any of the conditions pre-intervention for the GOALS group survived the cluster correction. The graph in the second panel shows the mean-centered mean brain scores for both groups on this LV (error bars represent the 95% confidence intervals). A bootstrap ratio threshold of 3.0 was used to form the brain image in the top panel.

Table 4

Brain areas showing greater activity in the goal-oriented attentional self-regulation training group (GOALS) post-intervention for the scenes condition (LV1)

Region	Hem	*X* (mm)	*Y* (mm)	*Z* (mm)	BSR
Parahippocampal Gyrus	L	-18	-51	0	3.83
Superior Temporal Gyrus	R	63	-36	12	4.48
Dorsolateral PFC	R	39	39	27	3.69
Middle Frontal Gyrus (BA 6)	R	36	9	45	5.77
Anterior IPL	R	30	-60	39	4.87
Middle Frontal Gyrus (BA 6)	L	139	21	54	-5.11

Note: MNI coordinates of cluster maxima showing the patterns of activity depicted in figure 5; *Hem*=hemisphere; *R*=right; *L*=left; *BSR*=bootstrap ratio; *PFC*= prefrontal cortex; IPL= inferior parietal lobe

As can be seen in Figure 6B, this LV represents a significant difference in the pattern of activation between the GOALS and BHW group. Furthermore, GOALS training appears to be more strongly associated with this pattern more than the BHW group (as indicated by non-overlapping confidence intervals). Within the GOALS group there is a difference in brain activation patterns from pre- to post- intervention that is specific to the selective attention condition, Scenes (as indicated by the confidence intervals crossing the x-axis for the post-Categorize condition). This LV provides evidence for increased activation in brain regions for the GOALS group, occurring after the training, specific to the selective attention condition – i.e. the target of the GOALS training program.

Behavioral PLS (Structural and functional interactions)

There were no significant differences between the FA for the 1) ATR between the BHW (mean = .44, SD = .018) and GOALS group (mean = .45, SD = .018), *t* (20), *p* = .33; 2) SLF between the BHW (mean = .43, SD = .019) and GOALS group (mean = .43, SD = .018), *t* (20), *p* = .81 and 3) IFOF between the BHW (mean = .44, SD = .017) and GOALS group (mean = .43, SD = .018), *t* (20), *p* = .7.

The first LV (*p* < .001) from our behav-PLS, with average baseline FA of the SLF, ATR and IFOF as the correlate of functional brain response, accounted for 21.58% of the variance in the data and differentiated the Categorize, Scenes and Both condition by the GOALS and BHW group (Figure 8, Table5).

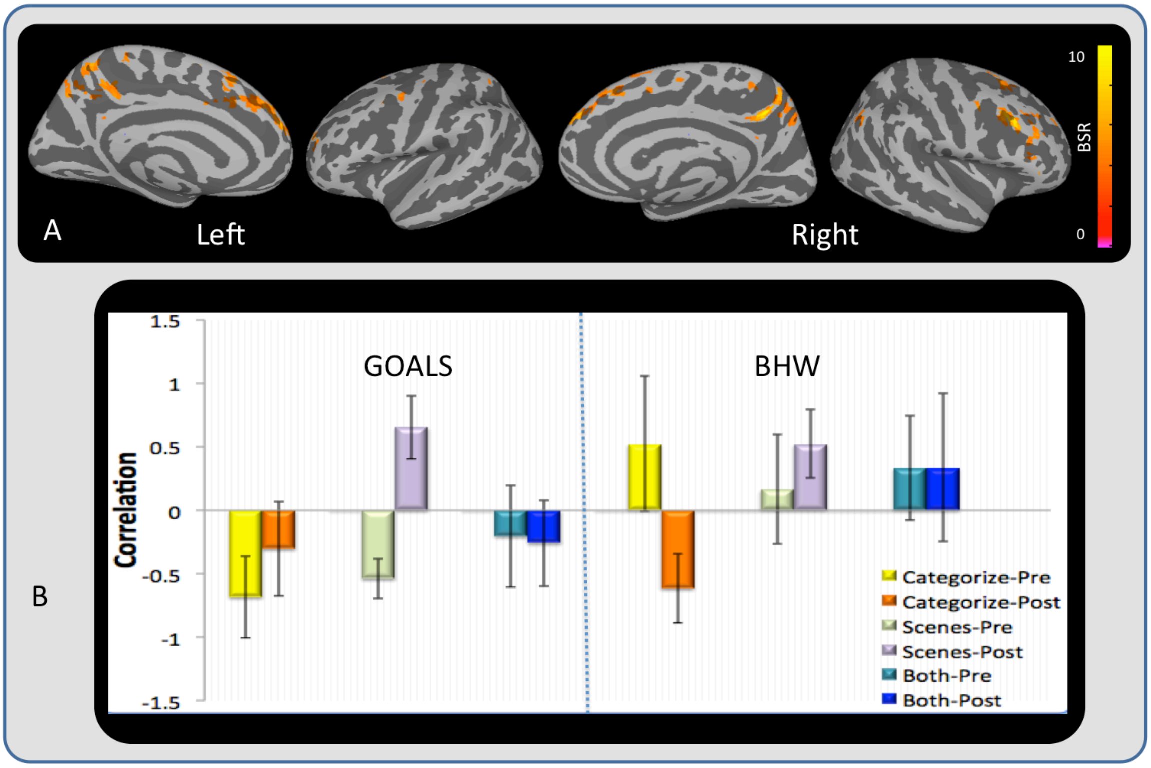

Figure 7. LV1 from the behav-PS analysis looking at the correlation between modulations of activity across Categorize, Scenes in both groups pre- and post-intervention and baseline average FA of ATR, SLF and IFOF, shown on a cortical surface map. The pattern identified in the top panels show areas where activation is positively correlated with the baseline FA of the three white matter tracts for the goal-oriented attentional self-regulation training group (GOALS) specific to the select scenes condition post-intervention (shown in warm colors and associated with positive brain scores), cluster size *k*=10. No activation patterns related to any of the conditions pre-intervention for the GOALS group survived the cluster correction. A bootstrap ratio threshold of 3.0 was used to form the brain image in the top panel. The graph in the bottom panel shows the correlations between the brain scores and FA for each tract for both groups in this LV (error bars represent the 95% confidence intervals).

Table 5.
Activation in brain areas during task positively correlated with average FA of the ATR, SLF and IFOF.

Region	Hem	*X* (mm)	*Y* (mm)	*Z* (mm)	BSR
Dorsolateral PFC	R	27	-48	36	7.98
Rostrolateral PFC	L	-21	66	9	5.55
Rostrolateral PFC	L	-24	51	18	5.42
Dorsal Medial PFC	L/R	0	51	24	10.87
Middle Frontal Gyrus BA 9	R	42	18	30	8.44
Precuneus	R	6	-45	45	8.78
IPL/Angular Gyrus	R	48	-63	39	4.90
Precentral Gyrus	L	-45	-3	51	5.30
Middle Frontal Gyrus BA 6	R	24	15	45	5.41
Middle Frontal Gyrus BA 6	L	-27	21	57	6.32
Middle Frontal Gyrus BA 6	R	27	12	60	6.89
Superior Parietal Lobe	L	-27	-69	57	5.72
Superior Parietal Lobe	R	30	-60	63	5.52
Supplementary motor cortex	R	0	6	60	7.27

Note: MNI coordinates of cluster maxima showing the patterns of activity depicted in figure 7; *Hem*=hemisphere; *R*=right; *L*=left; *BSR*=bootstrap ratio; *PFC*= prefrontal cortex; *IPL*= inferior parietal lobe

This LV reflected a common correlation of baseline FA with brain activation patterns for these conditions, specifically for the pre- and post- Scenes condition in the GOALS group (confidence intervals crossing the x-axis for Categorize and Both for GOALS; Figure 8B). While the confidence intervals were also non-overlapping for the pre- Categorize condition in GOALS and post-Categorize for BHW*,* there were no significant patterns of brain activation correlated negatively with baseline FA.

The spatiotemporal pattern for LV 1 shows distinct temporal fluctuations in correlation patterns (Figure 8A). Only positive saliences survived our bootstrap ratio threshold of ±3, k =10 voxels, corresponding to patterns of activation most related to post-intervention performance in the GOALS group on the Scenes condition that are highly correlated with the average FA of the white matter tracts. Increased activation in the lateral frontal and parietal cortices (Table 5) was observed in the Scenes conditions, after GOALS training and was positively correlated with the underlying integrity of white matter measured at baseline.

Conjunction Analysis

The conjunction of the significant LV 1 ($p< .001$) from the task-PLS and LV 1 from the behav-PLS ($p< .001$) yielded three clusters (cluster size $k= 10$; see figure 9): bilateral middle frontal gyri (peak MNI coordinates: x = 39, y = -39, z = 27; x = 28, y = 51, z = 12) and precuneus (peak MNI coordinates: x = -6, y = -45, z = 54).

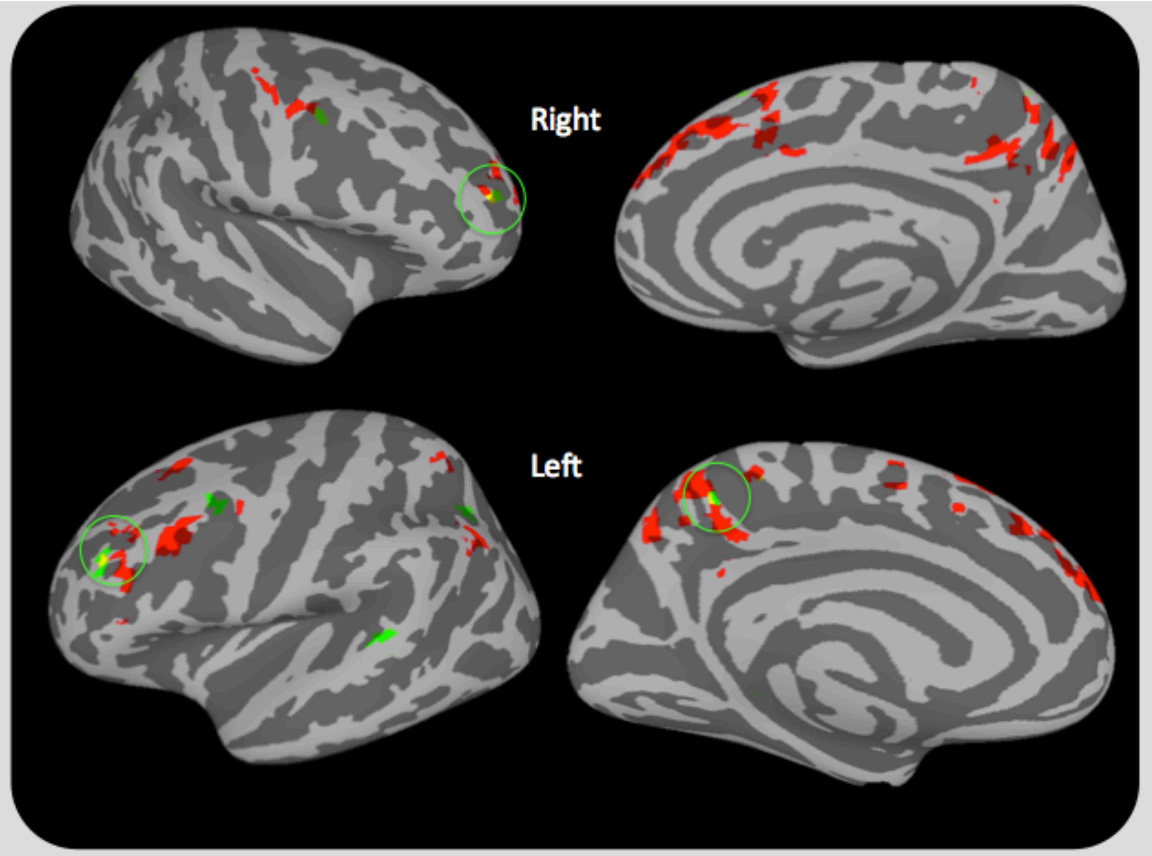

Figure 8. Conjunction map between LV 1 of the task-PLS (Fig 6, in green) and LV 1 of the behav-PLS (Fig 7, in red) shown in yellow. Regions of overlap include bilateral middle frontal gyri (peak MNI coordinates: x = -39 y = 39 z = 27; x = 28 y = 51 z = 12) and precuneus (peak MNI coordinates: x = -6 y = -45 z = 54).

Discussion

This study investigated functional brain changes within networks known to support GDC following GOALS training in a cohort of healthy older adults. Our primary aim was to investigate the neural mechanisms associated with GDC following GOALS training, one of the few theory-based, empirically supported interventions for enhancing GDC. As a secondary aim, we also investigated whether the structural integrity of white matter pathways connecting these distributed regions would be associated with functional brain changes post-training. Our findings show a significant effect of GOALS training on the functional recruitment of networks subserving GDC in older adults. Increases in middle frontal gyri (MFG) and anterior inferior parietal lobe (aIPL), nodes in the FPCN (Spreng et al., 2012; Vincent et al., 2008) and superior temporal gyrus and dorsolateral PFC, nodes in the DAN (Corbetta & Shulman, 2000) were observed exclusively in the condition requiring GDC (i.e. Scenes) after GOALS training and these changes were associated with structural integrity of frontal-posterior and frontal-subcortical white matter tracts. These findings are the first to provide evidence that GOALS training can lead to increases in activation within large-scale brain networks in healthy older adults. Moreover, these changes are associated with greater integrity of white matter tracts connecting structures known to subserve GDC.

Modulation of large-scale networks after GOALS training

GDC constitutes an ability to endogenously direct attention to a goal-relevant stimulus and simultaneously suppress goal-irrelevant or distracting information; it also requires one to hold the goal-relevant information in mind to successfully execute the goal-directed behavior (Gazzaley & Nobre, 2012). This complex cognitive ability has been shown to emerge from the large-scale functional interactions between nodes of the FPCN (Vincent et al., 2008), which plays a role in coupling networks such as the DAN and DMN involved in endogenous and exogenous attention. Our results provide evidence that the attentional self-regulation training leads to reliable activation increases in large-scale networks involved in attention and GDC. These results provide evidence for training-induced neural activity changes in older adults.

Prior intervention research in healthy aging has primarily focused on process-training approaches aimed at improving cognitive domain(s) through repetition of tasks designed to engage these domains (for a detailed review, see Lustig et al., 2009). However, there is a dearth of literature examining the neural correlates of more strategy-based training in older adults (Nyberg et al., 2003; Bergerbest et al., 2009; Lustig & Buckner, 2004; Soldan et al., 2008; Wiggs et al., 2006; Chapman et al., 2013;). Even fewer specifically target executive functioning abilities (Braver et al., 2009; Anguera et al., 2013; Erickson & Kramer, 2009). To our knowledge, these findings are the first to demonstrate changes in large-scale functional networks giving rise to GDC following a strategy-based training intervention in older adults using a controlled study design.

These results demonstrate that the post-intervention increases in network engagement were observed in nodes of the FPCN, specifically the right MFG and right aIPL and in a node of the DAN, the right dorsolateral PFC as well as the left parahippocampal place area (PPA) – a critical target of top-down modulation during our ‘Scenes condition. These findings converge with previous findings of working memory training-induced increases in activation patterns (Oleson et al, 2003; Hempel et al., 2004) in young adults. However, decreases in patterns of activations in neural regions and networks have also been reported. A recent meta-analysis conducted by Patel and colleagues (2013) looked at the neural correlates of training across a broad range of cognitive domains in young adults.

Their results showed that, regardless of training domain, training-related decreases were observed in regions overlapping with the FPCN and DAN in young adults, accompanied by related increases in the DMN. Similarly, a review examining working memory training induced plasticity in younger adults by Klingberg (2010) provides evidence for similar changes in fronto-parietal regions. One interpretation of these findings is that training young adults results in increased neural efficiency in networks supporting attention and GDC and this is reflected in a reduction in the engagement of these networks and improved task performance in the trained domains. On the other hand, there is now growing evidence suggesting that bilateral functional recruitment is compensatory for cognitive performance in older adults (see Park & Reuter-Lorenz., 2009; Grady et al., 2012). This bilateral recruitment, according to a model proposed by Park & Reuter-Lorenz (2009), is an adaptive reliance on alternative brain networks to help support cognition. Their scaffolding theory of cognition posits that to maintain behavior at a high level, older adults engage in compensatory scaffolding to sustain this performance, which is reflected in contralateral recruitment of neural substrates compared to young adults. The current results provide evidence for a unilateral engagement in networks after the attentional training, which can be interpreted as a reduction in reliance on secondary networks or scaffolds secondary to training. The MFG, one of the core nodes of the FPCN (Vincent et al., 2008; Spreng et al., 2012) has been shown to have right- lateralized activation in conjunction with the parahippocampal place area in a task similar to ours in young adults (Chaddick & Gazzaley, 2012). Older adults who have completed the GOALS training, show comparable lateralized patterns of engagement of the right MFG, strengthening our interpretation that in fact the intervention could be improving the neural efficiency of large-scale brain networks similar to those of young adults.

We observed that the left PPA also showed increases in activation during the Scenes condition post-intervention for the GOALS group. This region, comprised of the posterior aspect of the parahippocampal gyrus and adjacent lingual gyrus/medial fusiform cortex along with the collateral sulcus (Epstein & Kanwisher 1998; Epstein, 2008) is a functionally defined area shown to be critical for the processing of complex visual scenes. The nature of the goal-directed task employed in this study required older adults to consider the scene stimuli as goal-relevant and selectively attend to them and hold them in working memory to respond correctly on the task. Hence, the enhanced coupling of the left PPA with the other observed nodes in the DAN and FPCN, including the right MFG, dorsolateral PFC and aIPL, is congruent with previous literature showing that top-down modulation of sensory cortices arises from top-down control signals exerted by frontal-parietal regions (Corbetta & Shulman, 2000).

Relationship between large-scale network modulation and white matter integrity

Age-related declines in cerebral white matter integrity are well documented with predominant findings of decreased FA and increased mean diffusivity as a function of increasing adult age (for review see Bennett &

Madden, 2013). Cognitive declines that accompany this reduction in the structural architecture of the aging brain have been an area of focus in the literature and reports of a positive correlation between these two are now well established (Bennett & Madden, 2013). However, to our knowledge, this study is the first to investigate the relationship between changes within large-scale functional networks occurring as a result of a targeted attentional intervention and the underlying structural architecture of projection and association white matter tracts. While cognitive interventions have been shown to induce structural changes in the elderly (Lovden et al, 2010; Engvig et al., 2012; Scholz et al., 2009; Colom et al., 2012; Takeuchi et al., 2010), this study is the first to investigate the relationship between structure and function and a training intervention.

Role of the nodes showing increased activation in network engagement

GDC depends on interactions amongst distributed neuronal populations and brain regions (Spreng et al., 2013). The FPCN has been shown to give rise to GDC and is privileged in its functional and anatomical interposition between the DAN and DMN. This allows the network to modulate interactions between internally- and externally-directed cognition and interact with these networks to support GDC. Critical to this modulation is flexibility within nodes of the FPCN to allow for coordination between networks in the face of task demands. Recent work by Spreng and colleagues (2013) has focused on this particular aspect of large-scale network dynamics and identified nodes within the FPCN, DAN and DMN that are flexible in their network allegiance. Our findings of increased activation in the right dorsolateral PFC, aIPL and MFG converge with this account of flexible nodes within networks that allows for dynamic cognitive processes to occur at the neural level. Particularly, the dorsolateral PFC is aligned with DAN during task but with the FPCN at rest (Spreng et al., 2013); similarly, the right aIPL is aligned with both the FPCN and DAN at task. The MFG was aligned with the FPCN, but also showed reliable interactions with the DMN and DAN (Spreng et al., 2013). This interaction of the MFG with other networks converges with its role as a global hub (He et al., 2009). Our conjunction analysis investigating the overlap between the networks that show increases post-intervention and also correlate with white matter FA, showed that the precuneus and MFG were two regions that we see activated post-intervention and were also correlated with the structural integrity. In our initial analyses, the precuneus activation was sub-threshold; however in the conjunction analysis, it emerged as a significant cluster. The precuneus shows a strong affiliation with the default mode network, during rest and has been postulated as a network connector hub (Spreng et al., 2013).

Our results, in addition to providing evidence that attention training targeted at GDC increases activation in networks known to subserve this cognitive ability, also show that these nodes are critical in their functional interaction both within and between networks. Their flexibility in allegiance to networks can be interpreted as a property that allows them to be targeted by a highly specific intervention and is influenced by their structural connectivity with both distal and proximal nodes within the networks.

Evaluation of the specificity, transfer and maintenance of intervention effects

Our study was designed to include a comparison group to allow determination of the specificity of participating in cognitive training. The current comparison intervention (BHW) was designed to provide an assessment of test-retest effects and was matched for time, therapist interaction and difficulty of the tasks completed in session and homework. Yet the neural changes were limited to the GOALS group, highlighting the specificity of the changes to the active training intervention. Comparison conditions are rarely implemented in functional MRI studies of cognitive rehabilitation despite the strength they add to conclusions regarding the specificity of changes to the training intervention. However, a limitation is that although no significant effects of the BHW were observed, this does not preclude the possibility that our comparison might be lacking power due to the small sample of pre- and post BHW data.

Transfer of training effects to non-trained contexts is a major issue in the evaluation of interventions. While our study did not include this direct comparison to non-trained tasks, preliminary results show that our intervention led to improvement in cognitive and real-world functional tasks that the participants were not trained on, specifically those requiring executive functioning abilities (unpublished data). Similar findings have been reported using the GOALS training in a sample of acquired brain injury patients (Novakovic-Agopian et al., 2010; Chen et al., 2012). Also during the attentional training, participants were not exposed to the cognitive task they performed during the fMRI scanning, yet significant neural changes in large-scale networks were observed. Thus, we can conclude that these changes are not solely resulting due to practice effects.

Conclusions

To our knowledge this is the first study to report changes in large-scale neural networks known to subserve GDC in older adults after training and to associate these changes with the integrity of underlying white matter tracts. These results suggest that targeted executive control training can alter functional connectivity with large-scale brain networks and that these changes are dependent on their structural integrity. These results suggest that targeting functional brain activity in core nodes of networks underlying GDC, whether through behavioral training as demonstrated here, or possibly through neurostimulation techniques or pharmacological interventions, represents a new, brain-based approach to enhance complex cognitive functioning in older adulthood.

References

Andrews-Hanna, J. R., Snyder, A. Z., Vincent, J. L., Lustig, C., Head, D., Raichle, M. E., & Buckner, R. L. (2007). Disruption of large-scale brain systems in advanced aging. *Neuron*, *56*(5), 924-935. doi: 10.1016/j.neuron.2007.10.038

Anguera, J. A., Boccanfuso, J., Rintoul, J. L., Al-Hashimi, O., Faraji, F., Janowich, J., ... & Gazzaley, A. (2013). Video game training enhances cognitive control in older adults. *Nature*, *501*(7465), 97-101. doi:10.1038/nature12486

Ball, K., Berch, D. B., Helmers, K. F., Jobe, J. B., Leveck, M. D., Marsiske, M., ... & ACTIVE Study Group. (2002). Effects of cognitive training interventions with older adults: a randomized controlled trial. *Jama*, *288*(18), 2271-2281. doi:10.1001/jama.288.18.2271

Bartzokis, G., Sultzer, D., Lu, P. H., Nuechterlein, K. H., Mintz, J., & Cummings, J. L. (2004). Heterogeneous age-related breakdown of white matter structural integrity: implications for cortical “disconnection” in aging and Alzheimer’s disease. *Neurobiology of aging*, *25*(7), 843-851. doi: 10.1016/j.neurobiolaging.2003.09.005

Barulli, D., & Stern, Y. (2013). Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. *Trends in cognitive sciences*, *17*(10), 502-509. doi: 10.1016/j.tics.2013.08.012

Bennett, I. J., & Madden, D. J. (2013). Disconnected aging: cerebral white matter integrity and age-related differences in cognition. *Neuroscience*. Advance online publication. doi: 10.1016/j.neuroscience.2013.11.026

Bergerbest, D., Gabrieli, J. D. E., Whitfield-Gabrieli, S., Kim, H., Stebbins, G. T., Bennett, D. A., & Fleischman, D. A. (2009). Age-associated reduction of asymmetry in prefrontal function and preservation of conceptual repetition priming. *Neuroimage*, *45*(1), 237-246. doi: 10.1016/j.neuroimage.2008.10.019

Braver, T. S., Paxton, J. L., Locke, H. S., & Barch, D. M. (2009). Flexible neural mechanisms of cognitive control within human prefrontal cortex.*Proceedings of the National Academy of Sciences*, *106*(18), 7351-7356. doi: 10.1073/pnas.0808187106

Chadick, J. Z., & Gazzaley, A. (2011). Differential coupling of visual cortex with default or frontal-parietal network based on goals. *Nature neuroscience*, *14*(7), 830-832. doi:10.1038/nn.2823

Chapman, S. B., Aslan, S., Spence, J. S., Hart, J. J., Bartz, E. K., Didehbani, N., ... & Lu, H. (2013). Neural mechanisms of brain plasticity with complex cognitive training in healthy seniors. *Cerebral Cortex*, doi: 10.1093/cercor/bht234

Charlton, R. A., Barrick, T. R., Lawes, I. N. C., Markus, H. S., & Morris, R. G. (2010). White matter pathways associated with working memory in normal aging. *Cortex*, *46*(4), 474-489. doi: 10.1016/j.cortex.2009.07.005

Chen, A. J. W., Novakovic-Agopian, T., Nycum, T. J., Song, S., Turner, G. R., Hills, N. K., ... & D'Esposito, M. (2011). Training of goal-directed attention regulation enhances control over neural processing for individuals with brain injury. *Brain*, *134*(5), 1541-1554. doi: 10.1093/brain/awr067

Colom, R., Quiroga, M., Solana, A. B., Burgaleta, M., Román, F. J., Privado, J., ... & Karama, S. (2012). Structural changes after videogame practice related to a brain network associated with intelligence. *Intelligence*, *40*(5), 479-489. doi: 10.1016/j.intell.2012.05.004

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature reviews neuroscience*, *3*(3), 201-215. doi: 10.1038/nrn755

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical research*, *29*(3), 162-173. doi: 10.1006/cbmr.1996.0014

Dahlin, E., Bäckman, L., Neely, A. S., & Nyberg, L. (2009). Training of the executive component of working memory: subcortical areas mediate transfer effects. *Restorative neurology and neuroscience*, *27*(5), 405-419. doi: 10.3233/RNN-2009-0492

Davis, S. W., Dennis, N. A., Buchler, N. G., White, L. E., Madden, D. J., & Cabeza, R. (2009). Assessing the effects of age on long white matter tracts using diffusion tensor tractography. *Neuroimage*, *46*(2), 530-541. doi: 10.1016/j.neuroimage.2009.01.068

de Fockert, J. W., Ramchurn, A., Van Velzen, J., Bergström, Z., & Bunce, D. (2009). Behavioral and ERP evidence of greater distractor processing in old age. *Brain research*, *1282*, 67-73. doi: 10.1016/j.brainres.2009.05.060

Efron, B. (1981). Nonparametric estimates of standard error: the jackknife, the bootstrap and other methods. *Biometrika*, *68*(3), 589-599. doi: 10.1093/biomet/68.3.589

Engvig, A., Fjell, A. M., Westlye, L. T., Moberget, T., Sundseth, Ø., Larsen, V. A., & Walhovd, K. B. (2012). Memory training impacts short-term changes in aging white matter: A Longitudinal Diffusion Tensor Imaging Study. *Human brain mapping*, *33*(10), 2390-2406. doi: 10.1002/hbm.21370

Epstein, R. A. (2008). Parahippocampal and retrosplenial contributions to human spatial navigation. *Trends in cognitive sciences*, *12*(10), 388-396. doi: 10.1016/j.tics.2008.07.004

Epstein, R., & Kanwisher, N. (1998). A cortical representation of the local visual environment. *Nature*, *392*(6676), 598-601. doi:10.1038/33402

Erickson, K. I., & Kramer, A. F. (2009). Aerobic exercise effects on cognitive and neural plasticity in older adults. *British journal of sports medicine*, *43*(1), 22-24. doi:10.1136/bjsm.2008.052498

Fish, J., Evans, J. J., Nimmo, M., Martin, E., Kersel, D., Bateman, A., ... & Manly, T. (2007). Rehabilitation of executive dysfunction following brain injury:“Content-free” cueing improves everyday prospective memory performance. *Neuropsychologia*, *45*(6), 1318-1330. doi: 10.1016/j.neuropsychologia.2006.09.015

Friston, K. J., Penny, W. D., & Glaser, D. E. (2005). Conjunction revisited.*Neuroimage*, *25*(3), 661-667. doi: 10.1016/j.neuroimage.2005.01.013

Garrett, D. D., Kovacevic, N., McIntosh, A. R., & Grady, C. L. (2011). The importance of being variable. *The Journal of Neuroscience*, *31*(12), 4496-4503. doi: 10.1523/JNEUROSCI.5641-10.2011

Gazzaley, A., Cooney, J. W., Rissman, J., & D'Esposito, M. (2005). Top-down suppression deficit underlies working memory impairment in normal aging.*Nature neuroscience*, *8*(10), 1298-1300. doi:10.1038/nn1543

Gazzaley, A., & D'Esposito, M. (2007). Top-Down Modulation and Normal Aging. *Annals of the New York Academy of Sciences*, *1097*(1), 67-83. doi: 10.1196/annals.1379.010

Gazzaley, A., & Nobre, A. C. (2012). Top-down modulation: bridging selective attention and working memory. *Trends in cognitive sciences*, *16*(2), 129-135. doi: 10.1016/j.tics.2011.11.014

Grady, C. (2012). The cognitive neuroscience of ageing. *Nature Reviews Neuroscience*, *13*(7), 491-505. doi:10.1038/nrn3256

Grady, C. L., Protzner, A. B., Kovacevic, N., Strother, S. C., Afshin-Pour, B., Haring, A. E., Zhuravleva, T. Y., Alperin, B. R., Rentz, D. M., Holcomb, P. J., & Daffner, K. R. (2013). Age-related differences in enhancement and suppression of neural activity underlying selective attention in matched young and old adults. *Brain research*, *1499*, 69-79. doi: 10.1016/j.brainres.2013.01.003

Hamilton, L. S., Levitt, J. G., O'Neill, J., Alger, J. R., Luders, E., Phillips, O. R., ... & Narr, K. L. (2008). Reduced white matter integrity in attention-deficit hyperactivity disorder. *Neuroreport*, *19*(17), 1705. doi: 10.1097/WNR.0b013e3283174415

He, Y., Wang, J., Wang, L., Chen, Z. J., Yan, C., Yang, H., ... & Evans, A. C. (2009). Uncovering intrinsic modular organization of spontaneous brain activity in humans. *PloS one*, *4*(4). doi: 10.1371/journal.pone.000522

Hempel, A., Giesel, F. L., Caraballo, N. M. G., Amann, M., Meyer, H., Wüstenberg, T., ... & Schröder, J. (2004). Plasticity of cortical activation related to working memory during training. *American Journal of Psychiatry*,*161*(4), 745-747. doi: 10.1176/appi.ajp.161.4.745

Hillyard, S. A., Vogel, E. K., & Luck, S. J. (1998). Sensory gain control (amplification) as a mechanism of selective attention: electrophysiological and neuroimaging evidence. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, *353*(1373), 1257-1270. doi: 10.1098/rstb.1998.0281

Hughes, E. J., Bond, J., Svrckova, P., Makropoulos, A., Ball, G., Sharp, D. J., ... & Counsell, S. J. (2012). Regional changes in thalamic shape and volume with increasing age. *Neuroimage*, *63*(3), 1134-1142. doi: 10.1016/j.neuroimage.2012.07.043

Kabat-Zinn J. Full catastrophe living. New York, New York: Delacorte Press; 1990

Kantarci, K., et al. (2011). Diffusion tensor imaging and cognitive function in older adults with no dementia. *Neurology*, *77*(1), 26-34. doi: 10.1212/WNL.0b013e31822313dc

Kastner, S. & Ungerleider, L. G. (2000). Mechanisms of visual attention in the human cortex. *Annual review of neuroscience*, *23*(1), 315-341. doi: 10.1146/annurev.neuro.23.1.315

Kier, E. L., Staib, L. H., Davis, L. M., & Bronen, R. A. (2004). MR imaging of the temporal stem: anatomic dissection tractography of the uncinate fasciculus, inferior occipitofrontal fasciculus, and Meyer's loop of the optic radiation. *American Journal of Neuroradiology*, *25*(5), 677-691. doi: 10.3171/JNS/2008/108/4/0775

Klingberg, T. (2010). Training and plasticity of working memory. *Trends in cognitive sciences*, *14*(7), 317-324. doi: 10.1016/j.tics.2010.05.002

Krishnan, A., Williams, L. J., McIntosh, A. R., & Abdi, H. (2011). Partial Least Squares (PLS) methods for neuroimaging: a tutorial and review. *Neuroimage*, *56*(2), 455-475. doi: 10.1016/j.neuroimage.2010.07.034

Levine, B., Robertson, I. H., Clare, L., Carter, G., Hong, J., Wilson, B. A., ... & Stuss, D. T. (2000). Rehabilitation of executive functioning: An experimental–clinical validation of goal management training. *Journal of the International Neuropsychological Society*, *6*(03), 299-312. doi: 10.1017/S1092852914000108

Levine, B., Stuss, D. T., Winocur, G., Binns, M. A., Fahy, L., Mandic, M., ... & Robertson, I. H. (2007). Cognitive rehabilitation in the elderly: effects on strategic behavior in relation to goal management. *Journal of the International Neuropsychological Society*, *13*(01), 143-152. doi: 10.1017/S1355617707070178

Lövdén, M., Bodammer, N. C., Kühn, S., Kaufmann, J., Schütze, H., Tempelmann, C., ... & Lindenberger, U. (2010). Experience-dependent plasticity of white-matter microstructure extends into old age. *Neuropsychologia*, *48*(13), 3878-3883. doi: 10.1016/j.neuropsychologia.2010.08.026

Lustig, C., & Buckner, R. L. (2004). Preserved neural correlates of priming in old age and dementia. *Neuron*, *42*(5), 865-875. doi: 10.1016/j.neuron.2004.04.002

Lustig, C., Shah, P., Seidler, R., & Reuter-Lorenz, P. A. (2009). Aging, training, and the brain: a review and future directions. *Neuropsychology review*, *19*(4), 504-522. doi: 10.1007/s11065-009-9119-9

Mager, R., Bullinger, A. H., Brand, S., Schmidlin, M., Schärli, H., Müller-Spahn, F., ... & Falkenstein, M. (2007). Age-related changes in cognitive conflict processing: An event-related potential study. *Neurobiology of Aging*, *28*(12), 1925-1935. doi: 10.1016/j.neurobiolaging.2006.08.001

Makris, N., Kennedy, D. N., McInerney, S., Sorensen, A. G., Wang, R., Caviness, V. S., & Pandya, D. N. (2005). Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. *Cerebral Cortex*, *15*(6), 854-869. doi: 10.1093/cercor/bhh186

McIntosh, A. R. (2000). Towards a network theory of cognition. *Neural Networks*, 13, 861–870. doi: 10.1016/S0893-6080(00)00059-9

McIntosh, A. R., Bookstein, F. L., Haxby, J. V., & Grady, C. L. (1996). Spatial pattern analysis of functional brain images using partial least squares.*Neuroimage*, *3*(3), 143-157. doi: 10.1006/nimg.1996.0016

McIntosh, A. R., Chau, W. K., & Protzner, A. B. (2004). Spatiotemporal analysis of event-related fMRI data using partial least squares. *Neuroimage*,*23*(2), 764-775. doi: 10.1016/j.neuroimage.2004.05.018

Milewski-Lopez, A., Greco, E., Van den Berg, F., McAvinue, L. P., McGuire, S., & Robertson, I. H. (2014). An evaluation of alertness training for older adults. *Frontiers in aging neuroscience*, *6*. doi:10.3389/fnagi.2014.00067

Mori, S., Oishi, K., Jiang, H., Jiang, L., Li, X., Akhter, K., ... & Mazziotta, J. (2008). Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *Neuroimage*, *40*(2), 570-582. doi: 10.1016/j.neuroimage.2007.12.035

Moseley, M. (2002). Diffusion tensor imaging and aging–a review. *NMR in Biomedicine*, *15*(7-8), 553-560. doi: 10.1002/nbm.785

Nestor, P. G., Kubicki, M., Spencer, K. M., Niznikiewicz, M., McCarley, R. W., & Shenton, M. E. (2007). Attentional networks and cingulum bundle in chronic schizophrenia. *Schizophrenia research*, *90*(1), 308-315. doi: 10.1016/j.schres.2006.10.005

Nichols, T., Brett, M., Andersson, J., Wager, T., & Poline, J. B. (2005). Valid conjunction inference with the minimum statistic. *Neuroimage*, *25*(3), 653-660. doi: 10.1016/j.neuroimage.2004.12.005

Niendam, T. A., Laird, A. R., Ray, K. L., Dean, Y. M., Glahn, D. C., & Carter, C. S. (2012). Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. *Cognitive, Affective, & Behavioral Neuroscience*, *12*(2), 241-268. doi: 10.3758/s13415-011-0083-5

Novakovic-Agopian, T., Chen, A. J. W., Rome, S., Abrams, G., Castelli, H., Rossi, A., ... & D'Esposito, M. (2011). Rehabilitation of executive functioning with training in attention regulation applied to individually defined goals: a pilot study bridging theory, assessment, and treatment. *The Journal of head trauma rehabilitation*, *26*(5), 325-338. doi: 10.1097/HTR.0b013e3181f1ead2

Nyberg, L., Sandblom, J., Jones, S., Neely, A. S., Petersson, K. M., Ingvar, M., & Bäckman, L. (2003). Neural correlates of training-related memory improvement in adulthood and aging. *Proceedings of the National Academy of Sciences*, *100*(23), 13728-13733. doi:10.1073/pnas.1735487100

O' Sullivan, M., Jones, D.K., Summers, P.E., Morris, R.G., Williams, S.C.R., Markus, H.S., 2001. Evidence for cortical “disconnection” as a mechanism of age-related cognitive decline. *Neurology* 57, 632–638. doi: 10.1212/WNL.57.4.632

Olesen, P. J., Westerberg, H., & Klingberg, T. (2003). Increased prefrontal and parietal activity after training of working memory. *Nature neuroscience*, *7*(1), 75-79. doi:10.1038/nn1165

Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: aging and neurocognitive scaffolding. *Annual review of psychology*, *60*, 173. doi: 10.1146/annurev.psych.59.103006.093656

Patel, R., Spreng, R. N., & Turner, G. R. (2013). Functional brain bhanges following cognitive and motor skills training: A quantitative meta-analysis. *Neurorehabilitation and neural repair*, *27*(3), 187-199. doi:10.1177/1545968312461718

Protzner, A. B., & McIntosh, A. R. (2007). The interplay of stimulus modality and response latency in neural network organization for simple working memory tasks. *Journal of Neuroscience*, *27*, 3187–3197. doi: 10.1523/JNEUROSCI.4963-06.2007

Rieckmann, A., Karlsson, S., Karlsson, P., Brehmer, Y., Fischer, H., Farde, L., ... & Bäckman, L. (2011). Dopamine D1 receptor associations within and between dopaminergic pathways in younger and elderly adults: links to cognitive performance. *Cerebral Cortex*, doi: 10.1093/cercor/bhq266

Rorden, C., Bonilha, L., & Nichols, T. E. (2007). Rank-order versus mean based statistics for neuroimaging. *Neuroimage*, *35*(4), 1531-1537. doi: 10.1016/j.neuroimage.2006.12.043

Saad, Z. S., Glen, D. R., Chen, G., Beauchamp, M. S., Desai, R., & Cox, R. W. (2009). A new method for improving functional-to-structural MRI alignment using local Pearson correlation. *Neuroimage*, *44*(3), 839-848. doi: 10.1016/j.neuroimage.2008.09.037

Sasson E, Doniger GM, Pasternak O, Tarrasch R, Assaf Y (2013) White matter correlates of cognitive domains in normal aging with diffusion tensor imaging. *Front Neurosci* 7:32. doi: 10.3389/fnins.2013.00032

Sasson, E., Doniger, G. M., Pasternak, O., Tarrasch, R., & Assaf, Y. (2012). Structural correlates of cognitive domains in normal aging with diffusion tensor imaging. *Brain Structure and Function*, *217*(2), 503-515.doi: 10.1007/s00429-011-0344-7

Sasson, E., Doniger, G. M., Pasternak, O., Tarrasch, R., & Assaf, Y. (2013). White matter correlates of cognitive domains in normal aging with diffusion tensor imaging. *Frontiers in neuroscience*, *7* (32). doi:10.3389/fnins.2013.00032

Schmitz, T.W., Cheng, F.H.T., De Rosa, E., 2010. Failing to ignore: paradoxical neural effects of perceptual load on early attentional selection in normal aging. *Journal of Neuroscience*. 30 (44), 932 14750–14758. doi: 10.1523/JNEUROSCI.2687-10.2010

Scholz, J., Klein, M. C., Behrens, T. E., & Johansen-Berg, H. (2009). Training induces changes in white-matter architecture. *Nature neuroscience*, *12*(11), 1370-1371. doi: 10.1038/nn.2412

Schweizer, T. A., Levine, B., Rewilak, D., O'Connor, C., Turner, G., Alexander, M. P., ... & Stuss, D. T. (2008). Rehabilitation of executive functioning after focal damage to the cerebellum. *Neurorehabilitation and Neural Repair*, *22*(1), 72-77. doi: 10.1177/1545968307305303

Sepulcre, J., Masdeu, J. C., Pastor, M. A., Goni, J., Barbosa, C., Bejarano, B., et al. (2009). Brain pathways of verbal working memory: a lesion-function correlation study. *Neuroimage* 47, 773–778. doi: 10.1016/j.neuroimage.2009.04.054

Smith, S. M. (2002). Fast robust automated brain extraction. *Human brain mapping*, *17*(3), 143-155. doi: 10.1002/hbm.10062

Smith, S. M., et al. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*, *23*, S208-S219. DOI: 10.1016/j.neuroimage.2004.07.051

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., ... & Behrens, T. E. (2006). Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *Neuroimage*, *31*(4), 1487-1505. DOI: 10.1016/j.neuroimage.2006.02.024

Soldan, A., Gazes, Y., Hilton, H. J., & Stern, Y. (2008). Aging does not affect brain patterns of repetition effects associated with perceptual priming of novel objects. *Journal of cognitive neuroscience*, *20*(10), 1762-1776. doi: 10.1162/jocn.2008.20130

Spreng, R. N., Sepulcre, J., Turner, G. R., Stevens, W. D., & Schacter, D. L. (2013). Intrinsic architecture underlying the relations among the default, dorsal attention, and frontoparietal control networks of the human brain. *Journal of cognitive neuroscience*, *25*(1), 74-86. doi:10.1162/jocn_a_00281

Spreng, R. N., Stevens, W. D., Chamberlain, J. P., Gilmore, A. W., & Schacter, D. L. (2010). Default network activity, coupled with the frontoparietal control network, supports goal-directed cognition. *Neuroimage*, *53*(1), 303-317. doi: 10.1016/j.neuroimage.2010.06.016

Stadlbauer, A., Salomonowitz, E., Strunk, G., Hammen, T., & Ganslandt, O. (2008). Quantitative diffusion tensor fiber tracking of age-related changes in the limbic system. *European radiology*, *18*(1), 130-137.doi: 10.1007/s00330-007-0733-8

Stevens, W. D., Kahn, I., Wig, G. S., & Schacter, D. L. (2011). Hemispheric asymmetry of visual scene processing in the human brain: evidence from repetition priming and intrinsic activity. *Cerebral Cortex*, *22,* 1935-1949. doi: 10.1093/cercor/bhr273

Takeuchi, H., Sekiguchi, A., Taki, Y., Yokoyama, S., Yomogida, Y., Komuro, N., ... & Kawashima, R. (2010). Training of working memory impacts structural connectivity. *The Journal of neuroscience*, *30*(9), 3297-3303. doi: 10.1523/JNEUROSCI.4611-09.201

Turner, G. R., & Levine, B. (2004). Disorders of executive functioning and self-awareness. *Cognitive and behavioral rehabilitation*, 224-268.

van Hooren, S. A., et al. (2007). Effect of a structured course involving goal management training in older adults: A randomised controlled trial. *Patient education and counseling*, *65*(2), 205-213. doi: 10.1016/j.pec.2006.07.010

Vincent, J. L., Kahn, I., Snyder, A. Z., Raichle, M. E., & Buckner, R. L. (2008). Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. *Journal of Neurophysiology*, *100*(6), 3328-3342. doi: 10.1016/j.pec.2006.07.010

Voineskos, A. N., Rajji, T. K., Lobaugh, N. J., Miranda, D., Shenton, M. E., Kennedy, J. L., ... & Mulsant, B. H. (2012). Age-related decline in white matter tract integrity and cognitive performance: a DTI tractography and structural equation modeling study. *Neurobiology of aging*, *33*(1), 21-34. doi: 10.1016/j.neurobiolaging.2010.02.009

Von Cramon, D. Y., Cramon, G. M. V., & Mai, N. (1991). Problem-solving deficits in brain-injured patients: A therapeutic approach. *Neuropsychological Rehabilitation*, *1*(1), 45-64. doi: 10.1080/09602019108401379

Wig, G. S., Buckner, R. L., & Schacter, D. L. (2009). Repetition priming influences distinct brain systems: evidence from task-evoked data and resting-state correlations. *Journal of Neurophysiology*, *101*(5), 2632-2648. doi: 10.1152/jn.91213.2008

Wiggs, C. L., Weisberg, J., & Martin, A. (2006). Repetition priming across the adult lifespan—the long and short of it. *Aging, Neuropsychology, and Cognition*,*13*(3-4), 308-325. doi: 10.1080/ 138255890968718

Wojtowicz, M. A., Anderson, J. A. E., Churchill, N., & McIntosh, A. R. (2010). A multivariate analysis of age-related differences in default mode and task positive networks across multiple cognitive domains. *Cerebral Cortex, 20*, 1432–1447. doi: 10.1093/cercor/bhp207

Woolrich, M. et al. (2009). Bayesian analysis of neuroimaging data in FSL.*Neuroimage*, *45*(1), S173-S186. doi: 10.1016/j.neuroimage.2008.10.055

Zanto, T. P., & Gazzaley, A. (2013). Fronto-parietal network: flexible hub of cognitive control. *Trends in cognitive sciences*, *17*(12), 602-603. doi: 10.1016/j.tics.2013.10.001

Appendix A

Table A1

Z score ranges for subdomains for the goal-oriented attentional self-regulation training group (GOALS) and brain health workshop group (BHW). Z scores were calculated using normative data from standardized measures where accessible for each subtest. Subdomain z scores were calculated by averaging the z scores for component tests. The following neuropsychological tests were used to calculate each subdomain z score: the working memory subdomain included Consonant Trigrams and Letter Number Sequencing; the mental flexibility subdomain included the DKEFS Color Word interference Switching time and total switching errors, DKEFS Design Fluency switching, DKEFS Verbal Fluency switching and Trail Making Test B; the inhibition subdomain included DKEFS Color Word Inhibition word time and total errors for inhibition; the fluency subdomain included DKEFS Design Fluency conditions 1 and 2, DKEFS Verbal Fluency letter and category fluency; the planning subdomain included the Mazes Test and DKEFS Tower Test total achievement score and mean number of rule violations; the learning and short term memory subdomain included total recall on the HVLT and BVMT; the delayed recall subdomain included the delayed recall scores on the HVLT and BVMT; the speed of processing domain score was not comprised of further subdomains and included Trail Making Test A and Digit Span; the motor functioning domain score was not comprised of further subdomains and included dominant and non-dominant hand time on the Grooved Pegboard.

Subdomain Z Scores	**GOALS**	**BHW**
Executive Control Function	-0.89, 0.78	0.04, 0.77
Working Memory	-1.5, 1.2	-1.05, 0.86
Mental Flexibility	-0.37, 1.51	0.12, 0.84
Inhibition	-1.16, 0.83	-0.33, 1.16
Fluency	-0.89, 1.67	-0.11, 1.56
Planning	-0.28, 0.63	-0.39, 0.76
Learning and Memory	-1.13, 1.04	-1.77, 0.53
Learning and short term memory	-1.86, 0.87	-1.60, 1.48
Delayed Recall	-2.69, 0.68	-2.06, 0.94

Speed of Processing	-0.51, 0.54	-0.24, 0.52
Motor Functioning	-1.18, 1.07	-0.72. 0.88