



Neurocognitive enhancement in older adults: Comparison of three cognitive training tasks to test a hypothesis of training transfer in brain connectivity



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ABSTRACT

The ultimate goal of cognitive enhancement as an intervention for age-related cognitive decline is transfer to everyday cognitive functioning. Development of training methods that transfer broadly to untrained cognitive tasks (far transfer) requires understanding of the neural bases of training and far transfer effects. We used cognitive training to test the hypothesis that far transfer is associated with altered attentional control demands mediated by the dorsal attention network and trained sensory cortex. In an exploratory study, we randomly assigned 42 healthy older adults to six weeks of training on Brain Fitness (BF—auditory perception), Space Fortress (SF—visuomotor/working memory), or Rise of Nations (RON—strategic reasoning). Before and after training, cognitive performance, diffusion-derived white matter integrity, and functional connectivity of the superior parietal cortex (SPC) were assessed. We found the strongest effects from BF training, which transferred to everyday problem solving and reasoning and selectively changed integrity of occipito-temporal white matter associated with improvement on untrained everyday problem solving. These results show that cognitive gain from auditory perception training depends on heightened white matter integrity in the ventral attention network. In BF and SF (which also transferred positively), a decrease in functional connectivity between SPC and inferior temporal lobe (ITL) was observed compared to RON—which did not transfer to untrained cognitive function. These findings highlight the importance for cognitive training of top-down control of sensory processing by the dorsal attention network. Altered brain connectivity – observed in the two training tasks that showed far transfer effects – may be a marker for training success.

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Introduction

Even without descent into Alzheimer's disease, cognitive decline in non-demented older people has real-life consequences, such as impaired financial and medical decision-making (Agarwal et al., 2009; Boyle et al., 2012; Moyer and Marson, 2007). Yet, there is evidence that protective factors against cognitive decline exist. Educational attainment (Yu et al., 1989), multi-lingualism (Chertkow et al., 2010; Craik et al., 2010), and habitual “cognitive activity” (Wilson et al., 2003) all confer some protection against late-life cognitive decline and even against Alzheimer-related pathology (Landau et al., 2012; Li et al., 2013). This epidemiological evidence suggests advantages to developing cognitive training into a daily activity as a lifestyle intervention against cognitive aging. Several different methods for enhancing neurocognitive functioning in healthy populations have been previously examined, including non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), as described in other papers in this special issue. Our

approach used cognitive training to test a neurocognitive hypothesis that far transfer of training – ideally enhancing everyday cognitive functioning – depends on altered gray and white matter connectivity between the dorsal attention network and trained neocortex.

The ultimate goal of cognitive training in older people is far transfer of training to broadly enhance cognitive functioning. While near transfer occurs readily when trained and untrained tasks are very similar (Thorndike and Woodworth, 1901), far transfer to untrained abilities that share few cognitive and perceptual elements with training has been harder to demonstrate. Nevertheless, several investigators have recently shown far transfer in young people from working memory training to fluid ability, measured by the Raven's Progressive Matrices (Jaeggi et al., 2008, 2010, 2011; Klingberg et al., 2002, 2005). In contrast, of four studies that assessed far transfer in older adults from working memory training to fluid ability (Brehmer et al., 2011; Dahlin et al., 2008; Richmond et al., 2011; Schmiedeck et al., 2010), only one found transfer to the Raven's though not to other fluid ability measures (Schmiedeck et al., 2011). These four studies did find that working memory training transferred to working memory capacity (Schmiedeck et al., 2010), attention (Brehmer et al., 2011), and long-term memory retrieval (Brehmer et al., 2011; Richmond et al., 2011). Therefore, in both young and old working memory training leads to far transfer. Complex skills training can also induce far transfer in older adults. Although in the healthy old,

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studies that trained reasoning, speed, or memory did not obtain far transfer (Ball et al., 2002; Edwards et al., 2002; Neely and Backman, 1995; Rebok et al., 2007), studies that trained complex strategy use, task-switching, and problem solving did obtain far transfer (Basak et al., 2008; Karbach and Kray, 2009; Stine-Morrow et al., 2008). It should be noted that the literature is not balanced, such that working memory training is the predominant type studied in young people, but complex task training is the predominant type studied in older people.

That far transfer of cognitive training in older people has been obtained with certain types of tasks suggests the existence of an important common function. One candidate function is selective attention, which is important for cognitive learning and may be a driving factor in far transfer of training (Dayan et al., 2000; Jaeggi et al., 2008; Lewis et al., 2009; Tang and Posner, 2009). If far transfer of training depends on attentional control, then changes in neural networks associated with attention should be observed following training. Consistent with that, the superior parietal cortex (SPC) – a node of the dorsal attention network (Corbetta et al., 2002; Posner and Petersen, 1990) – appears to be particularly subject to training-related change. Parietal white matter (Scholz et al., 2009; Takeuchi et al., 2010) and gray matter function and structure (Dahlin et al., 2008; Draganski et al., 2004; Landau et al., 2007; Lewis et al., 2009; Olesen et al., 2004) have been consistently altered by a range of training tasks. The SPC projects to cortical sensory areas in the inferior and superior temporal lobes (Cavada and Goldman-Rakic, 1989), and has been shown to exert top-down attentional control over sensory processes (Baluch and Itti, 2011; Bouvier, 2009; Bressler et al., 2008; Desimone and Duncan, 1995; Kastner and Ungerleider, 2000; Sereno and Amador, 2006). This capability of the SPC to exert top-down attentional control and to rapidly undergo structural and functional change in training argues for an important role in training-related far transfer.

Brain connectivity – both structural and functional – is well-suited for assessing training-related transfer effects because of (a) previously demonstrated relevance for cognitive function (reviewed in Madden et al., 2009a), (b) susceptibility to change following training (Engvig et al., 2011; Lewis et al., 2009; Lovden et al., 2010; Voss et al., 2012), and (c) plasticity with expertise (Bengtsson et al., 2005; Hanggi et al., 2010; Jancke, 2009). Evidence that neuronal firing heightens myelination over weeks (Wake et al., 2011) and that re-myelination occurs in aged monkey visual cortex (Peters and Sethares, 2003) predicts that cognitive training could alter myelin integrity in aged white matter tracts. In older adults, white matter integrity is an important marker of neural structural change and cognitive function (Madden et al., 2009a). Cognitive training in older adults appears to affect integrity in frontal white matter tracts (Engvig et al., 2011; Lovden et al., 2010). However, the body of literature on training-related white matter changes in older adults is small and characterized by region-of-interest analyses that limit the interpretation of findings.

Training can also induce rapid changes in resting-state functional connectivity – a marker of spontaneous brain activity that closely resembles activity in task-related brain networks and codes prior task-related functional activity (Albert et al., 2009; Hasson et al., 2009; Lewis et al., 2009; Waites et al., 2005). In a study of training on a complex videogame, altered resting state connectivity was found in a host of frontal, parietal, and temporal regions that are part of the dorsal attention and executive function networks, indicating altered attentional control of sensory information (Voss et al., 2012). Also, a novel visual perceptual task decreased connectivity between trained visual cortex and the dorsal attention network, including the SPC and intraparietal sulcus (Lewis et al., 2009). This evidence points to dynamic changes induced by training in functional connectivity that may depend on altered parietal cortex-dependent attentional processes.

Hypothesis and predictions

Based on this evidence, we advance a working neurocognitive hypothesis that training resulting in far transfer leads to changes in

connectivity between SPC and trained cortex. By this view, the changed connectivity provides a durable neural infrastructure supporting transfer of training. An important role for the SPC in training is based on evidence that the SPC is altered structurally by training (Scholz et al., 2009; Takeuchi et al., 2010) and is critical for top-down attentional control over sensory processes (Baluch and Itti, 2011; Bouvier, 2009; Bressler et al., 2008; Desimone and Duncan, 1995; Kastner and Ungerleider, 2000; Sereno and Amador, 2006). We tested this hypothesis in an exploratory study by randomly assigning healthy older people to one of three training tasks. This design avoids the problematic use of a “no-contact” control group (Shipstead et al., 2012). Instead of examining whether some cognitive training is better than no training, we asked which type of training leads to broadly improved cognitive performance in older people. We selected videogame-like tasks that (a) varied in their targeted cognitive component processes, (b) have been successfully used as training tasks in healthy older people, and (c) have induced far transfer (described in *Methods*). We assessed structural connectivity (white matter integrity and functional connectivity), transfer to untrained cognitive functions, and the relation of performance on transfer tasks to measures of structural connectivity.

Based on our hypothesis that training-induced far transfer is accompanied by connectivity changes between SPC and trained cortex, we made the following predictions. (1) For the Rise of Nations (RON, BigHugeGames.com) training – a complex strategy game, we predicted far transfer to reasoning and connectivity changes between the SPC and medial frontal cortex. This is based on evidence that RON training transferred to the Raven's (Basak et al., 2008) and changed the volume of medial PFC (Basak et al., 2011). Medial PFC is part of the “cingulo-opercular network,” important in goal-directed activity and maintenance of task set, which in turn is important in carrying out a strategy (Dosenbach et al., 2007). No studies have assessed brain connectivity changes following RON training, but RON does emphasize strategic control, shown in fMRI studies to depend on dorsal prefrontal cortex function (Taren et al., 2011; Venkatraman et al., 2009). (2) For Brain Fitness (BF, PositScience.com) – an auditory perception game, we predicted changes in SPC-auditory temporal lobe connectivity based on evidence implicating the supramodal SPC in attentional control of auditory sensory processes (Shomstein and Yantis, 2004). No studies have assessed far transfer or brain connectivity changes following BF training. Based on auditory perception research, the temporal lobe should play a role in BF training (Binder et al., 1997; Grady et al., 1997; Lauter et al., 1985; Lockwood et al., 1999; Scheich et al., 1998; Wessinger et al., 2001). (3) For Space Fortress (Mane and Donchin, 1989) – a complex skill acquisition game, we predicted SPC-visual temporal lobe connectivity changes based on extensive previous work that identified the temporal lobe as part of the ventral pathway involved in object processing (Goodale and Milner, 1992; Haxby et al., 1991). SF transferred to untrained flight performance in young fighter pilots (Gopher et al., 1994) and to working memory in older adults (Stern et al., 2011), but no far transfer was observed in a study with comprehensive assessment of transfer in young adults (Boot et al., 2010). This predicts transfer to working memory performance and perhaps also to cognitive processes relevant for real-world demands. A resting state fMRI study finding functional connectivity increases and decreases in temporal, parietal, and frontal regions following SF training (Voss et al., 2012) predicts brain connectivity changes in the same regions involved in visual attention and executive control.

Regarding the direction of functional connectivity change related to training, there is little previous evidence on which to base predictions. The most relevant study trained young people intensively over days on a visual search task. They found that correlations between trained visual cortex and the dorsal attention network (including SPC and intraparietal sulcus) approached zero before training but were negatively correlated after training. The negative correlation was related to improved performance (Lewis et al., 2009). This finding predicts that successful training is associated with decreased functional connectivity in the dorsal attention network.

Regarding the direction of structural connectivity, there is substantial evidence on which to base predictions. Based on evidence of (a) greater diffusion-derived white matter integrity associated with better cognitive performance (Madden et al., 2009b) and (b) cognitive training-related white matter changes near the SPC (reviewed above), we predicted that successful training is associated with increased integrity of white matter subjacent to the SPC.

Methods

Participants

Initially, 46 healthy older individuals with no self-reported history of neurologic and psychiatric disorders began participation in the training study. Following standards used by ADNI, clinical signs for cognitive dysfunction were assessed with the Mini Mental State Exam (MMSE, cut-off: raw score <24) (Folstein et al., 1975; Kovacevic et al., 2009). T2-weighted FLAIR MRI images sensitive for lesion detection were acquired and evaluated by a neuroradiologist to screen for significant injuries and brain pathology. No adults were excluded based on their MMSE scores or clinical MRI evaluations, but four withdrew from the study at an early stage of participation because of time constraints or because they disliked the training game to which they were assigned. Therefore, a final sample of 42 adults completed the study (see Table 1 for demographics). In two of these individuals, resting state data was not acquired in the pre-training MRI session; due to technical problems, resting state data from two participants could not be included in the functional connectivity data analysis, resulting in a reduced sample size of 38 adults for the functional connectivity analysis. All procedures were approved by the Institutional Review Board at George Mason University. Prior to testing, written informed consent was obtained from each participant. Participants received monetary compensation for their time and effort.

Description of training tasks

Rise of Nations

RON is an off-the-shelf real-time strategy computer game used for training in this study. The complexity of game actions engages perceptual, attentional, motor, and various cognitive processes, including working memory, reasoning, visuospatial short-term memory, and task-switching (Basak et al., 2008, 2011). In the beginning of each game session, participants selected a nation to represent with the ultimate goal of extending that nation's territory. During the game, they encountered a complex environment consisting of the player's and another nation's settlement, characters, building structures, and a variety of tools available to the player to achieve victory (building cities, factories, institutions, and armies; extraction of rare resources; development of technologies; war). In each session, an emphasis on a specific game strategy (e.g., "quick battle") was selected by the experimenter according to a schedule that was fixed for all participants in the RON group. Within this strategy, options were selected that varied the difficulty (easiest, easy, moderate), speed of the game, and objectives for victory. Successful territory expansion was rewarded with points that were displayed on the screen. Participants were instructed to flexibly use a variety of game strategies to win. Headphones were provided for sound effects output (e.g., background music). Participants were instructed to end a session after 1 h and to continue an unfinished game on the next day, when necessary.

Brain Fitness (BF)

BF is an adaptive auditory perception computer game. Participants completed six types of tasks that were presented aurally (via headphones) and aurally-visually. They made judgments about frequency differences of sweeps (high or low), discriminated confusable syllables (tell us apart), matched pairs of confusable syllables (match it), recognized sequences of confusable syllables (sound replay), reconstructed

verbal instructions (listen and do), and identified details from a verbally presented story (story teller). BF has been shown to increase speed and accuracy of auditory perception in healthy older adults (Mahncke et al., 2006a, 2006b; Smith et al., 2009) as well as in cognitively impaired patient populations (Barnes et al., 2009; Rosen et al., 2011). The game is made adaptive through continuous adjustments of the difficulty of the tasks so that a correct response rate of approximately 85% is maintained throughout the game sessions (Smith et al., 2009). Tasks were displayed in the upper half of the screen and decisions were made by mouse click on designated fields. Performance feedback and praise (through infrequent animations) were also displayed there. In the lower half of the screen, an obscured object was shown that morphed on each trial to become increasingly defined (independently of participants' performance). At the end of a run, consisting of 5–10 trials, the object's identity was revealed. In each session, participants played 15-minute runs of four of the six game tasks. The task schedule varied across training sessions.

Space Fortress (SF)

SF – a challenging computer game developed by psychologists to study complex skill acquisition – was the third cognitive training task used in this study (Mane and Donchin, 1989; Shebilske et al., 2005). A visual display of several symbols representing a space fortress, spaceship, missiles, mines, and resources was given. Participants were required to increase the vulnerability of the fortress and destroy it, use the ship to evade mines and rockets fired by the fortress, and control ship movement within a given hexagon-shaped path. Changing symbols were used to assign friend or foe status to mines at the beginning of a run. Points were gained for destroying the fortress or foe mines and point accumulation was displayed on the screen. The right hand used a sensitive joystick to control the ship's movement and velocity through a frictionless environment and also to fire missiles. The left hand used a computer mouse to identify mines and select bonuses (points or missiles). Headphones were provided for sound effects output (firing of missiles and explosions). Parameters such as the speed of hostile elements and time allowed before the fortress fired at the ship were varied to adjust difficulty across sessions. In each training session, 12 runs of the game for 4 min each for a total of approximately 1 h of play were completed. Participants followed a variable emphasis training schedule that required them to learn individual aspects of the game (improving ship control and velocity or improving speed) separately for the first ten days of training, followed by a fixed priority period where no particular strategy was emphasized for the remainder of the training.

Experimental design

Participants were randomly assigned to the RON, SF, or BF cognitive training tasks as they entered the study. Initial sessions of each game were conducted in the laboratory with tutorials that used a variable priority (Gopher et al., 1989) approach in which important game skills were emphasized separately before being practiced together. During initial sessions, a trained research assistant guided the participant through the tutorials. Once participants were able to play independently, they were equipped to train at home with a laptop and the game, headphones, and a joystick (for SF only). They then followed a specific training schedule for each game for about six weeks. They were required to

Table 1
Demographics and cognitive function means and standard deviations.

Training group	Age	Gender	Education	MMSE ¹
BF	69.70 +/- 6.9	6M/8F	17.0 +/- 2.5	28.6 +/- 2.0
SF	68.52 +/- 5.6	6M/8F	16.5 +/- 2.5	28.4 +/- 1.7
RON	69.41 +/- 2.3	5M/9F	15.9 +/- 3.5	28.9 +/- 1.5

¹ Mini-Mental State Exam (Folstein et al., 1975).

train six days a week for 1 h each day. They were required to play at home for 1 h of training three days a week and to come to the laboratory for 1 h of supervised training also three days a week. Participants were instructed to refrain from conversations, radio, and TV during training at home to reduce potential distraction. When they came to the laboratory for supervised sessions with the laptop, stored games played at home were downloaded for analysis. Before and after the training, participants underwent cognitive and MRI assessment, as detailed below.

Pre- and post-training neuropsychological and information-processing testing

The assessment battery was chosen to assess a range of abilities: reasoning/problem-solving, episodic memory, and working memory.

Reasoning

Reasoning was assessed with the WAIS III Matrix Reasoning subtest (Wechsler, 1997), the Everyday Problems Test (EPT, Willis and Marsiske, 1993) for everyday reasoning, and the Word Series and Letter Series tests (Schaie, 1985) for analogical reasoning. For Matrix Reasoning, participants were asked to correctly complete an incomplete design by selecting from five choices the part of the design needed (26 items). The total raw score was used for further analyses. For EPT, questions were posed about such daily problems as interpreting a phone bill rate chart or a prescription label. Parallel A and B versions (42 items each) were available for this test and therefore given at pre- and post-training sessions to avoid practice effects. Accuracy and the time to complete the test (minutes) were recorded. Finally, the Word Series and Letter Series tests were used to measure analogical reasoning (30 items each). Letters and words for months and days of the week were presented in a logical order and participants were required to complete each series according to the logical rule encountered. The percentage correct for Letter and Word Series tests were computed for further analyses.

Episodic memory

To assess episodic memory, the Wechsler Memory Scale Logical Memory subtest (immediate and delayed recall) was administered with the stories from WMS-III and WMS-IV used as parallel forms for pre- and post-training sessions (Wechsler, 1987, 2009). Participants were instructed to retain as much information as possible from an aurally presented short biographical story and then to retrieve as much information as possible immediately and after a 30 minute delay. The numbers of recollected items at immediate and delayed recall were recorded.

Working memory

Spatial working memory was assessed with an information-processing visuospatial delayed match-to-sample task. Auditory working memory was assessed by the Letter Number Sequencing subtest of the Wechsler Adult Intelligence Scale III (WAIS III, Wechsler, 1997). The spatial working memory task manipulated both working memory load and target-test distance (Greenwood et al., 2005; Parasuraman et al., 2005). Participants were shown one, two, or three target dots and asked to judge whether the location of a test dot, displayed after a 3 s delay, matched the location of one of the target dots. Target-test dot location distances varied between 2°, 4°, and 8° of visual angle. The accuracy from trials with a medium working memory load (two target dots) and the closest target-test dot distance (2° visual angle, hardest discrimination) were used for further analyses. The Letter Number Sequencing subtest of the Wechsler Adult Intelligence Scale III (Wechsler, 1997) assessed auditory working memory. Participants were read sequences of alternating digits and letters in scrambled order and required to immediately retrieve them in ascending numeric

followed by alphabetical order (21 items). The total raw score was retained for further analyses.

Analysis of training outcome measures

Statistical analyses of all outcome measures were conducted using the PASW statistical package (www.spss.com) with alpha set to $p < 0.05$ (two-tailed). The three groups were compared on the number of training sessions completed, age, years of education, and overall cognitive functioning (MMSE raw score) using the Kruskal–Wallis test for non-parametric analyses in independent samples ($p < 0.05$). For the RON game, the average scores from the first and last three sessions were compared to assess improvement on composite defense and offense scores. The defense composite score is the sum of scores for resources spent on economy, research, and territory development. The offense composite score is the sum of combat (the percentage of the total resource value of all destroyed enemy units and buildings) and armies killed (the total number of destroyed enemy units) scores. For the BF game, the average scores from sessions two through four and the last three sessions across the six BF tasks (high or low, tell us apart, match it, sound replay, listen and do, story teller) were computed to obtain a total improvement score. The first session of each participant used for practicing the task was excluded from this analysis because it is designed so that participants are provided with the correct answers. The scores were then added across tasks to yield a composite score of performance to assess performance change on this game. For SF, the average scores from the first and last three sessions were compared to assess overall improvement on the task using the total score (sum of points obtained for successful ship defense and attacks, speed, velocity, and ship control subscores). To assess whether pre-to-post-training changes in performance were significant, paired samples t-tests on the pre- and post-training game scores were computed for each group (RON, BF, SF) separately.

Analysis of cognitive outcome measures

Behavioral analyses were performed using PASW 18 with alpha set to $p < 0.05$ (two-tailed). Two MANOVAs were conducted on the cognitive data. MANOVA requires that there be more cases than dependent variables and power is increased when groups are equal and the correlation between dependent variables is high and negative (Tabachnick and Fidell, 2001). These restrictions argue for (a) limiting the number of dependent variables and (b) selecting them based on inter-correlations. Tests that yielded high, positive inter-correlations with the included measures of interest (Letter Series was positively correlated with Word Series and WMS Logical Memory immediate recall was positively correlated with WMS Logical memory delayed recall) were excluded from the MANOVA. WMS Logical Memory immediate was selected because it is a widely-used cognitive assessment instrument. Word Series was selected over Letter Series arbitrarily.

The first omnibus MANOVA was conducted to assess whether the groups differed at pre-test on the cognitive measures of interest as dependent variables (Matrix Reasoning raw score, EPT time to complete the test, Word Series percent correct, working memory accuracy, Logical Memory raw score at immediate recall, and Letter Number Sequencing raw score). A second omnibus MANOVA was conducted to assess whether the groups (BF, SF, RON) differed in transfer of training to untrained cognitive performance. Dependent variables were post-pre-training differences in the same six cognitive measures listed above. To assess the dependent variables for their importance, univariate F-tests were computed and corrected for multiple comparisons with the Bonferroni–Holm procedure (Holm, 1979). For those outcome measures that yielded significant group differences, post-hoc pair-wise comparisons were computed using the Tukey HSD test. In addition, we computed a discriminant function analysis to determine the effectiveness of these dependent variables in predicting the three training groups.

Structural and functional MRI data

MRI data acquisition

A Siemens Allegra head-only MRI scanner equipped with a standard quadrature transmit/receive head coil was used for MRI data collection. Diffusion tensor imaging (DTI) was used to acquire brain images in axial plane using a diffusion-weighted single-shot echo-planar sequence with 12 gradient directions (1000 s/mm²; TE = 75 ms; TR = 10,000 ms; slice thickness = 3 mm, 50 slices, acquisition matrix = 128 mm × 128 mm) and 3 repetitions. Functional connectivity images were acquired at rest with participants' eyes open in axial plane with a single-shot echo-planar sequence sensitive to change in the blood oxygenation level dependent (BOLD; TR = 2500 ms, TE = 30 ms, 42 slices, 3 × 3 × 3 mm resolution, flip angle 70°).

Diffusion imaging data processing

DTI images were processed using FSL 4.1.8 (Smith et al., 2004). Diffusion-derived indices of white matter integrity were obtained by first correcting for head movements and eddy currents, then creating a brain mask on non-diffusion-weighted reference images, followed by a voxel-wise fitting of the diffusion tensor model using the mask. The resulting diffusion output yielded maps for axial diffusivity (AD), radial diffusivity (RD), mean diffusivity (MD), and fractional anisotropy (FA) for each participant. AD is defined as the eigenvalue of the largest eigenvector in the diffusion tensor model, whereas RD is the average of the two smaller eigenvalues (Basser, 1995). MD is defined as the mean of the three eigenvalues (Basser, 1995; Pierpaoli et al., 1996). FA is a scalar index of white matter integrity calculated by the magnitude of the anisotropic part of the diffusion tensor divided by the entire diffusion tensor to quantify directionality of water diffusion in the brain (Basser, 1995; Pierpaoli et al., 1996).

Tract-based spatial statistics (TBSS; Smith et al., 2006) was used to assess significant differences between diffusion indices pre- compared to post-training on the whole-brain level. Standard TBSS processing was combined with a longitudinal TBSS approach described in Engvig et al. (2011) aimed at optimizing the within-subject alignment of pre- and post-training diffusion maps. First, the pre- and post-training FA maps for each participant were aligned using the FSL SIENA script that yielded pre-training FA maps that are halfway registered to post-training FA maps and vice versa (Smith et al., 2002). Specifically, SIENA was used to estimate two-time point percentage brain volume change by considering brain and skull information from the pre- and post-training diffusion data. These within-subjects aligned pre- and post-training FA maps were separately subjected to the following TBSS procedures: removal of brain edge outliers from the diffusion tensor fitting, non-linear registration to FMRIB58_FA standard space, linear transformation of registration parameters into 1 mm isotropic MNI152_T1 space, averaging of normalized maps to create mean FA maps across participants, and skeletonization of mean FA maps to restrict data analyses to voxels with an FA > 0.2. These procedures were then also applied to the within-subjects aligned AD, RD, and MD maps using the TBSS-non-FA script. Then, post-pre training differences of the diffusion data were computed, yielding four data input files (for AD, RD, MD, and FA) for subsequent statistical analyses. To obtain a skeletonized mask file that included pre- and post-training data for all participants, the halfway registered pre- and post-training FA maps were averaged for each participant and the TBSS processing stream was applied to the averaged FA maps for all subjects from all groups. The mask was used for analyses of the four DTI indices.

Statistical analyses of AD, RD, MD, and FA data

The pre-post-training AD, RD, MD, and FA difference maps were fed into three-sample independent F-tests to assess group differences in the four diffusion indices and contrasts were set up to assess training-related changes in pairs of groups. FSL's randomize tool with threshold-free cluster-enhancement (tfce) thresholding was used to conduct these

statistical tests and to correct for multiple comparisons (Nichols and Holmes, 2002). Statistical maps were overlaid onto a rendered brain volume (MNI152_T1_1mm) for display purposes. The Juelich White Matter Labels and Juelich Histological Atlas implemented in FSL 4.1.8 were used to determine the identity of white matter tracts that revealed significant effects. Results from the pairwise comparisons were used to define masks for subsequent fiber tractography analyses to obtain further information about the pathways of the identified tracts.

Functional connectivity data processing

Resting state images were processed using FSL 4.1.8 following the seed-based approach described in Van Dijk et al. (2010). The first four volumes were discarded to account for T1 equilibrium effects. Preprocessing included head motion correction with rigid body translation and rotation, slice scan time order correction, high pass filtering (12.5 s), and spatial smoothing with a 6 mm full-width-at-half-maximum Gaussian filter. Images were registered to MNI152_T1_2mm standard space and resampled to 2 mm³ to allow for group analyses.

To perform a whole-brain seed-based correlation analysis in the dorsal attention network, we submitted the preprocessed and registered pre- and post-training connectivity maps to a regression analysis (one-sample t-test, General Linear Model) with the right SPC signal as regressor of interest, six nuisance parameters to control for head motion (translation and rotation), and six additional nuisance parameters to control for physiological noise from cardiac and respiratory cycles. The SPC signal was extracted from a 2 mm spherical region for which previous work found functional connectivity changes following sensory training (Lewis et al., 2009; MNI coordinates: 14, −67, 53). The motion parameters were available from the head motion correction performed during preprocessing. Physiological noise nuisance parameters were estimated from the averaged whole brain, deep white matter, and cerebrospinal fluid (CSF) signals. The white matter signal was extracted from a region in the right frontal white matter (MNI: 26, 40, 2; 6 mm sphere) and the CSF signal was extracted from the left lateral ventricle (MNI: −20, −38, 16; 4 mm sphere). Z-transformed whole brain average, white matter, and CSF signals were used as nuisance parameters. In addition, first derivatives (the rate of change from one value to the next value in the time series) of these z-transformed parameters were also included as nuisance regressors. Pre-post training difference maps of the resulting SPC correlation maps were computed yielding the data input for subsequent statistical analyses.

Statistical analyses of functional connectivity data

The pre-post-training resting state connectivity difference maps were fed into a three-sample independent F-test to assess group differences in SPC connectivity changes and contrasts were set up to assess training-related changes in pairs of groups. FSL's randomize tool with threshold-free cluster-enhancement (tfce) thresholding was used to conduct these analyses and to correct for multiple comparisons. The resulting corrected maps were overlaid onto a rendered brain volume (MNI152_T1_2mm) for display purposes. The Harvard Oxford Cortical Structures Atlas and the Talairach Daemon Labels, implemented in FSL 4.1.8 were used to determine the identity of gray matter structures that revealed significant effects.

Fiber tractography analyses

Single-seed probabilistic tractography implemented in FSL 4.1.8 was used to create white matter path distributions from white matter areas that showed significant effects in the DTI indices (TBSS results). Local diffusion directions for the two main fiber orientations in each voxel were computed using a fully automated Bayesian estimation method (BedpostX; Behrens et al., 2007). Tractography was performed on each participant's data (post-training scans) in standard space using Probtrackx to construct fiber tracts that pass through the seeded white matter voxels (5000 samples drawn through the probability

distributions of each seed voxel; step length = 0.5 mm; curvature threshold of 0.2).

Masks including all voxels at peak intensity in the corrected statistical maps from significant F tests and contrasts were created in standard space. For each seed region, the white matter connectivity map of each participant was computed and thresholded at 50% to include pathways that were evident in at least half of the samples that were drawn through each voxel. To create group overlays, the thresholded maps were binarized and summed for all participants. These maps yielded the highest values in areas with the most overlap of tracts among participants.

Correlational analysis between brain connectivity and cognitive performance

For the correlations between cognitive performance and white matter integrity, the average white matter integrity values were extracted from regions that showed significant training-related effects (in voxels of peak intensity). For the correlations between cognitive performance and functional connectivity, z-transformed connectivity values were extracted from regions that showed significant training-related effects (in voxels of peak intensity). White matter integrity and functional connectivity values were extracted from both the pre-training and post-training diffusivity maps. The pre-post-training difference between these values was computed for each connectivity measure. Post-training connectivity and pre-post-training connectivity difference scores were correlated with scores from the neuropsychological and cognitive measures that showed transfer effects using the pre-post-training difference scores. This allowed us to demonstrate a direct link between training-related brain connectivity changes and training-related performance changes in untrained transfer tasks. Showing this link is important because it provides correlational evidence for the importance of brain connectivity changes in transfer of training to untrained tasks.

Results

Training outcome measures

The three training groups were comparable on background characteristics including age (mean, SD; RON: 69.6, 3.7; BF: 69.5, 7.0; SF: 68.2, 5.4; $p = 0.64$), years of education (RON: 15.7, 3.3; BF: 17.1, 2.6; SF: 16.2, 2.7; $p = 0.46$), and general cognitive ability (MMSE; RON: 28.6, 1.6; BF: 28.4, 2.1; SF: 28.3, 1.7; $p = 0.86$). They also did not differ significantly on the number of completed training sessions (mean: RON: 31, BF: 35, SF: 33, $p = 0.10$).

Improvement on the RON game was evident in changes in the total defense but not in the total offense score (defense: $t = -2.59$, $p < 0.05$; offense: $t = -0.21$, $p = 0.83$, corrected for multiple comparisons). BF game data from one participant was not recorded accurately and therefore excluded from the analysis. Improvement on the BF game was evident in a significant post- versus pre-training difference on the total score (sum of points for high or low, tell us apart, match it, sound replay, listen and do, and story teller tasks), indicating training-related improvement in game performance ($t = 4.76$, $p < 0.001$). Improvement on the SF game was evident in a significant post- versus pre-training difference on the total score (sum of points obtained for successful ship defense and attacks, speed, velocity, and ship control subscores), indicating training-related improvement in game performance ($t = 3.05$; $p < 0.01$).

Neuropsychological and information-processing measures

A MANOVA comparing participants in the three groups on their pre-training scores of neuropsychological and laboratory measures (Matrix Reasoning raw score, EPT time to complete test, Word Series percent correct, working memory accuracy, Logical Memory raw score at immediate recall, and Letter Number Sequencing raw score) showed no difference

in performance at baseline ($p > 0.05$). A MANOVA comparing participants in the three groups on the z-transformed post-pre-training difference scores of these measures revealed a significant multivariate main effect for training group, Wilks' $\lambda = 0.45$, $F(14, 66) = 2.34$, $p < 0.01$, partial eta squared = 0.332. Power to detect the effect was 0.954. Levene's test of equality of error variances revealed that the hypothesis of equal covariance matrices could not be rejected. To assess the dependent variables for their importance, univariate F-tests were computed. Significant univariate main effects of training group were obtained for difference scores for EPT Time ($F(2,39) = 5.34$, $p < 0.01$, partial eta squared = 0.215), working memory accuracy ($F(2,39) = 5.03$, $p < 0.001$, partial eta squared = 0.205), and Matrix Reasoning ($F(2,39) = 3.40$, $p < 0.044$, partial eta squared = 0.148). These findings held after correction for multiple comparisons using the Bonferroni-Holm procedure. Results from the univariate ANOVA are plotted in Fig. 1. Supplementary Table S1 contains pre- and post-training means and standard deviations for each transfer measure assessed. In addition, that table contains effect sizes (partial eta squared) of a pre vs. post comparison for each training group. A discriminant function analysis was also conducted on the same data, which showed an overall accuracy of 66.7% in classifying all three groups. There was 64% accuracy in classifying BF, 78.6% accuracy in classifying RON, and 57.1% accuracy in classifying SF.

Regarding transfer to working memory, the post-pre-training increase was largest in the SF group, whereas RON training transferred negatively. Post-hoc Tukey tests revealed that the difference in working memory change between SF and RON was significant ($p < 0.01$). BF had little effect on working memory performance. Regarding transfer to Matrix Reasoning, the post-pre-training difference was largest in the BF group, a smaller gain was found in the RON group. SF transferred negatively. Post-hoc Tukey tests revealed that the difference in Matrix Reasoning change between SF and BF was significant ($p < 0.05$), and there was a trend for a difference between RON and SF ($p = 0.1$). Regarding transfer to EPT, a decrease in time to complete the test was found for the BF and SF groups, both indicating positive training transfer. In contrast, RON training did not transfer to shorter times to complete the EPT test, with post-training times being essentially the same as pre-training times. Post-hoc Tukey tests revealed that the differences in EPT time change between both SF and RON ($p < 0.01$), and BF and RON ($p < 0.05$), were significant. Auditory working memory (Letter Number Sequencing), episodic memory (WMS Logical Memory immediate recall), and Word Series performance did not differ significantly as a function of training condition.

In what follows, we describe the effects of cognitive training on white matter integrity, functional connectivity, and the relation of each to cognitive performance.

White matter measures

1. How did cognitive training change white matter integrity?

To answer this question, we assessed whether cognitive training changed diffusion-derived white matter integrity from pre- to post-training. The three-sample independent F tests conducted on the pre-post-training difference maps for AD, RD, MD, and FA revealed significant effects of training group only for AD. The overall F test revealed an increase in AD in small regions of the left lingual gyrus ($p < 0.0005$, tfce-corrected; MNI, $-12, -84, -2$) and right thalamus ($p < 0.05$, tfce-corrected; MNI, $5, -16, -7$). Probabilistic fiber tracking from the lingual gyrus revealed occipito-temporal pathways (Fig. 2a). The second fiber orientation revealed tracts that interconnect areas in the occipital cortex. Probabilistic fiber tracking from the thalamus revealed pathways that connect the thalamus with the ventral frontal pole (Fig. 2b). The second fiber orientation revealed tracts that connect the somatosensory cortex with spinal areas.

Analyses of pairs of training groups revealed the following significant results. AD changed from pre- to post-training in the BF group

more strongly than in the SF group in white matter of the right temporo-occipital junction ($p < 0.05$, tfce-corrected; Fig. 2c). To determine the direction of change, extraction of pre- and post-training AD values from peak voxels in this region revealed that BF training increased AD while SF training decreased AD from pre- to post-training (Table 2). Significant voxels in the right temporo-occipital junction were found in the inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), corpus callosum, and posterior thalamic radiation. The IFOF connects the frontal lobes with occipital, parietal, and temporal lobe areas, ILF connects temporal and occipital lobes, and the posterior thalamic radiation contains sensory fibers from the thalamus (e.g., optic and acoustic radiations). Probabilistic fiber tracking from peak intensity voxels revealed occipito-superior temporal pathways (Fig. 2c).

Significant changes were also found between BF and RON. AD changed from pre- to post-training in the BF group more strongly than in the RON group in white matter of the right temporo-occipito-parietal junction ($p < 0.05$, tfce-corrected; Fig. 2d). To determine the direction of change, pre- and post-training AD values were extracted from peak voxels in this region. Results revealed an AD increase for BF and an AD decrease for RON from pre- to post-training (Table 2). Significant white matter voxels in the right temporo-occipito-parietal junction were found in the superior longitudinal fasciculus (SLF, temporal part), IFOF, ILF, posterior thalamic radiation, internal capsule (retrolenticular part), acoustic radiation (near Heschl's gyrus), white matter subjacent to BA 39, and corpus callosum. Probabilistic fiber tracking from peak intensity voxels revealed pathways within the occipital lobe and occipito-temporal tracts (Fig. 2d). In sum, we found that AD increased in occipito-temporal white matter following BF training, whereas AD decreased

there for SF and RON. Further, these differences in AD were significant for BF compared to the two other games.

2. What was the relationship between cognitive performance and white matter integrity change?

To answer this question, we assessed correlations between cognitive performance and white matter integrity using the respective change measures from pre- to post-training. The correlational analyses between AD from the *thalamus* mask and cognitive measures yielded a significant positive correlation between the pre-post-training difference in thalamic AD and the pre-post-training difference in spatial working memory accuracy ($\rho = 0.44$; $p < 0.005$), indicating that a greater increase in thalamic AD was associated with a greater gain in working memory performance. The correlational analysis between occipito-temporal AD (based on the *BF vs. SF contrast*) and cognitive measures yielded significant findings for EPT time to complete the test and spatial working memory accuracy. For EPT time, a negative correlation was found between the pre-post-training AD difference and the pre-post-training difference in EPT time ($\rho = -0.32$, $p < 0.05$), indicating that a larger increase in occipito-temporal AD was associated with a greater reduction in time to complete the EPT. For working memory, a negative correlation was found between the pre-post-training difference in AD and the pre-post-training difference in spatial working memory accuracy ($\rho = -0.35$; $p < 0.05$), indicating that a larger increase in occipito-temporal AD was associated with a smaller gain in working memory accuracy. The correlational analysis between occipito-temporo-parietal AD (based on the *BF vs. RON contrast*) and cognitive measures yielded a significant finding for spatial working memory accuracy. Specifically, a negative correlation was found

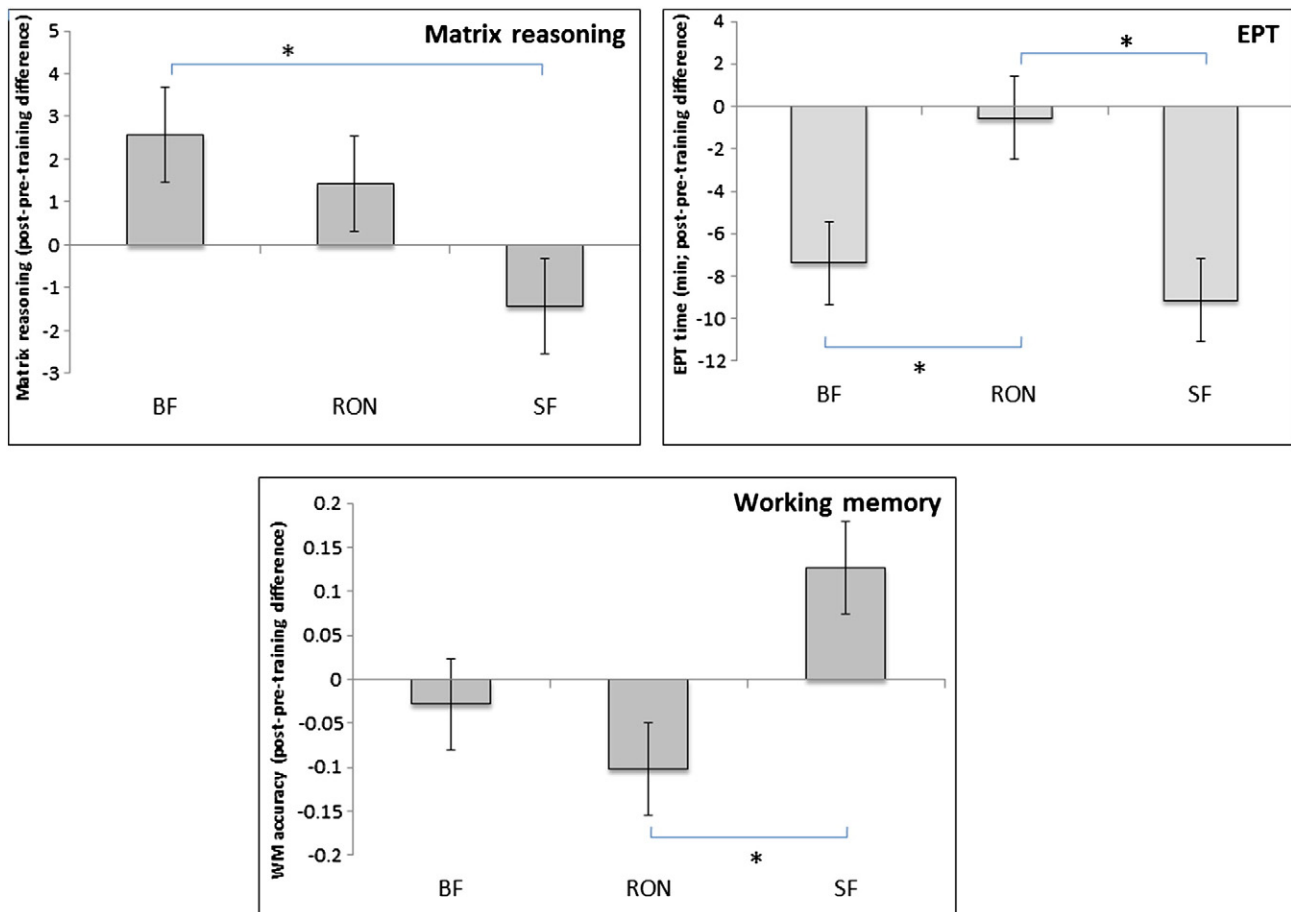


Fig. 1. Transfer effects. Post-pre-training difference scores from the neuropsychological and laboratory performance measures. Top left: Post-pre-training difference scores from matrix reasoning. Top right: Post-pre-training difference scores from the EPT time to completion measure. Bottom: Post-pre-training difference scores from the working memory task under the difficult non-match condition under which target (memory) and test (stimulus) locations were about 1° (visual angle) apart.

between the pre–post-training difference in AD and the pre–post-training difference in working memory accuracy ($\rho = -0.40$; $p < 0.05$), indicating that a larger increase in occipito-temporo-parietal AD was associated with a smaller gain in working memory accuracy.

Functional connectivity measures

1. How did cognitive training change functional connectivity?

The three-sample independent F-test conducted on the pre–post-training difference maps (whole-brain z-transformed SPC correlation maps) revealed a trend for a significant effect of group in the left posterior ITL ($p = 0.08$; tfce-corrected; MNI: $-64, -46, -18$) and left anterior ITL ($p = 0.1$; tfce-corrected; MNI: $-66, -12, -24$). Analyses of pairs of groups revealed significant differences between SF and RON. Specifically, functional connectivity between the right SPC and the left posterior ITL changed from pre- to post-training in the SF group more strongly than in the RON group ($p = 0.02$, tfce-corrected; Fig. 3a). Extraction of the functional connectivity values from the posterior ITL peak intensity voxels revealed that a positive ITL–SPC connectivity at pre-training in the SF group decreased to a negative connectivity at post-training, thereby indicating a training-related connectivity decrease in this group. In RON, ITL–SPC connectivity was negative at pre-training and became less negative at post-training (Table 3). In sum, SF training decreased connectivity while RON training increased connectivity between the SPC and posterior ITL. These changes were statistically significant.

Significant differences were also found between BF and RON. Specifically, functional connectivity between the right SPC and the left anterior ITL changed from pre- to post-training in the BF group more strongly than in the RON group ($p = 0.03$, tfce-corrected; Fig. 3b). Extraction of the functional connectivity values from the anterior ITL peak intensity

voxels revealed that a negative ITL–SPC connectivity at pre-training in the BF group became more negative at post-training, indicating a training-related connectivity decrease in this group. In RON, ITL–SPC connectivity was negative at pre-training and positive at post-training (Table 3). In sum, BF training decreased connectivity while RON training increased connectivity between the SPC and anterior ITL. These changes were statistically significant.

2. What was the relationship between cognitive performance and functional connectivity changes?

The correlational analysis between SPC–posterior ITL connectivity from the mask that was based on the SF vs. RON contrast and cognitive measures yielded a significant finding for EPT time to complete the test. Specifically, a positive correlation was found between the pre–post-training difference in SPC–posterior ITL connectivity and the pre–post-training difference in EPT time ($\rho = -0.57$, $p < 0.001$), indicating that a greater decrease in SPC–posterior ITL connectivity from pre- to post-training was associated with a greater reduction in time to complete the EPT.

Discussion

Summary of findings

In the present study, we tested a neurocognitive hypothesis that far transfer of cognitive training – the ultimate goal of interventions aimed at cognitive enhancement in older people – depends on changed connections involving the dorsal attention network (Corbetta et al., 2008), specifically the SPC. As reviewed earlier, that hypothesis was based on a small but consistent literature showing that training selectively affects nodes of the dorsal attention network (Draganski et al., 2004; Klingberg et al., 2002; Lewis et al., 2009; Scholz et al., 2009; Takeuchi et al., 2010).

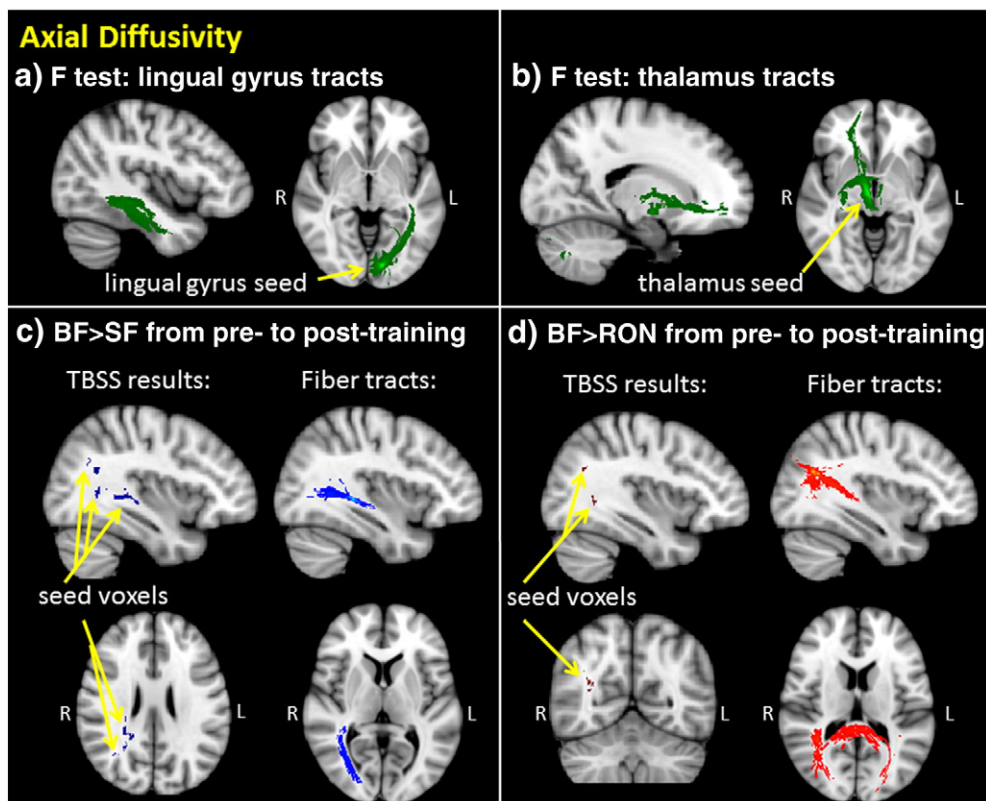


Fig. 2. Axial diffusivity. Results from the tract-based spatial statistics (TBSS) and associated fiber tractography analyses are displayed. a/b. Probabilistic tractography results are shown for the significant areas in the F statistical map of the comparison of pre–post-training changes in the three groups: lingual gyrus connections with the temporal lobe (a); thalamus connections with the frontal pole (b). c. TBSS and probabilistic tractography findings from the BF versus SF contrast, indicating occipito-temporal connections. d. TBSS and probabilistic tractography findings from the BF versus RON contrast, indicating occipito-temporal and occipito-occipital connections. R, right; L, left.

Table 2
Means of extracted pre- and post-training axial diffusivity.

Training group	Temporo-occipital (contrast BF > SF)		Temporo-occipito-parietal (contrast BF > RON)	
	Pre-training	Post-training	Pre-training	Post-training
BF	0.001199	0.001245	0.001467	0.001511
SF	0.001185	0.001179	–	–
RON	–	–	0.001487	0.001478

BF, Brain Fitness; SF, Space Fortress; RON, Rise of Nations.

However, these training-related changes in parietal cortex have not previously been related to *transfer* of training – the objective of the present study. Overall, the results provided partial support for the proposed hypothesis by finding involvement of both ventral and dorsal attention networks in cognitive training that induced far transfer.

Brain Fitness

We found the strongest training effects in older people following auditory perception (BF) training which resulted in positive far transfer to everyday problem solving and reasoning. BF training was also associated with changes in both the dorsal and the ventral attention networks. In the dorsal network, we found reduced functional connectivity between the SPC and the ITL. In the ventral network, we found changed integrity of occipito-temporal white matter following BF training, compared to each of the other training tasks. This change was associated with improved untrained everyday problem solving.

Space Fortress

We also found positive far transfer effects following complex skill acquisition training (SF) in older people, with far transfer to everyday problem solving and working memory. The hypothesized role of the dorsal attention network in that transfer was supported by the functional connectivity findings. SPC–ITL connectivity decreased more strongly following SF compared to RON training. This change was associated with improved untrained everyday problem solving. No effects were found on white matter integrity from SF training.

Rise of Nations

No evidence of positive transfer of complex strategy training (RON) in older people was found. RON training had no effect on everyday problem solving or reasoning, but reduced working memory performance. No effects were found on white matter integrity or functional connectivity from RON training.

Transfer of training to untrained tasks and possible neural underpinnings

Brain Fitness

We found positive transfer to untrained reasoning and everyday problem solving, consistent with previous research showing that fluid ability can benefit from cognitive training (Buschkuhl and Jaeggi, 2010), including in older adults (Basak et al., 2008; Karbach and Kray, 2009; Stine-Morrow et al., 2008).

In contrast, BF training did not transfer to auditory or visuospatial working memory. The location of the white matter changes that we found (discussed below) and the negative correlation between white matter integrity and working memory changes support this conclusion. Two previous studies found that BF training in healthy old transferred to auditory memory (Mahncke et al., 2006b; Smith et al., 2009). However, both these studies used a composite score of the auditory memory subtests of the Repeatable Battery for the Assessment of the Neuropsychological Status (RBANS). Therefore, it is unclear which specific types of memory experienced transfer effects in those studies and it is difficult to compare their results with our findings.

That BF training did transfer to fluid ability – the first such report – is particularly interesting in light of studies that found working memory

Table 3
Means of extracted pre- and post-training ITL connectivity with the SPC.

Training group	Anterior ITL (contrast BF > RON)		Posterior ITL (contrast SF > RON)	
	Pre-training	Post-training	Pre-training	Post-training
BF	–0.134	–1.505	–	–
SF	–	–	0.303	–1.076
RON	–0.663	0.232	–0.858	–0.439

training in young people transferred to untrained fluid abilities (Jaeggi et al., 2008, 2010, 2011; Klingberg et al., 2002, 2005).

What are the neural mechanisms that might underlie the far transfer from BF perception training? Although our hypothesis predicted involvement of the dorsal attention network in far transfer of training, our evidence implicates both dorsal and ventral attention networks. Regarding the ventral network, we found that BF training increased AD in occipito-temporal connections relative to the other two training tasks. We saw these changes in white matter pathways connecting core regions of the ventral attention system, including the right temporo-occipito-parietal junction, right lateral occipital cortex, and right ventral frontal cortex (Corbetta et al., 2008). The ventral attention system is thought to be engaged during bottom-up reorienting toward novel, behaviorally-relevant stimuli (Corbetta et al., 2008) and the occipito-temporal and ventral fronto-thalamic pathways that were altered following BF training connect regions critically involved in reorienting attention. This evidence suggests that BF training remodeled the connections of the ventral attention system.

Alternatively, the observed changes in integrity of white matter connecting the occipital and temporal lobes may indicate altered auditory–visual information integration following BF training. Comparing BF with each of the other games revealed effects on projections to the superior temporal lobe, which facilitate multimodal interactions between the visual and auditory domain (Calvert et al., 2001). That the increased AD in occipito-temporal white matter was correlated with improved everyday problem solving performance suggests that remodeling of these occipito-temporal connections may be one mechanism underlying the observed transfer of training to untrained abilities.

What do the observed changes in AD reflect and how are they related to cognitive change? Animal research indicates that AD may reflect integrity of axon morphology (Budde et al., 2009; Song et al., 2003). A few previous studies, including four training studies, have related AD to cognitive performance, with mostly inconclusive results (Bennett et al., 2010; Davis et al., 2009; Engvig et al., 2011; Keller and Just, 2009; Lovden et al., 2010). In one study, AD was altered following attention state training in some white matter fibers, but not in others (Tang et al., 2012). Most commonly, cognitive performance and training-related changes have been linked to changed FA and, to some extent also to MD and RD (Madden et al., 2009b). We assessed these diffusion measures but did not find them altered by cognitive training. RD – thought to be related to the degree of axonal myelination and density (Nair et al., 2005; Song et al., 2002, 2003, 2005) – was previously reported to be altered following training by four separate training studies (Engvig et al., 2011; Keller and Just, 2009; Lovden et al., 2010; Tang et al., 2012). However, of those, only Engvig et al. (2011) used non-biased analysis methods. Based on findings from these studies and evidence that neuronal firing heightens myelination (Wake et al., 2011), we predicted that training on a new task would increase neuronal activity and thereby myelination or axon density in affected networks, seen as a decrease in RD. Given that we did not find RD changes, the training effect on white matter that we observed is not attributable to heightened myelination, but may rather indicate some change in axon morphology.

This pattern we observed of increased AD in the absence of FA, RD, or MD changes has not been previously reported in the context of life span development or cognitive interventions. Change in AD in aging – increased or decreased AD, depending on the specific tract

assessed – has been seen in combination with increased RD (Bennett et al., 2010; Burzynska et al., 2010; Sullivan and Pfefferbaum, 2006). This increased RD/decreased AD aging pattern was previously reported for the retrolenticular part of the internal capsule (Bennett et al., 2010), a tract we found to be affected by training. Based on that, a training-related increase in AD in this tract may indicate a process that counteracts age-related AD decline.

Emphasizing the importance of the observed AD change, we found a correlation between AD change and performance improvement in everyday problem solving (EPT). This finding underscores the significance of increased AD for training-related gain. Based on the Tang et al. (2012) study that found decreased AD following attention state training, and the otherwise inconclusive AD findings reported in the training literature, it is possible that increased AD following BF training signals a decrease in white matter integrity. However, we found an AD increase that (a) correlated positively with EPT performance and (b) was specific to BF training (observed in comparison to both other training groups), suggesting that an AD increase may indicate improved integrity of white matter due to remodeling by training. In general, the complex relationships between the different diffusion indices and cognitive performance are not fully understood. Only a small number of cognitive training studies have assessed AD and further studies are needed to increase understanding of training-related AD changes.

Our results also implicate the dorsal attention network in BF training. Transfer of BF training was accompanied by reduced functional connectivity between the SPC and the ITL. Although there is little previous work, our results are consistent with a recent training study that also heavily engaged sensory functions and also found that training decreased functional connectivity in young adults (Lewis et al., 2009). Lewis et al. found a negative correlation between the trained visual cortex and the dorsal attention network at post-training assessment. Because the size of the negative correlation after training was related to improved task performance, this was interpreted as a change from attention-dependence early in training to attention-independence late in training. Although we trained auditory perception (pitch, phoneme, and speech perception in BF) while Lewis et al. (2009) trained visual perception (visual search), both studies found a training-related reduction in connectivity between trained sensory cortex and the dorsal attention network.

Our finding of changed connectivity in the anterior but not in the posterior ITL following BF training was unexpected. The anterior ITL plays an important role in the processing of auditory semantic stimuli, whereas the posterior ITL is thought to link semantic with phonological information (Hickok and Poeppel, 2007). However, both semantic and more basic language aspects were trained through BF training. We speculate that the decreased functional connectivity between the SPC and the anterior ITL in the BF group indicates that six weeks of training reduced demands on the SPC for attentional control of the auditory sensory cortex.

Space Fortress

We found improved everyday problem solving following SF (along with BF) training – an ability not assessed in previous studies of SF. This result is in accordance with the ACTIVE study of cognitive training in healthy older people where transfer of reasoning training to “instrumental activities of daily living” (taking medication as prescribed, managing money, use of common technologies) was found (Willis et al., 2006). Our finding of transfer to everyday cognitive performance is somewhat consistent with a study that revealed positive transfer from SF training to test flight performance during military fighter pilot training (Gopher et al., 1994). Although SF ship control and flying a fighter jet have some overlap in sensorimotor integration, the latter is certainly the more complex and demanding task. We speculate that transfer to everyday cognitive performance and working memory may be due to the working memory training during SF, although we did not test this hypothesis in the present study.

Previous work with SF has yielded contradictory results with regard to far transfer of training. One study found evidence of near but not far transfer following SF training based on a comprehensive assessment of transfer in young adults (Boot et al., 2010). Another study in older adults, however, did find transfer to untrained auditory working memory performance assessed with the Letter Number Sequencing subtest of the Wechsler Intelligence Scale (Stern et al., 2011). However, we did not find transfer to Letter Number Sequencing. We did find transfer to working memory performance from SF training, but that could be considered a near transfer effect as SF training requires processing of spatial relations in working memory. There is overlap between required memory for symbols in the SF task and our spatial working memory task (matching of spatial locations).

What are the neural mechanisms that underlie transfer of SF training to broad cognitive ability? Our functional connectivity results provide evidence that remodeling of the SPC occurs following SF training. We found a stronger decrease in SPC–ITL connectivity following SF compared to RON training (which showed an increase). A previous study assessing effects of SF training on functional connectivity in younger adults did not find altered connectivity in the SPC associated with SF training (Voss et al., 2012), however. A previous study assessing effects of SF training on regional activation found brain activation changes in the superior frontal gyrus of the dorsal attention network during ship navigation; other aspects of the game, such as working memory, were not assessed in that fMRI study (Lee et al., 2012). Therefore, a fair comparison with the present findings is not possible. Because of the paucity of previous imaging studies on SF, our evidence suggesting remodeled SPC connectivity following SF training should be interpreted with caution.

Nevertheless, our finding of decreased SPC–ITL connectivity following SF training is consistent with results from the sensory training study conducted by Lewis et al. (2009) using a visual perception task in young adults. That study also found decreased connectivity between the SPC and trained sensory cortex, indicating reduced attentional control demands following training. We found SPC connectivity changes with the posterior ITL which is part of the ventral cortical visual processing pathway (Goodale and Milner, 1992; Haxby et al., 1991). Because the posterior ITL is important in the analysis of shape discrimination and object recognition (Baizer et al., 1991; Kobatake et al., 1998), and the SF task requires rapid categorization of shapes which symbolize points, missiles, and mines, SF training may have altered attentional demands on the SPC for visual control as signaled by reduced SPC–posterior ITL connectivity. That the decreased SPC–ITL connectivity found in our study was correlated with improved everyday problem solving performance suggests that dorsal attention network remodeling may be one mechanism underlying the observed transfer of training to untrained abilities. It is important to note that both BF and SF showed far transfer of training and decreased functional connectivity between SPC and ITL (Fig. 3).

Rise of Nations

We did not find positive transfer from RON training, in contrast to a previous study which reported transfer to task-switching, working memory, and reasoning (Basak et al., 2008). Nor did we find evidence that RON transferred to everyday problem solving. Rather, RON training resulted in poorer working memory performance compared to SF training, although RON training also showed a non-significant tendency to transfer positively to matrix reasoning. It is possible that the benefits of RON training were not assessed optimally by our test battery.

Although far transfer from RON training has been observed by others, the underlying neural mechanisms have not been assessed. One study found altered gray matter structure in attention and sensory networks following RON training (Basak et al., 2011), but did not assess brain connectivity. We found no evidence that RON training altered white matter integrity or functional SPC–ITL connectivity. More work is needed to understand the effects of strategy training on brain connectivity.

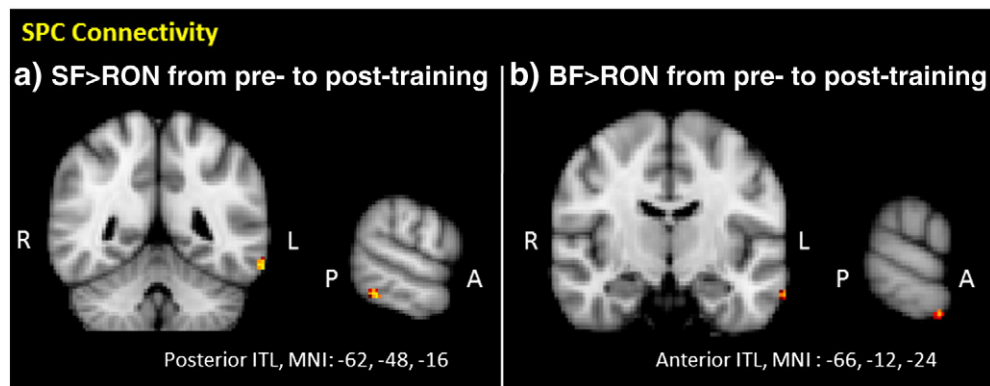


Fig. 3. SPC connectivity. Results from the right superior parietal cortex (SPC) seed-based correlation analysis are displayed. a. Connectivity between SPC and posterior inferior temporal lobe (ITL) showed a greater decrease in the SF compared to the RON group from pre- to post-training ($p < 0.05$, tfce-corrected). b. Connectivity between SPC and anterior ITL showed a greater decrease in the BF compared to the RON group from pre- to post-training ($p < 0.05$; tfce-corrected). R, right; L, left; A, anterior; P, posterior.

Significance and limitations

Our findings are important for several reasons. First, this study provided a strong test of our neurocognitive hypothesis by comparing three randomly assigned training tasks for their effects on cognition and brain connectivity. This design allowed us to identify distinctive cognitive signatures associated with each task, thereby providing information about the usefulness of the training approaches used in this study, both for research and clinical practice. Second, this study assessed the hypothesis of remodeled brain connectivity following training by assessing two measures of brain structure in the same group of participants – white matter integrity and functional connectivity. We found that different cognitive training tasks evoke distinct changes in these measures. In contrast to most other training studies in older adults, we observed our findings on the whole-brain level, thereby reducing bias toward a priori selected tracts. Future work will be needed to determine which specific elements of the training tasks are important for those connectivity changes. Third, we found that auditory perception training (BF) transferred to fluid ability and altered connectivity in the ventral attention network, suggesting that perception training may lead to changes in neural infrastructure important for far transfer, including to everyday functioning. The present results also provide the first evidence for far transfer of complex skill acquisition training (SF) to everyday cognitive functioning.

The present study compared three different training tasks, and did not use a “no-contact” control group. Use of such a control may spuriously heighten training effects (Shipstead et al., 2012). Rather than asking whether cognitive intervention is better than no intervention, we asked which type of intervention leads to improved cognitive performance in older people and whether such training shows broad transfer effects. One drawback to the present design is that neural benefits common to all three tasks were less detectable.

No simple conclusions can be drawn regarding the observation of increases and decreases in some transfer measures following training. There is no a priori reason to expect a given training task to induce only positive transfer. Some of the cognitive training that we used was effective enough to induce brain connectivity remodeling detectable on the whole-brain level. Training-related connectivity and cognitive changes appear to be complex, including both benefits and costs. Further studies are needed to investigate the mechanisms underlying reduced cognitive function and also negative correlations between changes in brain connectivity and cognitive function following cognitive training.

Our findings are notable for showing that perception training may be particularly effective as an intervention against cognitive aging. This is in contrast to many previous investigations of cognitive interventions for older people that have assumed that it is important to train vulnerable abilities such as memory. Perception training may be effective

because the remodeled connections between sensory cortex and attention networks provide the substrate needed for far transfer. Several other methods for enhancing neurocognitive functioning, including TMS and tDCS, have been examined in healthy populations. In the future, it will be important to examine whether combining cognitive training with brain stimulation methods can provide additional insights into the effects of cognitive enhancement on brain connectivity.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.neuroimage.2013.07.069>.

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