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Higher-order cognitive training effects on processing speed–related neural activity: a randomized trial

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ABSTRACT

Higher-order cognitive training has shown to enhance performance in older adults, but the neural mechanisms underlying performance enhancement have yet to be fully disambiguated. This randomized trial examined changes in processing speed and processing speed–related neural activity in older participants (57–71 years of age) who underwent cognitive training (CT, N = 12) compared with wait-listed (WLC, N = 15) or exercise-training active (AC, N = 14) controls. The cognitive training taught cognitive control functions of strategic attention, integrative reasoning, and innovation over 12 weeks. All 3 groups worked through a functional magnetic resonance imaging processing speed task during 3 sessions (baseline, mid-training, and post-training). Although all groups showed faster reaction times (RTs) across sessions, the CT group showed a significant increase, and the WLC and AC groups showed significant decreases across sessions in the association between RT and BOLD signal change within the left prefrontal cortex (PFC). Thus, cognitive training led to a change in processing speed–related neural activity where faster processing speed was associated with reduced PFC activation, fitting previously identified neural efficiency profiles.

1. Introduction

Across a range of cognitive functions, cognitive decline in normal aging has been shown to begin relatively early and progress more rapidly with advancing age (e.g., Baltes and Lindenberger, 1997; Park et al., 2002; Salthouse, 1991, 2009). Evidence is emerging, however, suggesting that higher-order cognitive training and the transfer of cognitive training to lower-order cognitive functions (e.g., Anand et al., 2011; Basak et al., 2008) can mitigate senescence-related cognitive declines. The potential transfer of higher-order cognitive training to lower-order cognitive functions raises the possibility that higher-order cognitive training might benefit either lower-order supporting cognitive functions or mediating higher-order common functions.

Processing speed has been shown to underlie and mediate senescence-related decreases in a host of higher-order cognitive functions (Earles and Salthouse, 1995; Salthouse, 1992, 1996). Measures of processing speed have been designed to be simple enough to minimize the influence of memory and strategy on performance but complex enough to assess more than mere sensorimotor function, with processing speed indexed by the time taken to correctly make perceptual/cognitive decisions (Buckhalt, 1991; Salthouse, 1992) and the total number of correct decisions made within a limited amount of time (Ekstrom et al., 1979; Wechsler, 2008). Senescence-related declines in higher-order cognitive functions have been proposed to result from cascading failures originating in lower-order operations, thus, slowing overall processing speed (Jensen, 1992; Salthouse, 1996). The proposed essential role of processing speed in senescence-related changes in higher-order cognitive functions (Salthouse, 1996) and previously shown transfer of higher-order cognitive training to supporting lower-order cognitive functions (Baniqued et al., 2015; Basak et al., 2008; Motes et al., 2014; Mudar et al., 2016; Vas et al., 2016; Venza et al., 2016), however, raise the possibility that effective forms of higher-order cognitive training might affect processing speed in the elderly.

Although research suggests that failure cascades in lower-order processes contribute to senescence-related declines in processing

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speed and higher-order cognitive functions (Salthouse, 1996), functional magnetic resonance imaging (fMRI) research suggests that prefrontal cortex (PFC) resources can be used by older adults to compensate for lower-order processing failures, which decrease processing speed (Motes et al., 2011; Rypma and D'Esposito, 2000). For example, faster working memory retrieval has been associated with lower PFC activation in younger adults but higher PFC activation in older adults (Rypma and D'Esposito, 2000). Furthermore, on a computer-adapted measure of digit-symbol coding (Wechsler, 2008), a measure of processing speed, faster processing speed has been associated with reduced PFC activation for younger adults but greater PFC activation for older adults (Motes et al., 2011). The results from these studies suggest that faster processing speed in younger adults is associated with reduced involvement of the PFC; whereas faster processing speed in older adults is associated with greater involvement of the PFC, suggesting that faster processing speed among older adults requires the use of PFC resources to compensate for lower-order processing failures.

In addition to comparing age-differences in processing speed–related neural activity, intra-individual dynamics in processing speed–related neural activity have been investigated using fMRI (Rao et al., 2014). Examination of associations between reaction time (RT) and fMRI blood oxygenation level-dependent (BOLD) signal change across trials when completing a computer-adapted version of digit-symbol coding (Wechsler, 2008) revealed positive correlations. Specifically, faster trial RTs were associated with reduced BOLD signal change, within medial and lateral PFC, parietal, occipital, subcortical, and insular brain regions. Thus, across a broad set of brain regions, including PFC, faster processing speed has been associated with reduced brain activation, suggesting that minimal PFC recruitment is required when subprocesses, mediated by other brain regions, operate efficiently in handling cognitive demands.

The present fMRI study examined the effects of a higher-order cognitive training program, the Strategic Memory Advanced Reasoning Training (SMART) program (Chapman et al., 2016; Vas et al., 2016) on processing speed–related neural activity in older adults. Participants in cognitive training (CT), wait-listed control (WLC), and physical exercise active control (AC) groups worked through the previously used computer-adapted version of digit-symbol coding (Wechsler, 2008), that is, the Digit-Symbol Verification Task (DSVT; Biswal et al., 2010; Motes et al., 2011; Rao et al., 2014; Rypma et al., 2006), while fMRI data were collected during 3 assessment sessions: baseline, mid-training, and post-training for the CT and AC groups and comparable durations for the WLC group. Performance on the DSVT has been shown to correlate with digit-symbol coding performance (DSVT RT $r = -0.48$, $p < 0.05$, and DSVT proportion correct $r = 0.35$, $p < 0.05$; Rypma et al., 2006). In addition, other computerized measures of processing speed, similar to the DSVT, have been shown to correlate with standardized measures of processing speed ($0.35 < r < 0.90$) and age ($0.35 < r < 0.60$) and to account for age-related variance in a host of measures of cognitive abilities (Salthouse, 1996). The correlations provide convergent validation for DSVT and similar computerized tasks as measures of processing speed.

Prior work supports the potential for higher-order cognitive training and SMART (Chapman et al., 2016; Vas et al., 2016), in particular, to be linked to changes in lower-order processes. SMART teaches cognitive control strategies that require integrative and specialized component processes. The training has been shown to facilitate focused learning, deeper encoding of meaning, and the flexible ability to derive a multitude of interpretations and solutions (Chapman et al., 2015, 2016). In addition, findings have shown transfer of SMART to lower-order processes, including inhibition, nonverbal reasoning, working memory, immediate and delayed memory, and switching (Motes et al., 2014; Mudar et al., 2016; Vas et al., 2016; Venza et al., 2016), in both healthy and patient samples. Other forms of higher-order cognitive training also have been shown to transfer to executive processes (Basak et al., 2008) and even processing speed (Baniqued et al., 2015). The distal cognitive functions to which SMART previously has been shown to transfer, particularly, executive processes (Anand et al., 2011; Motes et al., 2014; Vas et al., 2011), also have been shown to be associated with processing speed (e.g., Jensen, 1992; Kail, 1991; Salthouse, 1996) and PFC structure and function (e.g., Alvarez and Emory, 2006; Buchsbaum et al., 2005; Motes and Rypma, 2010; Rypma & D'Esposito, 2000; Yuan and Raz, 2014).

Although research has shown that higher-order cognitive training in older adults can transfer to lower-order processes, no known study has examined transfer to processing speed–related neural activity in a randomized trial. Thus, the present study examined the potential for higher-order cognitive training, as represented by SMART, to affect neural mechanisms underlying processing speed. In particular, based on prior evidence that SMART and other forms of higher-order cognitive training seem to recruit and strengthen PFC-mediated executive functions and that PFC function has been shown to mediate age-related change in processing speed, the study allowed for testing the prediction that higher-order cognitive training would transfer to processing speed–related neural activity within the PFC. Aerobic exercise training served as an AC condition for the study in that aerobic exercise training has been shown to lead to improvements in processing speed (Colcombe and Kramer, 2003; Smith et al., 2010; Young et al., 2015) and functional changes within frontal and other brain regions (Hillman et al., 2008; Voelcker-Rehage and Niemann, 2013), including, BOLD signal change increases within the PFC while working on a computer-adapted measure of digit-symbol coding (Rosano et al., 2010).

2. Material and methods

2.1. Participants

A total of 57 cognitively normal older adults ($M = 63.2$; 56–71 years of age) were randomly assigned to a higher-order CT (n = 19), WLC (n = 19), or AC (n = 19) group. All participants underwent Telephone Interview of Cognitive Status-Modified to prescreen for dementia, Montreal Cognitive Assessment to detect early cognitive impairment, Beck Depression Inventory-II to screen for depressive symptoms, and complete medical, physical, and laboratory assessments by a physician to ensure good general health. Inclusion criteria included no history of neurological or psychiatric conditions, intelligence quotient within the normal range, English as the native language, and a minimum of a high school education. Exclusionary criteria included magnetic resonance scanning contraindications, cognitive status impairment (Telephone Interview of Cognitive Status-Modified <28 and Montreal Cognitive Assessment <26), depression indication (Beck Depression Inventory-II >14), left-handedness, elevated body mass (body mass index >40, BMI $= \frac{\text{mass(kg)}}{\text{height(m}^2\text{)}}$), abnormal electrocardiographic response, significant hypertensive blood pressure response to exercise, or inability to reach 85% of age-related maximum predicted heart rate. In addition, participants were excluded if they reported regular aerobic activity of more than twice a week for 20 minutes or more or if they reported exercising regularly for at least 3 months before enrolling in the study. The experiment was conducted according to the principles expressed in the Declaration of Helsinki, and written informed consent was obtained from all subjects in accordance with the Institutional Review Board of our academic institutions: The University of Texas at Dallas and the University of Texas

Table 1
Participant characteristics (mean ± standard deviation)

Screening measures	CT (n = 12)	WLC (n = 15)	AC (n = 14)
Age	63.1 ± 3.1	63.8 ± 3.4	62.9 ± 3.3
IQ	121.7 ± 8.9	119.5 ± 11.4	117.3 ± 9.7
MoCA	28.4 ± 1.2	28.1 ± 1.4	28.1 ± 1.4
TICS-M	29.8 ± 2.5	29.6 ± 2.0	31.0 ± 1.8

Key: AC, active control; CT, cognitive training; IQ, intelligence quotient; MoCA, Montreal cognitive assessment; TICS-M, Telephone Interview of Cognitive Status-Modified; WLC, wait-listed control.

Southwestern Medical Center. During consenting, participants were told that they would be randomly assigned to receive cognitive training following the baseline assessment session or to be given the opportunity to receive cognitive training following the third assessment session (i.e., be in the WLC or AC group).

Although all participants completed the cognitive measurements at the baseline assessment session, some participants in the groups did not complete all assessment sessions (CT, n = 4; WLC, n = 1; and AC, n = 3), had high motion during a scanning session (>3 mm and >3°; CT, n = 2; WLC, n = 2; and AC, n = 0), or poor brain image normalization in preprocessing (CT, n = 1; WLC, n = 1; AC, n = 2). As a result, the final behavioral and MRI data analyses were conducted on 12 (6 females) participants in the CT group, 15 (11 females) in the WLC group, and 14 (10 females) in the AC group. No significant between-group differences were noted in any of the demographic or cognitive screening measures (all p's > 0.08), as shown in Table 1.

2.2. Procedure

2.2.1. SMART program

The cognitive training was delivered by a trained instructor in small groups (n ≤ 5) of one 1-hour session per week for 12 weeks (hours = 12). Initially, the SMART strategies (Table 2) were overviewed, with an emphasis on the use of the strategies on mental tasks throughout one's daily routine. The sessions then focused on the use of strategic attention, integrative reasoning, and innovation cognitive control functions (Table 2 *Function*) via integrated practice with a wide range of everyday type tasks, such as, reading newspaper articles, conversing about movies, or discussing investments with a financial planner (Chapman, 2014). Overall, SMART teaches metacognitive strategies (1) to enable better time and cognitive resource management by prioritizing goal setting, blocking distractions, and inhibiting irrelevant information; (2) to engage deeper level synthesis of incoming information by "boiling the meaning down to its essence,"; and (3) to encourage fluid and flexible thinking (Chapman et al., 2015, 2016).

In addition to the once a week group sessions, participants also completed personally selected homework assignments related to each session. These homework activities involved 2 additional 1-hour sessions per week for 12 weeks (total hours logged = 24). Record logs of time and notation of assignment completion were kept for the homework to chart compliance. The amount of time spent on homework varied across participants, and although all participants completed the homework, not all participants required investing the full 24 hours. Trainers provided feedback to reinforce understanding and utilization the strategies.

2.2.2. Active control exercise

The active control physical exercise program trained participants to meet 2008 physical activity guidelines of 150 minutes per week. Training consisted of 3 aerobic exercise training sessions per week, 60 minutes each, over 12 weeks. Aerobic exercise alternated between bike and treadmill exercise sessions. Biking sessions consisted of a 5-minute warm-up at 43 watts, cycling for 50 minutes at a speed that increased their heart rate to 50%–75% of their maximum achieved heart rate on VO_2max testing, and a 5-minute cool-down at 43 watts. Treadmill sessions consisted of a 5-minute warm-up at 2 mph, walking on treadmill for 50 minutes at a speed that increased their heart rate to 50%–75% of their maximum achieved heart rate on VO_2max testing, and a 5-minute cool-down at 2 mph. An exercise physiologist and a nurse practitioner assessed whether participants reached their target heart rate at each session.

2.2.3. Test of Strategic Learning as a proximal assessment of cognitive training

The Test of Strategic Learning (TOSL) served as a proximal assessment of SMART (Chapman and Mudar, 2014; Chapman et al., 2015; Vas et al., 2016). TOSL was developed to assess the ability to

Table 2
SMART strategies emphasized over 12 sessions

Sessions	Function	Strategy	Illustration
1–3	Strategic attention: reduce the load of incoming details by inhibiting less relevant information	Filter/single task/mental breaks	Tackle mental tasks without distractions, set fixed time (~30 min) to focus attention while consciously blocking extraneous stimulation. Example: Read article and delete "unimportant" information.
4–5	Integrative reasoning: combine ideas to form condensed meanings. Interpret in a broader context. Apply to real-life contexts.	Synthesize Zoom Out Zoom deep and wide	Create synthesized abstracted meanings Devise broader viewpoints/solutions based on acquired new knowledge. Construct interpretive messages of application to current contexts/problems. Example: Write sentences that synthesize important information in an article into one's own words. Give an alternative interpretation and application to a current context.
6–8	Innovation: derive multiple ways to approach mental tasks and minimize fear of failure or unknown	Infinite	Fluidly generate a multitude of alternative solutions/perspectives
9–10		Paradox/unknown	Identify daily low performance on tasks and find ways to push new approaches; seek new tasks/contexts/frontiers. Example: Given a problem and solution or scenario and outcome, create alternative solutions or paths to alternative outcomes. Consider ways to encourage thinking of and using the alternatives.
11–12	Booster sessions	Review strategies	Discuss applications of strategies to real-life scenarios.

Key: SMART, Strategic Memory Advanced Reasoning Training.

synthesize abstract meanings from complex information. Participants read a complex passage (approximately 600 words) and were then instructed to generate a high-level summary of the text. A TOSL abstraction score was computed based on a manualized objective scoring system where each abstracted idea in the summary received 1 point and verbatim or paraphrased ideas did not receive any points. The final abstraction score then reflected the total number of accurately abstracted meanings from the text. Three different versions of the TOSL were constructed and administered at the 3 assessment periods in a counter-balanced order across participants.

2.2.4. Processing speed task

Participants completed the DSVT (Rypma et al., 2006) as a measure of processing speed while in the scanner. A table containing 9 digit-symbol pairs and a single digit-symbol probe (Fig. 1) appeared simultaneously on each trial for 3.5 seconds, and participants had the full 3.5 seconds to indicate whether the probe pair matched a digit-symbol pair in the key or not. The symbols paired with the 9 digits in the key varied across trials to discourage the use of memory-based strategies, and the symbol paired with the probe number and the probe number itself also varied across trials. There were 52 trials all completed in 1 scanning run. The probe pair matched one of the pairs in the key on half of the trials, and the probe pair did not match one of the pairs in the key on the other half of the trials. On trials when the probe pair did not match a pair in the key, the probe symbol was present in the key, but it was paired with a different number than in the probe pair. Interstimulus intervals varied from 0.5 to 16.5 seconds, constituting the baseline, rest periods in the jittered, rapid, event-related design. RT, as an index of processing speed, was measured from the onset of a trial to the time of the response (right thumb button press "yes" and left for "no"). Three versions of the task were constructed with the trial order randomized across the versions.

The rear-projected trials were viewed by the participants using an angled mirror sitting above the receiving coil ($\approx$12 cm above the participant's eyes). Black symbols and digits (in both key and probe pair) appeared within white squares on a black background. Each symbol or number square measured 0.40 $\times$ 0.40 cm at the mirror ($\approx$1.95° visual angle), with the full key measuring approximately 4.00 $\times$ 0.85 cm ($\approx$18.6° $\times$ 4.05° visual angle) and the top of the key to the bottom of the probe measuring 1.75 cm ($\approx$8.3° visual angle).

2.2.5. Neuroimaging acquisition parameters and data processing pipeline

Imaging data were collected at 3 assessment sessions: baseline, mid (6-week for the CT group), and post (12-week for the CT group). The imaging data were collected on a Philips Achieva 3T scanner equipped with an 8-element, sensitivity encoding (SENSE), receive-only head coil. High-resolution anatomical images (magnetization prepared rapid gradient echo [MPRAGE]: 1 mm^3; sagittal; echo time [TE] = 3.7 ms; flip angle = 12°) and functional images using echo planar imaging (EPI) (voxel = 3.5 $\times$ 3.5 $\times$ 4 mm; 36 slices/volume; 150 volumes/run; repetition time [TR] = 2000 ms, TE = 30 ms; flip angle = 70°; matrix = 64 $\times$ 64; axial; inferior to superior interleaved) were collected. Six discarded scans occurred at the beginning of the functional run to remove T1 saturation effects.

Previous research on the present sample of participants showed cognitive training–related increases in global and regional resting-state cerebral blood flow (CBF; Chapman et al., 2015) with the increases linked to improved executive function. In addition, age-related reductions in cerebrovascular reactivity (CVR) have been observed in the PFC (Lu et al., 2010; Yezhuvath et al., 2012),

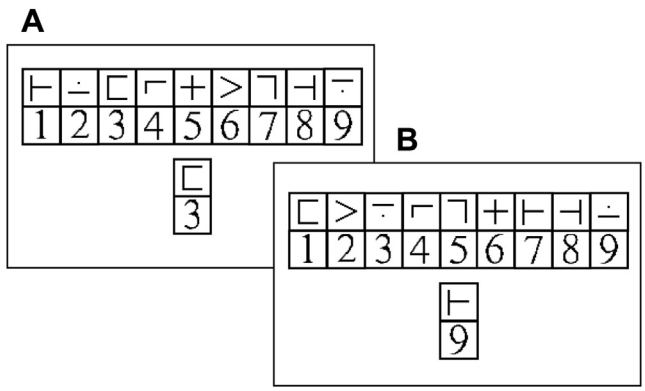

Fig. 1. Example of stimuli from the DSVT. Participants in the present study completed the DSVT while fMRI data were collected. On each trial, a key containing 9 digit-symbol pairs and a single digit-symbol probe pair appeared simultaneously for 3.5 seconds, and participants were to judge whether the probe pair was in the key (A) or not (B). The digit-symbol pairings in the key and the probe pair varied across trials. On half of the trials, the probe pair matched a digit-symbol pair in the key, and on half of the trials, the probe pair did not match a digit-symbol pair in the key. There were 52 trials in a run, and interstimulus intervals varied from 0.5 to 16.5 seconds. Abbreviations: DSVT, Digit-Symbol Verification Task; fMRI, functional magnetic resonance imaging.

and CVR has been shown to be associated with BOLD signal change on the DSVT (Kannuripatti et al., 2011). During the imaging session, pseudocontinuous arterial spin labeling (pCASL) (Aslan et al., 2010) and CVR data (Yezhuvath et al., 2012), based on hypercapnia using BOLD fMRI, were also collected during resting-state runs separate from the DSVT fMRI run. These data allowed for assessing whether training-related fMRI changes were associated with possible training-related changes in resting blood flow and vascular reactivity. Imaging parameters for pCASL experiments were as follows: single-shot gradient-echo EPI, field-of-view = 240 $\times$ 240 mm^2, matrix = 80 $\times$ 80, voxel size = 3 $\times$ 3 mm^2, 27 slices acquired in ascending order, slice thickness = 5 mm, no gap between slices, labeling duration = 1650 ms, time interval between consecutive slice acquisitions = 35.5 ms, TR/TE = 4020/14 ms, SENSE factor 2.5, number of controls/labels = 30 pairs, radio frequency duration = 0.5 ms, pause between radio frequency pulses = 0.5 ms, labeling pulse flip angle = 18°, bandwidth = 2.7 kHz, echo train length = 35, and scan duration 4.5 minutes. The hypercapnia BOLD imaging parameters were as follows: single-shot gradient-echo EPI sequence, TR/TE/flip = 2000 ms/25 ms/80°, 43 axial slices, slice thickness = 3.5 mm, field-of-view = 220 $\times$ 220 mm^2, matrix size = 64 $\times$ 64, and scan duration 7 minutes 18 seconds. Hypercapnia was administered using a Douglas bag with a 2-way valve to switch between blocks of 5% CO_2-breathing (mixed with 21% O_2 and 74% N_2) and air-breathing. Physiologic parameters, including end-tidal (Et) CO_2, breathing rate, heart rate, and arterial oxygenation (SO_2), were recorded during the scan (MEDRAD, Pittsburgh, PA, USA and Novametrix Medical Systems, Wallingford, CT, USA).

The fMRI BOLD data were analyzed using AFNI software (Cox, 1996). The data for individual participants were corrected for slice-timing offset and motion. The time series was then spatially smoothed with an iterative gaussian kernel to a final full-width at half-maximum (FWHM) smoothness of 8 mm (based on the residual maps generated after an initial deconvolution). The smoothed time series data were then deconvolved using voxel-wise linear regression to obtain task-related and RT-related signal change estimates. A task-related regressor was constructed by convolving a task-reference delta function for correct responses by

the hemodynamic response model (a gamma-variate function; Cohen (1997) parameters $b = 8.6$, $c = 0.547$; maximum amplitude = 1.0). A second regressor was created to obtain RT-related effects (i.e., trial-level processing speed effects). For the RT-related regressor, the task-related regressor was proportionally scaled based on the corresponding trial RT, with

$$y(t) = \sum_{k=1}^{K} (a_k - \overline{a}) h(t - \tau_k),$$

where t = time in the time series, k = trial for the condition, a_k = reaction time for the kth trial, $\overline{a}$ = mean reaction time, τ_k = time of the onset of the kth trial for the condition, and $h(t - \tau_k) = t^{8.6} \exp(-[t - \tau_k]/0.547)$. The task-related regressor was then regressed from the RT-scaled model, removing the canonical hemodynamic response model component and leaving orthogonalized RT-related and task-related regressors for the deconvolution. Thus, regression allowed for obtaining estimates of task-related and RT-related BOLD signal change from the baseline rest periods for each participant for each assessment session. Nuisance regressors for incorrect responses and long RTs (i.e., RT >2.5 SD from the participant's mean RT), motion correction parameters, and for linear, quadratic, and cubic trends also were included in the deconvolution design matrix. At each voxel, the smoothed data were then expressed in terms of percent signal change relative to the mean (i.e., 100 * yt/My, t = time point), and the final deconvolution was performed on these smoothed, scaled data. The parameter estimate matrices for the task-related and RT-related regressors were spatially normalized to Montreal Neurological Institute (MNI) space by first registering the MPRAGE for each participant to an MNI template via a set of linear and nonlinear spatial transformations and then applying the transformation parameters to the task-related and RT-related parameter estimate maps.

The primary aim of the study was to evaluate training-related effects, so separate voxel-wise linear interaction contrasts were used to test for group differences in change from the baseline assessment session in the behavioral data and the task-related and RT-related BOLD signal change parameter estimates, with contrast coding allowing for bi-directional differences. Group status (i.e., CT, WLC, or AC) was a between-groups factor, and assessment session (i.e., baseline, mid, and post) was a within-group factor. Cluster thresholding was used to control family-wise error rates. It was performed separately for CT versus WLC and AC combined, CT versus WLC and CT versus AC comparisons. Cluster thresholding involved computing residuals for the Group × Assessment Session linear interaction contrasts, generating a null distribution by randomizing the signs of the residuals per subject, iteratively repeating t-tests on these residual matrices 10,000 times, and then using the 10,000 matrices to determine false positive probabilities of clusters of a given size with different voxel-wise p-value thresholds (as implemented in 3dClustSim; Cox et al., 2017). The permutation tests were implemented to address inflated false-positive rate concerns raised regarding fMRI studies (Eklund et al., 2016). Cox et al. showed accurate to slightly conservative false-positive rates using this nonparametric approach to cluster thresholding with degrees of smoothness varying with FWHM = 4–10 mm, voxel-wise thresholds from $p = 0.01$ to $p = 0.001$, and various task designs, including rapid event-related designs like the DSVT. Based on this approach, minimum cluster sizes were $k = 86$ for CT comparisons to the combined WLC and AC groups, $k = 116$ for CT comparisons to the WLC group, and $k = 126$ voxels for CT comparisons to the AC group, with voxel-wise $\alpha = 0.001$ to meet a cluster-wise $\alpha = 0.05$.

After identifying regions in the BOLD data showing significant Group × Assessment Session linear interaction effects, data from the coordinates of the peak voxel for the Group × Assessment Session interaction effect within the cluster were extracted from each participant's BOLD, CBF, and CVR maps and tested for both Group × Assessment Session linear interaction effects and for the association of the fMRI BOLD effects with the behavioral data. CBF and CVR maps were generated as follows. The pCASL MRI data underwent routine processing (Aslan et al., 2010; also see Supplementary Materials S1), and pCASL image series were realigned to the first volume for motion correction (SPM's realign function). All data sets were within the applied motion threshold of 3 mm translation and 3° rotation. An in-house MATLAB (MathWorks, Natick, MA, USA) program was used to calculate the difference between averaged control and label images. Then, the difference image was corrected for imaging slice delay time to yield a CBF-weight image, which was normalized to the brain template in standard space using hierarchical attribute matching mechanism for elastic registration. Last, the absolute CBF was estimated in the units of mL blood/min/100 g of brain tissue (Aslan et al., 2010). CVR data analysis followed protocols established previously (Yezhuvath et al., 2012; also see Supplementary Materials S1). Briefly, BOLD data were motion corrected (2 data sets had motion over the selected threshold of 3 mm translation and 3° rotation) and smoothed (6 mm FWHM). A linear regression was performed between the $EtCO_2$ trace (extracted using in-house MATLAB scripts) and the BOLD signal time course to generate CVR maps in units of %BOLD/mmHg CO_2. Normalization of CVR maps to standard space followed a similar pipeline as the CBF data (for details on CBF and CVR calculations, see Chapman et al., 2015, 2016).

3. Results

3.1. Training-related change in TOSL abstraction score

Change in TOSL abstraction score served a proximal measure of SMART efficacy. As previously reported on this sample of participants (Chapman et al., 2015), the Group x Assessment Session linear interaction contrast revealed significant group differences in change in TOSL Abstraction over the assessment sessions when comparing the CT group to the combined control groups, $t(39) = 2.36$, $p = 0.023$,[1] and to the WLC group, $t(25) = 2.54$, $p = 0.018$, with a marginally significant effect for the comparison to the AC group $t(24) = 1.84$, $p = 0.078$ (Fig. 2A). Thus, the increase from baseline in TOSL abstraction for the CT group significantly differed from the decrease in baseline for the WLC and AC groups, providing validation for CT actually training higher-order cognitive processing in the form of abstracting meaning or essential gist from texts.

3.2. Training-related change in DSVT performance

Training-related changes in RT (for correct responses), accuracy, and RT variability (RT coefficient of variation [CV] [in SD/M]) were examined for transfer of cognitive training to performance on the DSVT (see Fig. 2B–D, respectively). Although the decrease in RT across assessment sessions was significant when averaging over groups, $t(40) = -4.70$, $p < 0.001$, and the increase in proportion

[1] Comparisons of group differences at baseline were not significant. Additionally, the difference on TOSL Abstraction Scores at the post assessment session, with the baseline assessment data used as a covariate, between CT and the combined WLC and AC groups was significant, $F(1, 38) = 4.37$, $p = 0.043$, between CT and WLC groups was marginally significant, $F(1, 24) = 2.93$, $p = 0.100$, and between CT and AC groups was significant, $F(1, 23) = 5.04$, $p = 0.035$.

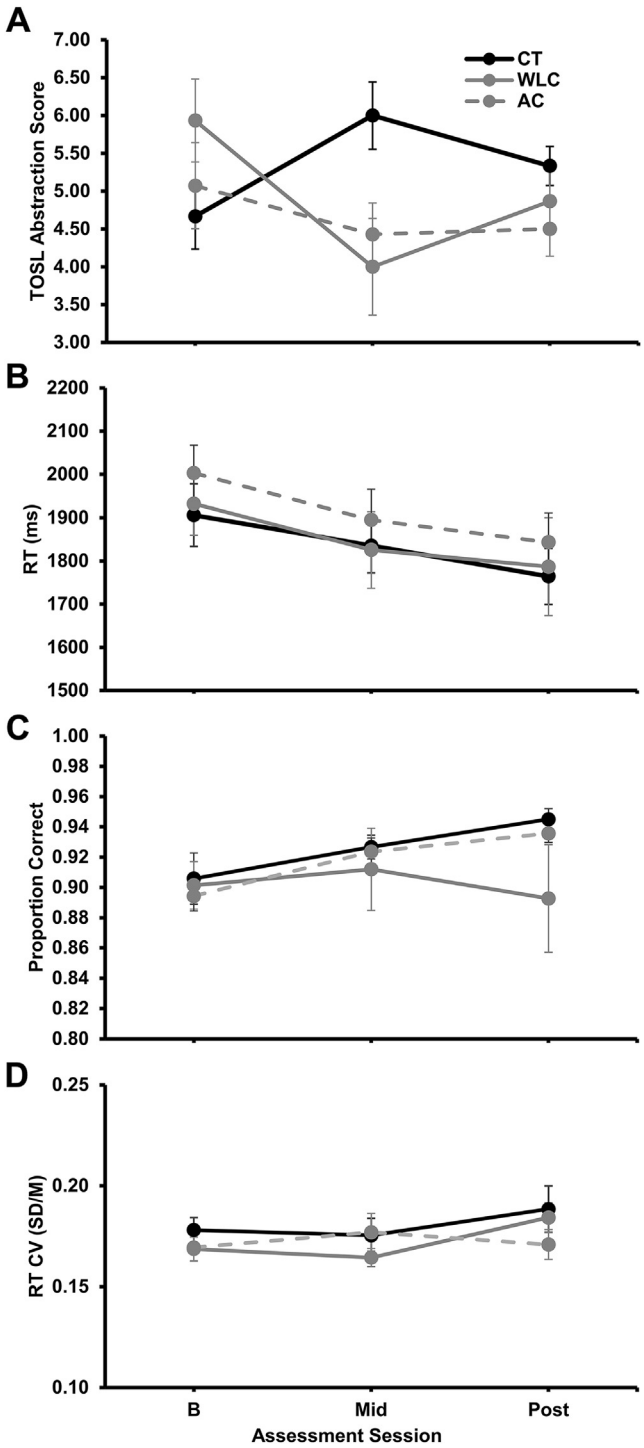

Fig. 2. (A) TOSL abstraction score and DSVT, (B) RT, (C) proportion correct, and (D) RT coefficient of variation (CV) as functions of group and assessment session. Errors bars show SEM. For assessment session, B = baseline; Mid = 6 weeks into the training or waiting period; and Post = post-training or post-waiting period; and black = CT group; gray = WLC group; and gray dashed = AC group. Abbreviations: AC, active control; CT, cognitive training; DSVT, Digit-Symbol Verification Task; RT, reaction time; TOSL, Test of Strategic Learning; WLC, wait-listed control.

correct and RT CV were marginally significant, $t(40) = -1.77$, $p = 0.085$, and $t(40) = 1.88$, $p = 0.067$, respectively, the group differences in change from baseline were not significant, all combined control group t's$(39) < 1.00$, WLC t's$(25) \leq 1.31$, p's ≤ 0.201, and AC t's$(24) < 1.00$.

3.3. Training-related change in fMRI BOLD signal change

Task-related signal change and RT-related signal change for each group at each assessment session were consistent with previously reported findings (see. Supplementary Fig. S3.1; Biswal et al., 2010; Motes et al., 2011; Rao et al., 2014; Rypma et al., 2006). However, Group × Assessment Session linear interaction contrasts on the RT-related regression coefficients (B) comparing the CT and combined WLC and AC groups revealed a single significant cluster ($k = 210$ voxels; cluster-wise $\alpha = 0.05$ requiring $k = 82$ voxels at a voxel-wise $Z = 3.28$ and $\alpha = 0.001$, based on the previously described nonparametric approach to cluster thresholding to control for false-positive rates, Cox et al., 2017) within the left PFC (Brodmann Area 9; Fig. 3A, statistical parameter map). In separate analyses, contrasts for CT versus WLC and for CT versus AC groups also revealed significant clusters ($k = 139$ and $k = 126$ voxels, respectively; cluster-wise $\alpha = 0.05$ requiring $k = 116$ and $k = 126$ voxels, respectively, at a voxel-wise $Z = 3.28$ and $\alpha = 0.001$) within the left PFC (see Fig. 3B and C, statistical parameter maps, respectively). For the CT versus AC group contrasts, significant clusters also were observed bilaterally within the cerebellum (see Supplementary Materials S3). Group × Assessment Session interaction contrasts on the task-related BOLD signal change did not reveal any clusters meeting the family-wise error cluster thresholds. For the left PFC cluster showing significant Group × Assessment Session effect on the RT-related BOLD signal change, the increase in the correlation between RT and BOLD signal change for the CT group significantly differed from the decrease in the correlation for the WLC and AC groups (illustrated in line graph; CT vs. combined WLC and AC group peak $t[39] = 5.19$, $p < 0.001$, MNI coordinates [−44L 26A 24S]; CT vs. WLC group peak $t[25] = 4.65$, $p < 0.001$, and AC group peak $t[24] = 4.65$, $p < 0.001$, MNI coordinates [−46 L 26A 26S] for both peaks).[2] Thus, across sessions and within the left PFC, the CT group showed an increase in the association between trial-level RT and BOLD signal change, with faster trial RT associated with less BOLD signal change; whereas the WLC and AC groups showed decreases in the association between trail-level RT and BOLD signal change.

3.4. Covariate analyses of training-related change in fMRI BOLD signal change

CBF and CVR data were extracted from the peak voxel within the significant left PFC cluster. Some participants in the groups did not have useable CBF (CT, n = 1; WLC, n = 0; and AC, n = 0) or CVR (CT, n = 2; WLC, n = 6; and AC, n = 4) data. As a result, the analyses were conducted on 11 CBF and 10 CVR data sets for participants in the CT group, 15 CBF and 9 CVR in the WLC group, and 14 CBF and 10 CVR in the AC group. Group differences in CBF or CVR change from baseline from the peak voxel for the Group × Assessment Session BOLD interaction effect within the left PFC cluster were not significant. Step-wise, hierarchical linear modeling was used to test for associations between cognitive training–related linear change in RT-related BOLD signal change within the left PFC cluster (i.e., data extracted from the peak voxel within the cluster) and change in CBF within the cluster, CVR within the cluster, RT, RT CV, proportion correct, and TOSL coherence. In a series of 7 separate step-wise, hierarchical linear models, the linear change in RT-related

[2] Comparisons of group differences at baseline did not reveal any clusters meeting the FWE cluster threshold. In addition, Group × Assessment Session contrasts on RT-related BOLD signal change estimates separately comparing baseline-to-mid and mid-to-post sessions did not reveal any cluster meeting the FWE cluster threshold.

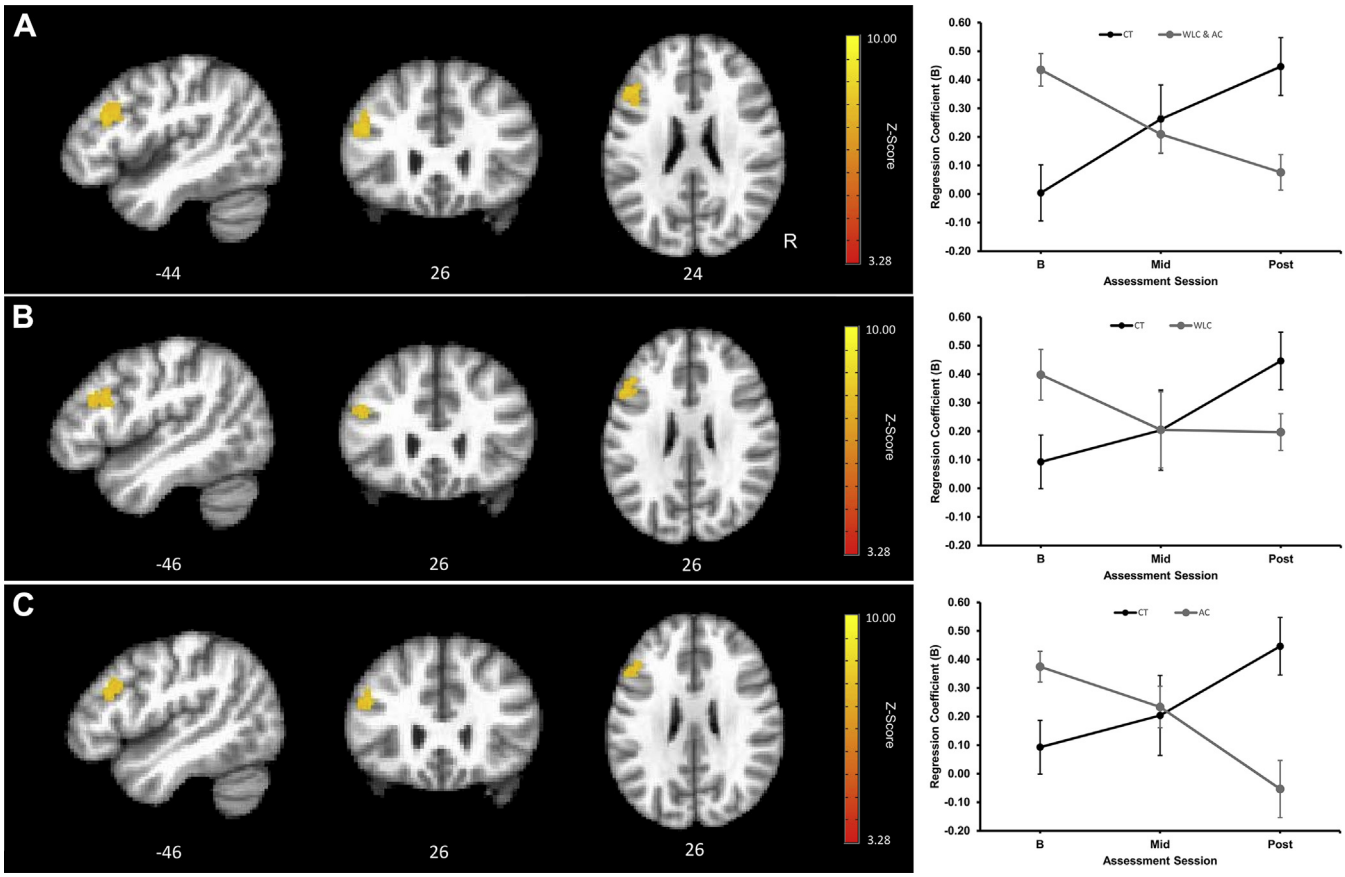

Fig. 3. Cluster showing significant Group × Assessment Session interaction contrast of RT-related parameter estimates and mean RT-related parameter estimates as a function of assessment session and group, extracted from the peak voxel within the cluster (peak voxel MNI coordinates shown below the images). Upper panel (A) shows a significant cluster in the left prefrontal cortex (PFC) for the CT versus combined WLC and AC group contrasts ($k = 210$ voxels; cluster-wise $\alpha = 0.05$ requiring $k = 82$ voxels at a voxel-wise Z = 3.28 and $\alpha = 0.001$); middle panel (B) shows significant cluster in the left PFC for the CT versus WLC group contrast ($k = 139$ voxels; cluster-wise $\alpha = 0.05$ requiring $k = 116$ voxels at a voxel-wise Z = 3.28 and $\alpha = 0.001$); and lower panel (C) shows significant cluster in the left PFC for the CT versus AC group contrast ($k = 126$ voxels; cluster-wise $\alpha = 0.05$ requiring $k = 126$ voxels at a voxel-wise Z = 3.28 and $\alpha = 0.001$). Image orientations are in neurological convention indicated with R = right. Red to yellow indicates increasing strength of the Group × Assessment Session interaction contrast. Errors bars show SEM. For assessment session, B = baseline; Mid = 6 weeks into the training or waiting period; and Post = post-training or post-waiting period; and black = CT group; gray = combined WLC and AC groups in (A); gray = WLC group in (B); and gray = AC group in (C). Abbreviations: AC, active control; CT, cognitive training; DSVT, Digit-Symbol Verification Task; RT, reaction time; WLC, wait-listed control.

regression coefficient (B) was regressed on (1) group (dummy coded as combined WLC and AC = 0 and CT = 1), followed by (2) group and the physiological or performance covariate of interest (i.e., change in CBF, CVR, RT, RT CV, proportion correct, or TOSL abstraction), and followed by (3) group, the physiological or performance covariate of interest, and a group × covariate interaction term (i.e., Group * Predictor). Significant change in R^2 was computed to determine whether the covariate or interaction added to or reduced the Group × Assessment Session linear contrast. However, none of the hierarchical models revealed significant change in R^2 from the initial effect of group on the linear contrast, with the original $R^2 = 0.47$ (CBF subgroup $R^2 = 0.43$; CVR subgroup $R^2 = 0.48$), for all covariates $R^2_{\text{change}} \leq 0.019$, $F_{change} \leq 1.37$, and all full models with interaction terms $R^2_{\text{change}} \leq 0.012$, $F_{change} \leq 0.89$. Thus, the cognitive training–related linear change in RT-related BOLD signal change was not found to be significantly accounted for by change in CBF, CVR, DSVT performance, or TOSL abstraction.

4. Discussion

The results provide evidence that higher-order cognitive training can affect processing speed–related neural activity within the PFC. Within the left PFC, Brodmann Area 9, the correlation between RT and BOLD signal change while working on the DSVT increased across the assessment sessions for the CT group but decreased for the WLC and AC groups. After cognitive training, faster RT for the CT group was associated with lower BOLD signal change. This post-cognitive training pattern is consistent with previously noted neural efficiency profiles (Motes et al., 2011; Rypma et al., 2006), particularly, intra-individual neural efficiency profiles observed in young adults (Rao et al., 2014). The results suggest that after cognitive training, minimal PFC recruitment was necessary on trials when lower-order processes could handle task demands (i.e., trials in which trained participants were faster) but also suggest that PFC-mediated cognitive functions were available and could be recruited when cascading lower-order processing failures were slowing processing speed (i.e., trials in which trained participants were slower).

The observed transfer of higher-order cognitive training to processing speed adds to previously reported findings on higher-order cognitive training effects on PFC function. Reasoning training, for example, has been associated with mean decreased left PFC activation on fMRI when performing other untrained reasoning tasks (Mackey et al., 2015), at least among young adults, suggesting

more efficient use of PFC resources (i.e., reduced PFC activation) after training. The present study, however, demonstrates cognitive training–related transfer to PFC mediation of trial-level processing speed, with faster processing speed across trials (i.e., faster RT) associated with lower PFC activation (i.e., BOLD signal change), rather than a reduction in PFC activation following cognitive training. As noted, previous research (Motes et al., 2011) has shown that faster processing speed among older adults was associated with greater use of PFC-mediated resources (i.e., greater PFC BOLD signal change among faster older adults than among slower older adults and faster younger adults), suggesting that processing speed for older adults depends on the availability of PFC resources for coordination of subprocess timing and output and to preserve cognitive functions in general (Park and Reuter-Lorenz, 2009; Rypma and Prabhakaran, 2009). However, the results from the present randomized training trial support the notion that cognitive training targeting higher-order cognitive processes can alter PFC involvement in processing speed and may serve to mitigate age-related changes in PFC function, in general.

The transfer of higher-order cognitive training to only PFC-mediated processing speed–related neural activity, and not to other brain regions associated with processing speed (Rao et al., 2014), suggests that transfer of higher-order cognitive training to lower-order cognitive functions (Baniqued et al., 2015; Basak et al., 2008; Motes et al., 2014; Mudar et al., 2016; Vas et al., 2016; Venza et al., 2016) might occur through higher-order cognitive training indirectly benefiting mediating higher-order common functions served by the PFC rather than indirectly benefiting a host of lower-order supporting functions. Across CT, WLC, and AC groups and assessment periods in the present study (Supplementary Fig. 1) and in a study of healthy young adults examining intra-individual dynamics in RT-BOLD association on the DSVT (Rao et al., 2014), faster processing speed was associated with reduced brain activation across a host of brain regions, including medial and lateral PFC, parietal, occipital, subcortical, and insula. However, in the present study, the observed CT versus WLC and AC group differences in change in intra-individual dynamics in processing speed–related neural activity were confined to the left lateral PFC and not other regions associated with processing speed. The localization of cognitive training effects to only the PFC suggests that higher-order cognitive training indirectly benefits PFC function in processing speed, and at this point, cognitive training does not appear to show transfer to lower-order supporting functions in processing speed, at least in older adults. Thus, the previously observed transfer of higher-order cognitive training to other lower-order cognitive functions (Baniqued et al., 2015; Basak et al., 2008; Motes et al., 2014; Mudar et al., 2016; Vas et al., 2016; Venza et al., 2016) also might result from cognitive training effects on common functions served by the PFC.

Aerobic exercise training served as the AC condition in the present study because aerobic training previously has been associated with improvements in processing speed (Colcombe and Kramer, 2003; Smith et al., 2010) and functional change within the PFC and other frontal regions (Hillman et al., 2008; Voelcker-Rehage and Niemann, 2013). Aerobic exercise, however, did not show processing speed–related neural activity benefits compared to cognitive training in the present cohort. Meta-analyses on the effects of aerobic exercise training on processing speed have shown relatively weak effect sizes (Hedge's $g = 0.27$ in Colcombe and Kramer, 2003; Hedge's $g = 0.16$ Smith et al., 2010), and aerobic exercise training alone (Hedge's $g = 0.10$) has been shown to produce weaker effects on processing speed than aerobic exercise combined with other training (e.g., strength training or yoga; Hedge's $g = 0.25$; Smith et al., 2010; see also Colcombe and Kramer, 2003). Furthermore, meta-analysis using more restrictive study inclusion criteria (i.e., randomized controlled trials with a minimum age requirement of 55 years and excluding studies on MCI, dementia, stroke, and depression) failed to show significant effects of aerobic exercise training compared to AC or WLC groups (Young et al., 2015). In addition, meta-analysis assessing association between aerobic fitness and cognitive performance, including processing speed, in older adults failed to show a significant relationship in cross-sectional designs and instead showed that increases in fitness were associated with decreases in cognitive performance in pre-post designs (Etnier et al., 2006; Colcombe and Kramer, 2003). Functional brain imaging studies suggest that exercise interventions of up to a year might be required before cognitive changes are observed in older groups. In a 2-year follow-up study of a 12-month exercise intervention in elderly participants, that included aerobic training, participants who completed and maintained their regimen after the intervention showed faster processing speed and increased BOLD signal change within the PFC when working through a computerized measure of digit-symbol coding compared with subjects who remained sedentary following the intervention (Rosano et al., 2010). In addition, 12 months of aerobic exercise training, but not 6 months of training or 12 months of nonaerobic stretching, in elderly participants was associated with increased functional connectivity within the PFC and parts of the default mode network (Voss et al., 2010). In summary, the present study showed evidence of transfer of higher-order cognitive training, but not aerobic exercise, to processing speed–related neural activity within the PFC, raising questions about the efficacy of short-term aerobic exercise to affect processing speed. However, more research is needed, particularly on protocol and participant characteristics, to elucidate the contribution of aerobic exercise on cognition, processing speed, and brain function.

5. Limitations

Whereas a number of studies are beginning to investigate the neural correlates of training in older adults (Brehmer et al., 2011; Heinzel et al., 2016), this investigation represents one of the first attempts to study the effects of higher-order cognitive training on processing speed–related neural activity. This evidence builds on prior findings showing corresponding enhanced cognitive and neural gains with cognitive training (i.e., SMART) in older adults (Chapman et al., 2015). Nonetheless, the current findings need to be interpreted cautiously in light of a few limitations. First, the sample sizes were relatively small and require replication in larger sample sizes. Still, the pattern of separate trends on processing speed–related neural activity for the CT versus WLC and AC randomized groups offers promise for achieving training-related benefits. Second, although we observed cognitive training–related changes in processing speed–related neural activity, we did not observe task-related performance differences between the CT, WLC, and AC groups. There might be limits to performance on the DSVT that prevented detecting training-related change, and given the improvement in the WLC group, there are clearly practice effects. Third, the population was homogeneous in relatively high educational attainment, and the results may not generalize to samples consisting of adults with more varied educational backgrounds. The homogenization of educational achievement, however, might have restricted the range of processing speed variability in the present sample, and thus, the effects observed in the present study might be stronger in a more varied sample. Fourth, the cognitive training–related change in processing speed-related PFC activation profiles was not correlated with changes in TOSL abstraction, the most proximal measure to the cognitive training. With the additional processes required for TOSL abstraction

compared to DSVT processing speed performance, however, weaker correlations would be expected between the 2 measures, and therefore, larger sample sizes might be required. Finally, there was an imbalance in the proportion of males to females across groups (CT females = 6, males = 6; WLC females = 11, males = 4; and AC females = 4, males = 10). However, the difference was not statistically significant, χ^2 (N = 41) = 1.91, $p = 0.385$, and previous studies on SMART in adults did not show sex differences.

6. Conclusions

In sum, the present results suggest that higher-order cognitive training in older adults can lead to PFC mediation of processing speed. Similar to previous observations in younger adults (Rao et al., 2014), after higher-order cognitive training, faster processing speed among older adults was associated with lower PFC activation. These results suggest that cognitive training can lead to improvement in PFC-mediated coordination of subprocess timing and output. Furthermore, evidence of increased PFC mediation of processing speed with higher-order cognitive training raises the possibility that such cognitive training might also lead to general increases in PFC function and resource availability and thus increases in a broad spectrum of neurocognitive functions in the elderly and across the lifespan. Increased PFC mediation of processing speed and resource availability might be mechanisms contributing to the previously shown transfer of higher-order cognitive training to improvements in executive functions (Anand et al., 2011; Chapman et al., 2015, 2016,; Motes et al., 2014; Vas et al., 2011).

Disclosure statement

The authors declare no competing financial interests.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2017.10.003.

References

Alvarez, J.A., Emory, E., 2006. Executive function and the frontal lobes: a meta-analytic review. Neuropsychol. Rev. 16, 17–42.
Anand, R., Chapman, S.B., Rackley, A., Keebler, M., Zientz, J., Hart Jr., J., 2011. Gist reasoning training in cognitively normal seniors. Int. J. Geriatr. Psychiatry 26, 961–968.
Aslan, S., Xu, F., Wang, P.L., Uh, J., Yezhuvath, U.S., van Osch, M., Lu, H., 2010. Estimation of labeling efficiency in pseudocontinuous arterial spin labeling. Magn. Reson. Med. 63, 765–771.
Baltes, P.B., Lindenberger, U., 1997. Emergence of a powerful connection between sensory and cognitive functions across the adult life span: a new window to the study of cognitive aging? Psychol. Aging 12, 12–21.
Baniqued, P.L., Allen, C.M., Kranz, M.B., Johnson, K., Sipolins, A., Dickens, C., Ward, N., Geyer, A., Kramer, A.F., 2015. Working memory, reasoning, and task switching training: transfer effects, limitations, and great expectations? PLoS One 10, e0142169.
Basak, C., Boot, W.R., Voss, M.W., Kramer, A.F., 2008. Can training in a real-time strategy video game attenuate cognitive decline in older adults? Psychol. Aging 2008, 765–777.
Biswal, B.B., Eldreth, D.A., Motes, M.A., Rypma, B., 2010. Task-dependent individual differences in prefrontal connectivity. Cereb. Cortex 20, 2188–2197.
Brehmer, Y., Rieckmann, A., Bellander, M., Westerberg, H., Fischer, H., Backman, L., 2011. Neural correlates of training-related working-memory gains in old age. Neuroimage 58, 1110–1120.
Buchsbaum, B.R., Greer, S., Chang, W.-L., Berman, K.F., 2005. Meta-analysis of neuroimaging studies of the Wisconsin card-sorting task and component processes. Hum. Brain Mapp. 25, 35–45.
Buckhalt, J.A., 1991. Reaction time measures of processing speed: are they yielding new information about intelligence? Pers. Individ. Dif. 12, 683–688.
Chapman, S.B., 2014. Make Your Brain Smarter: Increase Your Brain's Creativity, Energy, and Focus, first ed. Simon & Schuster.
Chapman, S.B., Aslan, S., Spence, J.S., Hart Jr., J.J., Bartz, E.K., Didehbani, N., Keebler, M.W., Gardner, C.M., Strain, J.F., DeFina, L.F., Lu, H., 2015. Neural mechanisms of brain plasticity with complex cognitive training in healthy seniors. Cereb. Cortex 25, 396–405.
Chapman, S.B., Aslan, S., Spence, J.S., Keebler, M.W., DeFina, L.F., Didehbani, N., Perez, A.M., Lu, H., D'Esposito, M., 2016. Distinct brain and behavioral benefits from cognitive vs. physical training: a randomized trial in aging adults. Front. Hum. Neurosci. 18.
Chapman, S.B., Mudar, R.A., 2014. Enhancement of cognitive and neural functions through complex reasoning training: evidence from normal and clinical populations. Front. Syst. Neurosci. 8, 69.
Cohen, M.S., 1997. Parametric analysis of fMRI data using linear systems methods. Neuroimage 6, 93–103.
Colcombe, S., Kramer, A.F., 2003. Fitness effects on cognitive function of older adults: a meta-analytic study. Psychol. Sci. 14, 125–130.
Cox, R.W., 1996. ANFI: software for analysis and visualization of functional magnetic resonance neuroimages. Comput. Biomed. Res. 29, 162–173.
Cox, R.W., Chen, G., Glen, D.R., Reynolds, R.C., Taylor, P.A., 2017. FMRI clustering in AFNI: false-positive rates redux. Brain Connect. 7, 152–171.
Earles, J.L., Salthouse, T.A., 1995. Interrelations of age, health, and speed. J. Gerontol. Psychol. Sci. 50, P33–P41.
Eklund, A., Nichols, T.E., Knutsson, H., 2016. Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. Proc. Natl. Acad. Sci. U. S. A. 113, 7900–7905.
Ekstrom, R.B., French, J.W., Harman, H.H., 1979. Cognitive factors: their identification and replication. Multivariate Behav. Res. Monogr. 79, 8–84.
Etnier, J.L., Nowell, P.M., Landers, D.M., Sibley, B.A., 2006. A meta-regression to examine the relationship between aerobic fitness and cognitive performance. Brain Res. Rev. 52, 119–130.
Heinzel, S., Lorenz, R.C., Pelz, P., Heinz, A., Walter, H., Kathmann, N., Rapp, M.A., Stelzel, C., 2016. Neural correlates of training and transfer effects in working memory in older adults. Neuroimage 134, 236–249.
Hillman, C.H., Erikson, K.I., Kramer, A.F., 2008. Be smart, exercise your heart: exercise effects on brain and cognition. Nat. Rev. Neurosci. 9, 58–65.
Jensen, A.R., 1992. The importance of intraindividual variation in reaction time. Pers. Indiv. Differ. 13, 869–881.
Kail, R., 1991. Developmental change in speed of processing during childhood and adolescence. Psychol. Bull 109, 490–501.
Kannuripatti, S.S., Motes, M.A., Rypma, B., Biswal, B.B., 2011. Increasing measurement accuracy of age-related BOLD signal change: minimizing vascular contributions by resting-state-fluctuation-of-amplitude scaling. Hum. Brain Mapp. 32, 1125–1140.
Lu, H., Xu, F., Rodrigue, K.M., Kennedy, K.M., Cheng, Y., Flicker, B., Hebrank, A.C., Uh, J., Park, D.C., 2010. Alterations in cerebral metabolic rate and blood supply across the adult lifespan. Cereb. Cortex 21, 1426–1434.
Mackey, A.P., Miller Singley, A.T., Wendelken, C., Bunge, S.A., 2015. Characterizing behavioral and brain changes associated with practicing reasoning skills. PLoS One 10, e0137627.
Motes, M.A., Biswal, B.B., Rypma, B., 2011. Age-dependent relationships between prefrontal cortex activation and processing efficiency. Cogn. Neurosci. 2, 1–10.
Motes, M.A., Gamino, J.F., Chapman, S.B., Rao, N.K., Maguire, M.J., Brier, M.R., Kraut, M.A., Hart Jr., J., 2014. Inhibitory control gains from higher-order cognitive strategy training. Brain Cogn. 84, 44–62.
Motes, M.A., Rypma, B., 2010. Working memory component processes: isolating BOLD signal-changes. Neuroimage 49, 1933–1941.
Mudar, R.A., Chapman, S.B., Rackley, A., Eroh, J., Chaing, H.-S., Parez, A., Venza, E., Spence, J.S., 2016. Enhancing latent cognitive capacity in mild cognitive impairment with gist reasoning training: a pilot study. Int. J. Geriatr. Psychiatry 32, 548–555.
Park, D.C., Lautenschlager, G., Hedden, T., Davidson, N.S., Smith, A.D., Smith, P.K., 2002. Models of visuospatial and verbal memory across the adult life span. Psychol. Aging 17, 299–320.
Park, D.C., Reuter-Lorenz, P., 2009. The adaptive brain: aging and neurocognitive scaffolding. Annu. Rev. Psychol. 2009, 173–196.
Rao, N., Motes, M.A., Rypma, B., 2014. Investigating the neural bases for intra-subject cognitive efficiency changes using functional magnetic resonance imaging. Front. Hum. Neurosci. 8.

Rosano, C., Venkatraman, V.K., Guralnik, J., Newman, A.B., Glynn, N.W., Launer, L., Taylor, C.A., Williamson, J., Studenski, S., Pahor, M., Aizenstein, H., 2010. Psychomotor speed and functional brain MRI 2 years after completing a physical activity treatment. J. Gerontol. A Biol. Sci. Med. Sci. 65, 639–647.

Rypma, B., Berger, J.S., Prabhakaran, V., Bly, B.M., Kimberg, D.Y., Biswal, B.B., D'Esposito, M., 2006. Neural correlates of cognitive efficiency. Neuroimage 33, 969–979.

Rypma, B., D'Esposito, M., 2000. Isolating the neural mechanisms of age-related changes in human working memory. Nat. Neurosci. 3, 509–515.

Rypma, B., Prabhakaran, V., 2009. When less is more and when more is more: the mediating roles of capacity and speed in brain-behavior efficiency. Intelligence 37, 207–222.

Salthouse, T.A., 1991. Theoretical Perspectives on Cognitive Aging. Lawrence Erlbaum Associates, Hillsdale, NJ.

Salthouse, T.A., 1992. What do adult age differences in the Digit Symbol Substitution Test reflect? J. Gerontol. Psychol. Sci. 47, P121–P128.

Salthouse, T.A., 1996. The processing-speed theory of adult age differences in cognition. Psychol. Rev. 103, 403–428.

Salthouse, T.A., 2009. When does age-related cognitive decline begin? Neurobiol. Aging 30, 507–514.

Smith, P.J., Blumenthal, J.A., Hoffman, B.M., Cooper, H., Strauman, T.A., Welsh-Bohmer, K., Browndyke, J.N., Sherwood, A., 2010. Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. Psychosom. Med. 72, 239–252.

Vas, A., Chapman, S., Aslan, S., Spence, J., Keebler, M., Rodriguez-Larrain, G., Rodgers, B., Jantz, T., Martinez, D., Rakic, J., Krawczyk, D., 2016. Reasoning training in veteran and civilian traumatic brain injury with persistent mild impairment. Neuropsychol. Rehabil. 26, 502–531.

Vas, A.K., Chapman, S.B., Cook, L.G., Elliott, A.C., Keebler, M., 2011. Higher-order reasoning training years after traumatic brain injury in adults. J. Head Trauma Rehabil. 26, 224–239.

Venza, E.E., Chapman, S.B., Aslan, S., Zientz, J.E., Tyler, D.L., Spence, J.S., 2016. Enhancing executive function and neural health in bipolar disorder through reasoning training. Front. Psychol. 7, 1676.

Voelcker-Rehage, C., Niemann, C., 2013. Structural and functional brain changes related to different types of physical activity across the life span. Neurosci. Biobehav. Rev. 13, 2268–2295.

Voss, M.W., Prakash, R.S., Erikson, K.I., Basak, C., Chaddock, L., Kim, J.S., Alves, H., Heo, S., Szabo, A.N., White, S.M., Wojcicki, T.R., Maily, E.L., Gothe, N., Olson, E.A., McAuley, E., Kramer, A.F., 2010. Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. Front. Aging Neurosci. 32.

Wechsler, D., 2008. Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV). NCS Pearson, San Antonio, TX.

Yezhuvath, U.S., Uh, J., Cheng, Y., Martin-Cook, K., Weiner, M., Diaz-Arrastia, R., van Osch, M., Lu, H., 2012. Forebrain-dominant deficit in cerebrovascular reactivity in Alzheimer's disease. Neurobiol. Aging 33, 75–82.

Young, J., Angevaren, M., Rusted, J., Tabet, N., 2015. Aerobic exercise to improve cognitive function in older people without known cognitive impairment. Cochrane Database Syst. Rev. 4, CD005381.

Yuan, P., Raz, N., 2014. Prefrontal cortex and executive functions in healthy adults: a meta-analysis of structural neuroimaging studies. Neurosci. Biobehav. Rev. 42, 180–192.