Cognitive and Neural Effects of Vision-Based Speed-of-Processing Training in Older Adults with Amnestic Mild Cognitive Impairment: A Pilot Study

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OBJECTIVES: To examine the cognitive and neural effects of vision-based speed-of-processing (VSOP) training in older adults with amnestic mild cognitive impairment (aMCI) and contrast those effects with an active control (mental leisure activities (MLA)).

DESIGN: Randomized single-blind controlled pilot trial.

SETTING: Academic medical center.

PARTICIPANTS: Individuals with aMCI (N = 21).

INTERVENTION: Six-week computerized VSOP training.

MEASUREMENTS: Multiple cognitive processing measures, instrumental activities of daily living (IADLs), and two resting state neural networks regulating cognitive processing: central executive network (CEN) and default mode network (DMN).

RESULTS: VSOP training led to significantly greater improvements in trained (processing speed and attention: $F_{1,19} = 6.61$, partial $\eta^2 = 0.26$, $P = .02$) and untrained (working memory: $F_{1,19} = 7.33$, partial $\eta^2 = 0.28$, $P = .01$; IADLs: $F_{1,19} = 5.16$, partial $\eta^2 = 0.21$, $P = .03$) cognitive domains than MLA and protective maintenance in DMN ($F_{1,\ 9} = 14.63$, partial $\eta^2 = 0.62$, $P = .004$). VSOP training, but not MLA, resulted in a significant improvement in CEN connectivity ($Z = -2.37$, $P = .02$).

CONCLUSION: Target and transfer effects of VSOP training were identified, and links between VSOP training and two neural networks associated with aMCI were found. These findings highlight the potential of VSOP training to slow cognitive decline in individuals with aMCI. Further delineation of mechanisms underlying VSOP-induced plasticity is necessary to understand in which populations and under what conditions such training may be most effective. **J Am Geriatr Soc 64:1293–1298, 2016.**

Key words: speed of processing; mild cognitive impairment; central executive network; default mode network

Amnestic mild cognitive impairment (aMCI), especially the multiple-domain subtype, is considered a symptomatic pre-Alzheimer's disease (AD) phase[1] and occurs during a period when the underlying pathobiology may be more receptive to modulation than when an individual has AD. Individuals with MCI are highly motivated to engage in activities to maintain cognitive and functional independence.[2]

One promising intervention is vision-based speed-of-processing (VSOP) training, a cognitive intervention widely used in community-dwelling older adults free of AD.[3,4] VSOP training primarily addresses visual processing speed and attention, which support most higher-order cognitive functions[5] and predict aMCI incidence and progression to AD.[6] A few weeks of VSOP training has been shown to improve multiple cognitive domains and everyday function in individuals with normal aging,[3,7,8] the human immunodeficiency virus,[9] and Parkinson's disease.[10] Moreover, individuals with lower baseline cognition are able to experience greater cognitive benefits from training.[11] Taken together, these findings suggest that VSOP training might be particularly beneficial for individuals with aMCI. A recent study demonstrated beneficial effects of VSOP training on trained domains (processing speed and attention) in different MCI subtypes.[12] However, it is unknown whether the effects of VSOP training in individuals with aMCI transfer to untrained cognitive and functional domains, which is the standard for evaluating the generalizability of improvement in training.

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Recent research suggests that neuroplasticity—the brain's ability to undergo beneficial restructuring or reprogramming in response to environmental stimuli—may be induced later in life, even in individuals with aMCI.[13] Evidence of neuroplasticity can indicate that the effects of training are not limited to cognitive operations (e.g., increasing task fluency). In healthy older adults, a recent VSOP intervention study showed significant improvement in event-related potential waveforms associated with processing speed and attention.[14] The current study focused on investigating plasticity in neural markers of neurodegeneration because such plasticity might indicate ways to modify AD pathology. Growing evidence conceptualizes AD as a neural connectivity syndrome.[15] The central executive network (CEN) and default mode network (DMN) are critical in maintaining visual processing speed and attention and are susceptible to normal and abnormal aging processes, including MCI.[5,16] The CEN includes the dorsolateral and ventromedial prefrontal cortex, insula, striatum, and posterior and anterior cingulate gyri. It directs engagement in tasks with high executive working load and error feedback.[17] The DMN includes the posterior cingulate cortex, ventromedial prefrontal cortex, lateral occipital cortex, hippocampus, and middle temporal cortex. DMN is related to memory encoding and storage.[18]

These networks are typically studied using resting state functional connectivity (rsFC), which examines task-independent, spontaneous fluctuations in functional connectivity to reveal brain networks where information is continuously processed and transported between structurally and functionally linked brain regions.[19] Recent studies have found that aMCI is associated with weaker connectivity in the DMN and stronger connectivity in the CEN than in cognitively healthly individuals.[17,20,21] Similar rsFC changes were also associated with greater beta-amyloid deposition in older adults, further suggesting that the DMN and CEN are sensitive to AD pathology.[20] To the knowledge of the authors of the current study, no studies have examined the effect of VSOP training on rsFC in individuals with aMCI.

This pilot trial addressed two unresolved questions in the VSOP training literature in relation to dementia prevention: whether VSOP training in individuals with aMCI would transfer to untrained cognitive domains and whether VSOP training could be linked to resting-state neural networks.[3,4] These questions are important for establishing the clinical relevance of VSOP training and better understanding VSOP-induced neuroplasticity. It was hypothesized that VSOP training would lead to greater and broader cognitive improvements and more efficient rsFC than MLA (less CEN and greater DMN connectivity).

METHODS

Participants

This was a randomized, controlled, single-blinded trial. Participants with aMCI were recruited from the University of Rochester Memory Care Program (MCP) using the clinical diagnosis of MCI due to Alzheimer's disease.[1] All participants had deficits in memory and executive function based on a comprehensive neuropsychological battery but intact activities of daily living and absence of dementia using the National Institute on Aging—Alzheimer's Association criteria according to assessments at MCP. Other inclusion criteria included stable use of AD medication, capacity to give consent based on clinician assessment, aged 60 and older, English speaking, adequate visual acuity for testing, and living in the community. Exclusion criteria included participation in another cognitive intervention study and active treatment with antidepressants or anxiolytics.

The University of Rochester Research subject review board approved the study. Twenty-four participants were enrolled and randomly assigned to the VSOP or MLA group after informed consent was provided and a baseline assessment was performed. Cognitive function and rsFC were assessed at baseline and after training. Interviewers were blinded to participants' group assignment. Three participants (2 from the VSOP group) withdrew after baseline assessment because of health concerns unrelated to the study. The baseline characteristics of the remaining 21 participants did not significantly differ between the two groups (Table 1).

Intervention

VSOP training used the INSIGHT online program (Posit Science, San Francisco, CA), which included five training tasks: eye for detail, peripheral challenge, visual sweeps, double decision, and target tracker.[14] Participants responded by identifying what object they saw or where they saw it on the screen. The training automatically adjusted the task difficulty and speed based on the participant's performance, ensuring that participants always

Table 1. Baseline Sample Characteristics

Characteristic	Vision-Based Speed-of-Processing Training, n = 10	Mental Leisure Activities Control, n = 11	Independent T-Test or Chi-Square Test (P-Value)
Age, mean ± SD	72.9 ± 8.2	73.1 ± 9.6	−0.05 (.96)
Male, n (%)	5 (50.0)	6 (54.5)	0.04 (>.99)
Education high school or lower, n (%)	1 (10.0)	5 (45.5)	3.23 (.15)
White, n (%)	7 (70.0)	10 (90.9)	1.49 (.31)
15-item Geriatric Depressive Scale score, mean ± SD	2.3 ± 1.9	3.6 ± 0.7	−1.39 (.18)
Frequency of engaging in mental leisure activities, mean ± SD (range 0 (daily) to 6 (never))	3.8 ± 0.7	4.44 ± 1.0	−1.56 (.14)
Montreal Cognitive Assessment score, mean ± SD	24.4 ± 2.6	25.6 ± 1.6	−1.25 (.23)

SD = standard deviation.

operated near their optimal capacity. The completion percentage and score of each task were recorded. Training performance was calculated relative to the normative data from the Posit Science database and expressed as a percentile. As expected, VSOP training resulted in significant performance increases (pretraining mean: $34.4 \pm 13.2\%$; posttraining mean: $52.2 \pm 16.5\%$; Wilcoxon test: $Z = -2.81$, $P = .005$).

MLA control activities were chosen to control for computer and online experience and amount of time, simulate participants' everyday mental activities, and entertain participants to prevent dropping out. Online crossword, Sudoku, and solitaire games were used.[3] Participants could choose to practice any combination of these games.

Both groups were asked to practice 1 hour per day 4 days per week for 6 weeks in their homes. Hours spent on training tasks were recorded in both groups; no significant differences were found (VSOP: 15.4 ± 6.6 hours; MLA: 19.3 ± 8.1, $t_{20} = -1.14$, $P = .27$). There were no correlations between training duration and training effects reported below in the entire sample (all $P > .10$). Of note, in VSOP training studies of healthy older adults, typical training duration is approximately 10 hours.[3,11,14]

Outcome Measures

Cognitive Measures

The Useful Field of View (UFOV) is a computerized test assessing visual processing speed and attention. Visual and attentional demands of UFOV are similar (although not identical) to the task demands in VSOP training.[22] A composite score of UFOV was developed by averaging the reaction times of three individual tasks (processing speed, selective attention, divided attention). The use of the composite score is consistent with the approach used in other clinical trials.[3,4]

The EXAMINER is a computerized test designed for clinical trials that measures three executive function domains: cognitive control (set shifting and flanker tasks), verbal fluency (phonemic and categorical fluency), and working memory (dot counting and 1-back). This three-domain model was determined using confirmatory factor analysis, and the generation of composite scores was based on item response theory methods. (For a detailed description see Chapter 11 in the User Manual.[23]) EXAMINER uses several comparable assessment packages to avoid using identical tests at different assessment points.[24]

Timed instrumental activities of daily living (TIADL) objectively measure performance speed and accuracy on multiple IADL domains. It is more sensitive measurement than the traditional self-report instruments in detecting subtle decline in everyday function in persons with MCI.[25] Time spent on each task was recorded, with adjustment on whether an individual accurately completed each task. A detailed description of the scoring process was provided in a previous study.[26] Average completion time of the tasks was used as the outcome measure.

Neuroimaging data were acquired using magnetic resonance imaging (TimTrio 3T system, Siemens, Erlangen, Germany) using a 32-channel head coil. High-resolution T1-weighted structural images were acquired using MPRAGE (inversion time = 950 ms, echo time (TE) = 3.87 ms, repetition time (TR) = 1,620 ms, 1-mm^3 resolution). A two-dimensional axial fast gradient-recalled echo pulse sequence was used to generate field maps, which were used to correct for field inhomogeneity distortions in echo-planar imaging sequences. Two 5-minute blood-oxygen-level-dependent functional scans were acquired for each assessment period using a gradient echo-planar imaging sequence (TR = 2 seconds, TE = 30 ms, 4-mm^3 resolution, 30 axial slices). Participants were instructed to relax with their eyes open without falling asleep.

rsFC data were analyzed using the FSL software (FMRIB Software Library; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). Data preprocessing consisted of motion correction, slice-timing correction, non-brain signal removal, and Gaussian spatial smoothing (5-mm full width at half maximum). Nuisance parameters (global, white matter and cerebrospinal fluid signals, motion) were removed using linear regression. Nonneuronal contributions were reduced using temporal filtering (0.01–0.08 Hz). The Multivariate Exploratory Linear Optimized Decomposition into Independent Components algorithm was used to generate resting state networks. The DMN and CEN were identified based on previous literature.[27] Network-specific regions of interest (ROIs) were selected using the Harvard-Oxford Atlas. Correlation of time courses between all possible pairs of within-network ROIs were computed and Fisher Z-transformed, with the average correlation coefficient representing the strength of the network.

Other data analysis was conducted using SPSS 21.0 (SPSS, Inc., Chicago, IL). To examine group differences at baseline, independent t-tests were conducted for continuous variables and chi-square tests for categorical variables. The Wilcoxon test was used to examine within-group effects of training. Baseline cognitive and neural outcomes did not significantly differ between the two groups except that participants in the VSOP training had worse working memory ($P = .03$). A repeated-measures general linear model was used to examine between-groups effects of training; the main and interacted terms of time and group were examined when controlling for baseline differences. For reported P-values, false-discovery rate was used to address for multiple comparisons across outcomes.

The sample size was based on a previous VSOP training study of multiple-domain aMCI, which reported an effect size (η^2) of 0.37 when comparing posttraining UFOV with a no-contact control group.[12] From this result, it was estimated that the minimum total sample size would be 14 (based on $\alpha = .05$, power = .80, two groups, two repeated measures, and 0.50 correlation between repeated measures). This compares favorably with the total sample size of 21.

RESULTS

Training Effects on Trained and Transferred Cognitive Outcomes

Within-group cognitive changes were first examined (Figure 1A, B, Table 2), contrasting baseline with posttraining outcomes. For the VSOP group, significant
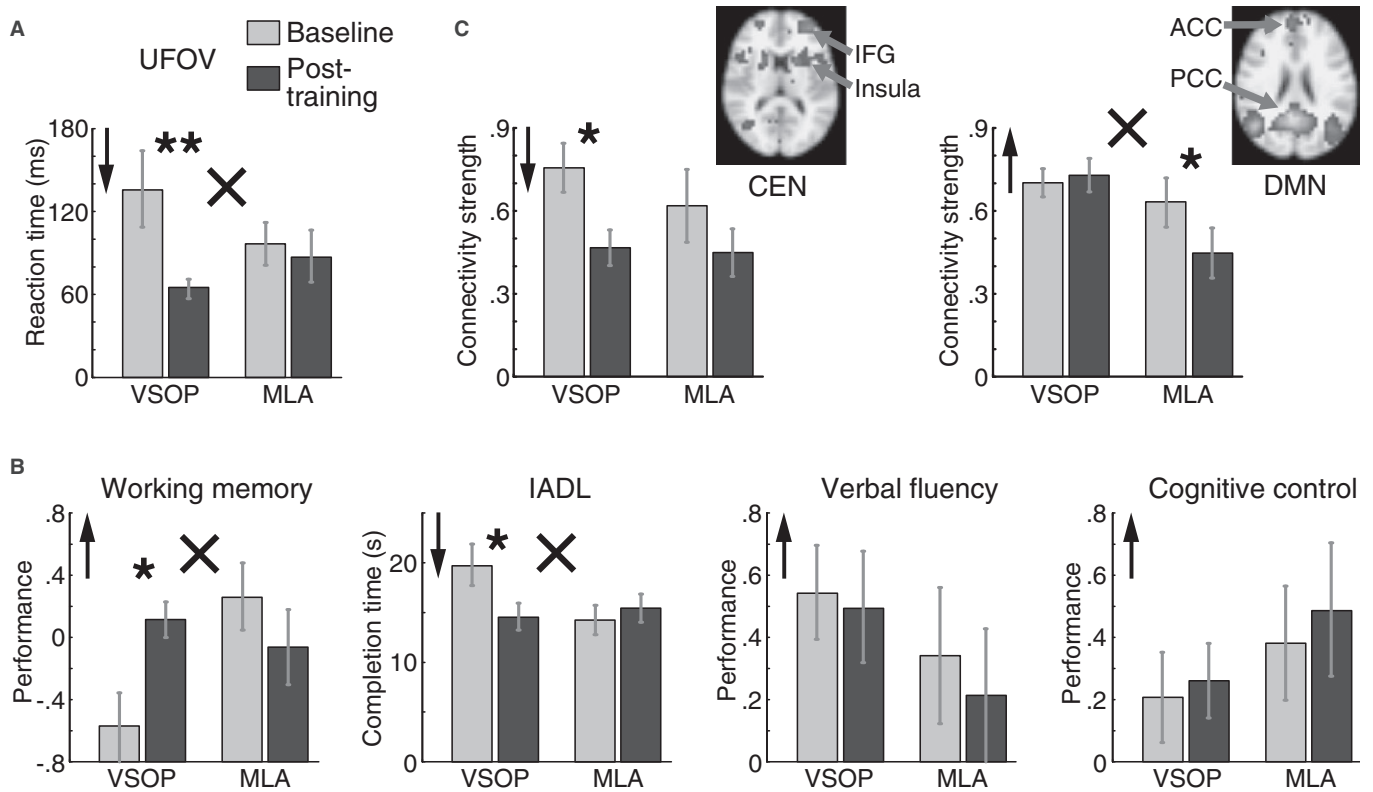
Figure 1. Effects of vision-based speed-of-processing (VSOP) training and mental leisure activities (MLA) control training on a range of cognitive and neural domains. (**A**) Effects of training on useful field of view (UFOV), the trained domain for VSOP training. (**B**) Effects of training on transfer domains: working memory, instrumental activities of daily living, verbal fluency, and cognitive control. (**C**) Effects of training on neural domains: resting state neural connectivity for the central executive network (CEN) and default mode network (DMN); inserts show horizontal brain slices that include regions of interest for each network (IFG = inferior frontal gyrus, ACC = anterior cingulate cortex, PCC = posterior cingulate cortex).
↑ Higher scores indicated better outcome; ↓ Lower scores indicated better outcome. Within-group (baseline vs after training) comparison: $P <$ *.05, **.01. Group (VSOP vs MLA) by time (baseline vs after training) comparison: ×$P < .05$.

Table 2. Baseline and Posttraining Cognitive and Neural Scores According to Group

Cognitive and Neural Outcomes	Vision-Based Speed-of-Processing Training (n = 10)				Mental Leisure Activities Control (n = 11)				Group × Time Interaction[a]		
	Baseline	Posttraining	Z	P-Value[b]	Baseline	Posttraining	Z	P-Value[b]	F	P-Value	Partial η^2
	Mean ± SD				Mean ± SD						
Useful field of view, mean reaction time, ms[c]	136.3 ± 87.4	64.0 ± 22.2	−2.70	.007[f]	96.6 ± 48.7	87.6 ± 59.5	−1.33	.18	6.61	.02[f]	0.26
Working memory[d]	−0.58 ± 0.71	0.11 ± 0.37	2.31	.02[f]	0.26 ± 0.68	−0.06 ± 0.76	−0.98	.33	7.33	.01[f]	0.28
Verbal fluency[d]	0.55 ± 0.48	0.50 ± 0.57	−0.46	.65	0.34 ± 0.69	0.21 ± 0.70	−0.18	.86	0.09	.77	0.005
Cognitive control[d]	0.21 ± 0.46	0.26 ± 0.38	0.68	.50	0.38 ± 0.58	0.49 ± 0.68	1.26	.21	0.14	.71	0.008
Instrumental activities of daily living, completion time, seconds[c]	19.8 ± 6.6	14.6 ± 4.2	−2.29	.02[f]	14.2 ± 4.6	15.4 ± 4.5	0.71	.48	5.16	.03[f]	0.21
Central executive network[e]	0.77 ± 0.23	0.47 ± 0.17	−2.37	.02[f]	0.62 ± 0.26	0.45 ± 0.17	−1.46	.14	2.03	.19	0.04
Default mode network[d]	0.70 ± 0.14	0.73 ± 0.16	1.04	.31	0.63 ± 0.18	0.45 ± 0.18	−1.83	.07	14.63	.004[f]	0.62

[a] Between-group comparison using repeated-measures general linear model controlled for group and main effects of time.
[b] Within-group comparison using Wilcoxon test.
[c] Higher is worse.
[d] Standardized composite score; lower is worse.
[e] Functional connectivity in standardized correlation coefficient; higher is worse.
[f] Significant level remained after false discovery rate adjustment.

improvements were found in the trained domain (UFOV, $Z = -2.70$, $P = .007$) and two transfer domains (working memory: $Z = 2.31$, $P = .02$, and IADL: $Z = -2.29$, $P = .02$) but no significant changes in two other transfer domains (verbal fluency and cognitive control). For the MLA group, there were no significant improvements (all $P > .10$).

The same pattern of results was evident in between-group comparisons (Figure 1A, B, Table 2). The VSOP group exhibited significantly greater improvements in UFOV (group-by-time interaction $F_{1, 19} = 6.61$, partial $\eta^2 = 0.26$, $P = .02$), working memory (group-by-time interaction $F_{1, 19} = 7.33$, partial $\eta^2 = 0.28$, $P = .01$), and IADL (group-by-time interaction $F_{1, 19} = 5.16$, partial $\eta^2 = 0.21$, $P = .03$) than the MLA group.

Training Effects on Resting-State Neural Networks

For the VSOP group, significant improvement was found in CEN connectivity ($Z = -2.37$, $P = .02$, as indexed according to poor connectivity strength) and no change in DMN (Figure 1C, Table 2). The MLA group showed no CEN changes and a trend for worsening of DMN ($Z = 1.83$, $P = .07$, as indexed according to poor strength of connectivity). Between-group analysis (Figure 1C, Table 2) showed that VSOP training resulted in significantly greater improvements than MLA (indexed according to greater connectivity) in the DMN (group-by-time interaction $F_{1, 9} = 14.63$, partial $\eta^2 = 0.62$, $P = .004$) but not CEN.

A summary of the results is presented in Table 2.

DISCUSSION

The present study shows that, in addition to the improvement in the trained domain, VSOP training led to improvements in working memory and IADLs. The results also link VSOP training with maintenance of DMN connectivity strength and a decrease in CEN connectivity.

The transfer of VSOP training to untrained cognitive and functional domains is of likely clinical significance. There may be several nonexclusive explanations of this transfer effect. First, because individuals with MCI have low baseline cognitive capacity, they have more room for improvement in the trained and untrained domains. Second, the VSOP training used here includes a rich combination of visual processing speed and attention tasks (see Methods). This is in contrast to previous studies that relied on a single task,[7] although transfer effects of the training exhibited a certain degree of specificity. For example, significant changes were not found in verbal fluency, which is probably due to the lack of linguistic stimuli in the training tasks. The specificity of transfer effects across different executive function domains requires further investigation with larger sample sizes.

The two brain networks examined in the present study provide a possible functional platform for disseminating training effects from one region to another. VSOP training in MCI was linked with lower CEN connectivity and maintenance of DMN connectivity. One explanation for the lower CEN connectivity is that VSOP training helped enhance the efficiency of information processing, which reduced the frontal lobe–oriented dependence. Weakening of DMN connectivity is a consistently identified marker of neurodegeneration.[28] Although the VSOP training did not enhance DMN connectivity, maintenance of DMN connectivity can be viewed as a positive outcome given naturally worsening processes in MCI. Supporting this argument, a trend for weakened DMN connectivity in the MLA group was found. This is not surprising, because a recent cohort study found MLA to be independent of brain pathology.[29]

Limitations of the study need to be acknowledged. First, the study was designed to investigate VSOP-training induced changes in various cognitive and neural measures. Although the sample size provided sufficient power to examine training-induced changes, it was insufficient to examine correlations between various cognitive domains and indexes of neural changes. Whether the cognitive changes correspond to neural changes is critical in linking the cognitive and neural effects and needs to be addressed in future studies with larger sample sizes. Second, although the five tasks within VSOP training share similar visual components, training effects of individual tasks were not specified (similar to other cognitive training studies[16]). Doing so will also require a much larger sample size. Third, although there were no significant differences in training duration between groups, this does not ensure that the "intensity" of the training was the same. Future research should determine whether, and to what degree, training intensity differences account for differences in the effects of VSOP and MLA training.

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REFERENCES

1. Albert MS, DeKosky ST, Dickson D et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270–279.

2. Lin F, Heidrich SM. Role of older adult's illness schemata in coping with mild cognitive impairment. J Psychosom Res 2012;72:357–363.

3. Wolinsky FD, Vander Weg MW, Howren MB et al. A randomized controlled trial of cognitive training using a visual speed of processing intervention in middle aged and older adults. PLoS ONE 2013;8:e61624.

4. Ball K, Berch DB, Helmers KF et al. Effects of cognitive training interventions with older adults: A randomized controlled trial. JAMA 2002;288:2271–2281.

5. Eckert MA. Slowing down: Age-related neurobiological predictors of processing speed. Front Neurosci 2011;5:25.

6. Sylvain-Roy S, Bherer L, Belleville S. Contribution of temporal preparation and processing speed to simple reaction time in persons with Alzheimer's disease and mild cognitive impairment. Brain Cogn 2011;74:255–261.

7. Rebok GW, Ball K, Guey LT et al. Ten-year effects of the advanced cognitive training for independent and vital elderly cognitive training trial on cognition and everyday functioning in older adults. J Am Geriatr Soc 2014;62:16–24.

8. Edwards JD, Valdes EG, Peronto C et al. The efficacy of insight cognitive training to improve useful field of view performance: A brief report. J Gerontol B Psychol Sci Soc Sci 2015;70B:417–422.

9. Vance DE, Fazeli PL, Ross LA et al. Speed of processing training with middle-age and older adults with HIV: A pilot study. J Assoc Nurses AIDS Care 2012;23:500–510.

10. Edwards JD, Hauser RA, O'Connor ML et al. Randomized trial of cognitive speed of processing training in Parkinson disease. Neurology 2013;81:1284–1290.

11. Ball K, Edwards JD, Ross LA. The impact of speed of processing training on cognitive and everyday functions. J Gerontol B Psychol Sci Soc Sci 2007;62B:19–31.

12. Valdes EG, O'Connor ML, Edwards JD. The effects of cognitive speed of processing training among older adults with psychometrically-defined mild cognitive impairment. Curr Alzheimer Res 2012;9:999–1009.

13. Simon SS, Yokomizo JE, Bottino CM. Cognitive intervention in amnestic Mild Cognitive Impairment: A systematic review. Neurosci Biobehav Rev 2012;36:1163–1178.

14. O'Brien JL, Edwards JD, Maxfield ND et al. Cognitive training and selective attention in the aging brain: An electrophysiological study. Clin Neurophysiol 2013;124:2198–2208.

15. Gomez-Ramirez J, Wu J. Network-based biomarkers in Alzheimer's disease: Review and future directions. Front Aging Neurosci 2014;6:12.

16. Takeuchi H, Kawashima R. Effects of processing speed training on cognitive functions and neural systems. Rev Neurosci 2011;23:289–301.

17. Agosta F, Pievani M, Geroldi C et al. Resting state fMRI in Alzheimer's disease: Beyond the default mode network. Neurobiol Aging 2012;33:1564–1578.

18. Raichle ME. Two views of brain function. Trends Cogn Sci 2010;14:180–190.

19. van den Heuvel MP. Hulshoff Pol HE. Exploring the brain network: A review on resting-state fMRI functional connectivity. Eur Neuropsychopharmacol 2010;20:519–534.

20. Mormino EC, Smiljic A, Hayenga AO et al. Relationships between beta-amyloid and functional connectivity in different components of the default mode network in aging. Cereb Cortex 2011;21:2399–2407.

21. Supekar K, Menon V, Rubin D et al. Network analysis of intrinsic functional brain connectivity in Alzheimer's disease. PLoS Comput Biol 2008;4:e1000100.

22. Lin F, Chen DG, Vance D et al. Trajectories of combined laboratory- and real world-based speed of processing in community-dwelling older adults. J Gerontol B Psychol Sci Soc Sci 2013;68B:364–373.

23. Executive Abilities: Measures and Instruments for Neurobehavioral Evaluation and Research (EXAMINER). Testing Forms C. NINDS: Domain Specific Tasks of Executive Function [on-line]. Available at http://memory.ucsf.edu/sites/all/files/download/ExaminerBatteryFormC-Adult.pdf Accessed March 14, 2016.

24. Possin KL, Feigenbaum D, Rankin KP et al. Dissociable executive functions in behavioral variant frontotemporal and Alzheimer dementias. Neurology 2013;80:2180–2185.

25. Jefferson AL, Byerly LK, Vanderhill S et al. Characterization of activities of daily living in individuals with mild cognitive impairment. Am J Geriatr Psychiatry 2008;16:375–383.

26. Owsley C, Sloane M, McGwin G Jr et al. Timed instrumental activities of daily living tasks: Relationship to cognitive function and everyday performance assessments in older adults. Gerontology 2002;48:254–265.

27. Damoiseaux JS, Rombouts SA, Barkhof F et al. Consistent resting-state networks across healthy subjects. Proc Natl Acad Sci USA 2006;103:13848–13853.

28. Dennis EL, Thompson PM. Functional brain connectivity using fMRI in aging and Alzheimer's disease. Neuropsychol Rev 2014;24:49–62.

29. Wilson RS, Boyle PA, Yu L et al. Life-span cognitive activity, neuropathologic burden, and cognitive aging. Neurology 2013;81:314–321.