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Research Article

Improved intraindividual variability in cognitive performance following cognitive and exercise training in older adults

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Abstract

Objective: Increased intraindividual variability (IIV) of cognitive performance is a marker of cognitive decline in older adults. Whether computerized cognitive training (CCT) and aerobic exercise counteracts cognitive decline by reducing IIV is unknown. We investigated the effects of CCT with or without aerobic exercise on IIV in older adults. **Methods:** This was a secondary analysis of an 8-week randomized controlled trial. Older adults (aged 65–85 years) were randomized to CCT alone ($n = 41$), CCT with aerobic exercise ($n = 41$), or an active control group ($n = 42$). The CCT group trained using the Fit Brains® platform 3×/week for 1 hr (plus 3×/week of home-based training). The CCT with aerobic exercise group received 15 min of walking plus 45 min of Fit Brains® 3×/week (plus 3×/week of home-based training). The control group received sham exercise and cognitive training (3×/week for 1 hr). We computed reaction time IIV from the Dimensional Change Card Sort Test, Flanker Inhibitory Control and Attention Test (Flanker), and Pattern Comparison Processing Speed Test (PACPS). **Results:** Compared with the control group, IIV reduced in a processing speed task (PACPS) following CCT alone (mean difference [95% confidence interval]: −0.144 [−0.255 to −0.034], $p < 0.01$) and CCT with aerobic exercise (−0.113 [−0.225 to −0.001], $p < 0.05$). Attention (Flanker congruent) IIV was reduced only after CCT with aerobic exercise (−0.130 [−0.242 to −0.017], $p < 0.05$). **Conclusions:** A CCT program promoted cognitive health via reductions in IIV of cognitive performance and combining it with aerobic exercise may result in broader benefits.

Keywords: Aging; Variability; Cognition; Aerobic training; Reaction time; Processing speed

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Introduction

The prevalence of cognitive impairment continues to increase with recent estimates suggesting higher worldwide prevalence than previously expected (e.g., ∼416 million individuals along the Alzheimer's disease spectrum) (Gustavsson et al., 2022). Unfortunately, effective dementia treatment options are not yet widely available and the prospect for disease-modifying pharmacological therapies is discouraging (Mehta et al., 2017). Thus, efforts to prevent or reduce the rate of cognitive decline via management of lifestyle factors have become a research priority (Baumgart et al., 2015; Rosenberg et al., 2020). As recently estimated, approximately 40% of dementia cases worldwide could be prevented with effective management of modifiable lifestyle risk factors (Livingston et al., 2020).

Considering that the pathophysiological processes underlying cognitive decline and dementia may take place decades before disease diagnosis (Villemagne et al., 2013), targeting risk factors prior to the onset of clinical symptoms could be critical for preventing or deaccelerating disease progression (Kivipelto et al., 2018). As an acceptable and feasible intervention (ten Brinke et al., 2020), computerized cognitive training is a promising strategy for promoting cognitive performance in older adults (Gavelin et al., 2020; Lampit et al., 2014). Benefits of this type of cognitive training have been reported on measures of global cognitive function and processing speed in healthy individuals (Gates et al., 2020). Positive effects have also been reported in those with mild cognitive impairment in global cognitive function, episodic memory, and working memory (Gates et al., 2019). Nonetheless, the benefits of computerized cognitive training to cognitive function are still very modest, with very small effect sizes across cognitive domains in healthy older individuals (Gavelin et al., 2020) and those with cognitive impairment (Gates et al., 2019). Small effect sizes in part reflect the fact that quality of the evidence from randomized controlled trials (RCTs) in older individuals remains critically low due to small sample sizes and high risk of bias on several study

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characteristics, including selection and reporting bias (Gates et al., 2020, 2019; Gavelin et al., 2020). Therefore, high-quality evidence from well-controlled RCTs of computerized cognitive training is warranted (Gavelin et al., 2020).

Maintaining a physically active lifestyle is another important strategy to foster healthy cognitive aging (Barnes et al., 2003; Bherer et al., 2013; Livingston et al., 2017; Lourida et al., 2019). Aerobic exercise training is a type of physical activity that benefits cognition in individuals with or without known cognitive impairment (Colcombe & Kramer, 2003; Erickson & Kramer, 2008; Liu-Ambrose et al., 2016). Aerobic exercise training is associated with improvements on measures of executive function, memory (Northey et al., 2017; Sanders et al., 2019), and processing speed (Barha et al., 2017; Smith et al., 2010) in older individuals with and without cognitive impairment. Nevertheless, meta-analytic evidence still indicates that the effect sizes of aerobic exercise on cognition remains small across cognitive domains, which is thought to reflect small sample sizes and variability of exercise training prescription and cognitive assessment (Barha et al., 2017; Falck et al., 2019; Northey et al., 2017; Sanders et al., 2019); thus, identifying strategies to maximize exercise-induced benefits on cognition would be helpful.

Emerging evidence suggests that multimodal behavioral interventions that include exercise and cognitive training may be more efficacious than single modality approaches to improve cognition (Gavelin et al., 2021; Kivipelto et al., 2018; Rosenberg et al., 2020). From a mechanistic point of view, the combined effects of multimodal behavioral interventions would result from synergistic and/or additive neuroplastic adaptations facilitated by the distinct, yet complimentary, nature of these strategies (Gavelin et al., 2021). Aerobic exercise is known to transiently increase neurotrophic factors associated with neurogenesis and neuroplasticity (Cotman et al., 2007). Cognitive training modalities like computerized cognitive training could further promote synaptic plasticity and the survival and functional integration of the newly formed neurons into neural networks (Gonçalves et al., 2016; Shors et al., 2012). When administered in immediate succession, engaging in moderate-intensity exercise prior to cognitive training could also augment cognitive benefits via increases in cortisol. That is, exercise transiently increases cortisol by stimulating the hypothalamic-pituitary-adrenal axis (Luger et al., 1987). Cortisol levels remain elevated for up to 2 hr after exercise cessation, a period in which cortisol can enhance learning, memory consolidation, and prefrontal lobe functions (Basso & Suzuki, 2017).

Furthermore, combining computerized cognitive training with exercise interventions may promote benefits to cognition while also impacting other health outcomes like physical function (Gavelin et al., 2021). This means that combining interventions can be a resource-effective approach for offsetting the impact of multiple dementia risk factors (Gavelin et al., 2021). Although the observed effects are small, the current literature supports this notion as combined interventions administering cognitive and physical training in older adults seem to benefit global and domain-specific cognition including executive function, processing speed, and memory as well physical function compared with either intervention alone (Gavelin et al., 2021). We showed that 8 weeks of combined computerized cognitive training and aerobic exercise benefitted cognition, promoting more widespread improvements than cognitive training alone (ten Brinke et al., 2020). Improvements resulting from the combined training were observed particularly in subdomains of executive function, which included response inhibition, set-shifting, and cognitive flexibility tasks (ten Brinke et al., 2020).

Nonetheless, current evidence shows the overall effect of behavioral interventions on cognition in older adults is small (Gavelin et al., 2021). Beyond the influence of limitations mentioned above (e.g., small sample sizes, selection bias), the observed small effects may be due to how cognition is measured in studies. In this regard, more sensitive measures to detect intervention-driven effects on cognition in older individuals are needed (Brydges & Bielak, 2019; MacDonald & Stawski, 2015; Vrinceanu et al., 2021). One of such approaches is utilizing intraindividual variability of cognitive performance to determine whether intervention effects span beyond average (i.e., mean) performance on a given task (MacDonald & Stawski, 2015).

Intraindividual variability of cognitive performance can characterize cognitive impairment and predict longitudinal cognitive and physical function outcomes (Chow et al., 2022; Graveson et al., 2016; Haynes, Bauermeister, et al., 2017). This is concomitant with the notion that cognitive processes become more unstable as one ages and increasing stability (i.e., reducing variability) would reflect improvements on overall cognitive performance (MacDonald & Stawski, 2015). Therefore, it is plausible that intervention effects on cognition could be more evident on measures of intraindividual variability than mean performance, as the former may be more sensitive to subtle improvements underling stability of cognitive processes even in the absence of changes in the latter (MacDonald & Stawski, 2015).

As an important limitation in the current literature, intra-individual variability has been poorly studied compared with measures of central tendency (e.g., mean, median) (Falck et al., 2019; Lampit et al., 2014). While dominant, measures of central tendency do not paint the full picture of cognitive functioning as they fail to account for inconsistency on task performance (MacDonald et al., 2006). As such, the study of intraindividual variability can shed light on understudied elements of cognitive decline in older adults (Haynes, Bauermeister, et al., 2017).

Intraindividual variability is defined as within-participant trial-to-trial variation in reaction time during cognitive tasks (Hultsch et al., 2008). Higher levels of intraindividual variability are associated with poorer cognitive performance (Bielak & Anstey, 2019; MacDonald et al., 2006) and likely result from compromised integrity of neurobiological substrates (Haynes, Bauermeister, et al., 2017; MacDonald & Stawski, 2015). For instance, evidence suggest that intraindividual variability could reflect gray matter neurodegeneration especially in frontal regions (MacDonald et al., 2006). Higher intraindividual variability has also been associated with age-related myelin degradation across the lifespan (Grydeland et al., 2013), as well as increased white matter hyperintensities burden (Bunce et al., 2013; Haynes, Bunce, et al., 2017; Nilsson et al., 2014), a marker of cerebral small vessel disease (Alber et al., 2019). There is also the possibility that higher intraindividual variability reflects alteration in neurofunctional states during complex cognitive tasks (Garrett et al., 2020; Garrett et al., 2014), and reduced cortical activation in regions responsible for efficient and dynamic regulation of attention and cognitive control (Johnson et al., 2015). Thus, intraindividual variability metrics are not merely noise in assessment of cognitive performance but rather proxy measures of stability within neurobiological correlates of cognition (MacDonald et al., 2006).

From a clinical perspective, intraindividual variability of cognitive performance might be a useful marker of cognitive

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and functional decline. A systematic review showed that higher reaction time intraindividual variability at baseline was associated with steeper cognitive decline, increased dementia risk, and overall higher mortality risk (Haynes, Bauermeister, et al., 2017). A meta-analysis further corroborates these findings wherein Mumme and colleagues report that greater intraindividual variability of cognitive performance is longitudinally associated with cognitive decline and subsequent conversion to dementia with a medium effect size ($r = 0.20$, 95% CI = 0.09 to 0.31) (Mumme et al., 2021). The association between intraindividual variability of cognitive performance and functional status is less understood. Nevertheless, both cognitive function and mobility contribute to one's functional status. High intraindividual variability is associated with poor gait and increased falls risk, which suggests that high intraindividual variability may also reflect compromised neurobiological substrates related to mobility and control of gait (Graveson et al., 2016).

Due to its adaptive and neuroplastic nature (MacDonald & Stawski, 2015), intraindividual variability can serve as a critical outcome measure in lifestyle interventions designed to improve cognitive health, and potentially strengthen the evidence on the efficacy of these interventions in older adults. In recent investigations, intraindividual variability has been shown to improve after different types of interventions such as cognitive training (Vrinceanu et al., 2021), as well as combined physical, cognitive, and social engagement (Brydges et al., 2021); however, not all types of interventions have shown change in intraindividual variability in older adults (Bielak & Brydges, 2019). Evidence from studies combining computerized cognitive training and aerobic exercise to improve intraindividual variability is still limited.

The goal of this study was to determine the effect of an 8-week computerized cognitive training program with or without aerobic exercise on intraindividual variability parameters. This is a secondary exploratory analysis of a completed RCT in healthy older adults (ten Brinke et al., 2020), the results of which we have mentioned above. It was expected that computerized cognitive training with or without additional aerobic exercise would result in significant reductions in intraindividual variability compared with an active control group.

Methods

The study protocol (ten Brinke et al., 2018) and the primary findings (ten Brinke et al., 2020) of this RCT have been published previously. The main aspects of the study protocol are summarized in the following sections.

Study design

This is a secondary analysis of an 8-week, single-blinded, proof-of-concept RCT (ClinicalTrials.gov identifier: NCT02564809) conducted at The University of British Columbia and Vancouver General Hospital, Vancouver, British Columbia, Canada. Outcome assessments were performed at baseline and trial completion (i.e., 8 weeks) by trained assessors blinded to group allocation.

Participants

Community-dwelling older adults from metro Vancouver were recruited between September 2015 and April 2017. After an initial screening, participants who met inclusion criteria and signed the informed consent were invited for baseline assessments. The study CONSORT diagram illustrating participant flow throughout the study has been published previously (ten Brinke et al., 2020). Briefly, 379 individuals were screened, 130 consented to participate in the study, and 124 were randomized after baseline assessments (see Table 1). Ethical approval was obtained from The University of British Columbia Clinical Research Ethics Board and the Vancouver Coastal Health Research Institute ethics board. All human data included in this manuscript were obtained in compliance with the Helsinki Declaration.

Inclusion and exclusion criteria

Community-dwelling older adults meeting the following criteria were included: (a) aged 65 to 85 years; (b) completed high school education; (c) no prior diagnosis of cognitive impairment or dementia; (d) had preserved general cognitive function as indicated by a score ≥24/30 on the Mini-Mental State Examination (MMSE) (Folstein et al., 1975); (e) scored ≥6/8 on the Lawton and Brody (Lawton & Brody, 1969) Instrumental Activities of Daily Living Scale; (f) were not expected to start or were stable on a fixed dose of antidementia medications (e. g., donepezil, galantamine) during the study period; and (g) were suitable to engage in 15 min of brisk walking based on the Physical Activity Readiness Questionnaire (Canadian Society of Exercise Physiology, 1994).

We excluded individuals who: (a) were diagnosed with dementia of any type; (b) had a neurodegenerative disease as the cause of mild cognitive impairment that was not Alzheimer's disease, vascular dementia, or both (e.g., multiple sclerosis, Parkinson's disease); (c) experienced clinically significant peripheral neuropathy or severe musculoskeletal or joint disease that impairs mobility; and (d) were taking medications that may negatively affect cognitive function.

Randomization

Participants ($N = 124$) were randomized at a 1:1:1 ratio to one of the following groups: Fit Brains® Training (FBT, $n = 41$), Exercise plus Fit Brains® Training (Ex-FBT, $n = 41$), or Balanced And Toned (BAT, $n = 42$) via www.randomization.com. Randomization was performed by a team member not involved in the study. Randomization took place after study enrollment and baseline assessments. Specifically, the study coordinator sent a list of participant identification numbers to an independent team member who provided the study coordinator with the group allocation. The study coordinator then informed participants of their group assignment. All outcome assessors were blinded after treatment allocation.

Sample size

The sample size for this study was calculated using the Rey Auditory Verbal Learning Test (RAVL) (Lezak, 1995) as the study primary outcome, which is reported elsewhere (ten Brinke et al., 2020, 2018). Briefly, based on previous work (Diamond et al., 2015), it was predicted that a RAVL mean change (z-score) of 0.31 for the FBT group, 0.40 for the Ex-FBT group, and −0.31 for the BAT group would occur. With a pooled standard deviation of 1.1, and alpha of 0.05, 36 participants were needed for a power of 0.80. With a 10% drop-out rate, the total sample size was 120 participants (i.e., 40 FBT, 40 Ex-FBT, and 40 BAT).

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Table 1. Baseline demographic and outcome data

Variables	BAT ($n = 42$)	FBT ($n = 41$)	Ex-FBT ($n = 41$)
Demographic information			
Age, years	71.36 (5.14)	72.88 (5.17)	72.46 (4.11)
Females, *n* (%)	23 (55)	30 (73)	22 (54)
Education, *n* (%)			
High school certificate or diploma	5 (11.9)	5 (12.2)	4 (9.8)
Trades or professional certificate	8 (19.0)	3 (7.3)	6 (14.6)
University certificate	8 (19.0)	11 (26.8)	12 (29.3)
University degree	21 (50.0)	22 (53.7)	19 (46.3)
Montreal Cognitive Assessment, score	25.12 (3.10)	25.49 (3.16)	24.63 (3.86)
Mini-Mental State Examination, score	28.36 (1.56)	28.78 (1.39)	28.68 (1.39)
Height, cm	166.06 (10.48)	163.36 (10.82)	166.27 (10.25)
Weight, kg	74.35 (18.30)	67.46 (14.41)	72.61 (17.20)
Body mass index, kg/m^2	26.74 (5.16)	25.15 (4.06)	26.02 (4.34)
Intraindividual variability parameters			
Dimensional change card sort			
Residual ISD, *T* score	7.20 (3.92)	7.07 (4.26)	7.30 (5.69)
Raw-score ISD, s	0.31 (0.17)	0.30 (0.18)	0.31 (0.25)
ICV, ratio	0.32 (0.12)	0.30 (0.13)	0.32 (0.16)
Flanker congruent			
Residual ISD, *T* score	5.34 (3.82)	4.95 (2.86)	3.55 (2.78)
Raw-score ISD, s	0.18 (0.13)	0.16 (0.10)	0.11 (0.09)
ICV, ratio	0.17 (0.07)	0.18 (0.09)	0.14 (0.06)
Flanker, cost			
Residual ISD, *T* score	−0.52 (4.62)	−2.28 (3.12)	−0.74 (2.11)
Raw-score ISD, s	0.14 (0.36)	0.01 (0.16)	0.06 (0.19)
ICV, ratio	0.03 (0.10)	−0.02 (0.11)	0.01 (0.08)
Pattern comparison processing speed[a]			
Residual ISD, *T* score	8.05 (4.82)	8.61 (6.29)	7.82 (4.37)
Raw-score ISD, s	0.60 (0.36)	0.64 (0.48)	0.57 (0.34)
ICV, ratio	0.24 (0.08)	0.24 (0.12)	0.24 (0.10)

Note: Data presented as either mean (SD) or *n* (%) unless otherwise stated. BAT = balanced and toned group; FBT = Fit Brains® training; Ex-FBT = exercise plus Fit Brains® training group; ISD = intraindividual standard deviation; ICV = intraindividual coefficient of variation.
[a]Data removed for one participant with only two reaction time trials.

Intervention

A detailed description of each of the intervention arms in this study has been published previously (ten Brinke et al., 2018).

Fit Brains® Training

Participants randomized to FBT performed computerized cognitive training targeting six cognitive domains (i.e., focus, speed, memory, visual, problem solving, and language). Training sessions were delivered using an iPad; participants performed training sessions 3×/week for 60 min at the research center, as well as 3×/week for 60 min at home. Cognitive training was individualized and adaptive throughout the 8-week program.

Exercise plus Fit Brains® Training

Participants randomized to Ex-FBT attended training sessions 3×/week for 60 min at the research center and 3x/week for 60 min at home. The 60-min sessions consisted of a 15-min brisk walk (i.e., up to 13–14 on the 6–20 Borg's Rating of Perceived Exertion scale) (Borg, 1982) followed by 45 min of computerized cognitive training. Cognitive training took place immediately after the end of the 15-min brisk walk. For home sessions, participants were asked to fill out logs with start time, number of steps taken, and end time for aerobic training, while the home cognitive training was tracked through the Fit Brains® program app.

Balanced and Toned

Participants randomized to BAT (i.e., active control) attended training sessions 3×/week for 60 min at the research center for 8 weeks. Specifically, at the research center, participants completed 8 hr of sham cognitive training wherein they played casual online games that do not significantly tap into complex cognitive abilities (e.g., executive function) (Baniqued et al., 2013), as well as group-based games (e.g., drawing using both dominant and non-dominant hand, writing captions on cartoons, and word games). We also delivered 8 hr of sham exercise training, which included stretching, range of motion, basic core-strength exercises, and balance training (e.g., Tai Chi-based forms like Crane and Tree Pose, tandem stand, tandem walking, and single leg stance). Participants also completed 8 hr of education relating to brain health (e.g., included lectures on sleep, goal setting, mindfulness, as well as educational project), which included a homework assignment (maximum of 3 hr/week).

Demographic variables

We collected demographic characteristics data at baseline (Table 1) including age, self-reported sex, education level, height, weight, and body mass index. We used the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) and MMSE (Folstein et al., 1975) to assess the cognitive status of the study participants. The MoCA score is more sensitive to mild changes in cognitive function, and we used it better characterize our sample (Nasreddine et al., 2005). The MMSE was applied to exclude participants with cognitive scoring indicating dementia (see "Inclusion and exclusion criteria" section) (Folstein et al., 1975).

Study outcomes

Change in intraindividual variability measures from baseline to trial completion were the outcomes in this investigation. We extracted reaction time data from three neuropsychological tests

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within the Cognition Battery of the National Institute of Health (NIH) Toolbox (Weintraub et al., 2013) namely the Dimensional Change Card Sort Test, the Flanker Inhibitory Control and Attention Test (Flanker), and the Pattern Comparison Processing Speed Test. The NIH Toolbox Cognition Battery is a computerized and automated battery to assess key cognitive domains affected by age- and pathology-related decline (Weintraub et al., 2013). The three tasks above were selected to derive intraindividual variability because these tasks rely heavily on reaction time latencies to assess participant's performance, wherein accurate and/or faster responses indicate better performance (Weintraub et al., 2013) Furthermore, for the current secondary analysis, the NIH Toolbox Cognitive Battery tasks were also chosen as they assess cognitive domains which would be sensitive to the training intervention. The Fit Brains® program included 38 games in its mobile form (iPads) targeting six cognitive subdomains (i.e., focus, speed, memory, visual, problem solving, and language) (ten Brinke et al., 2018). The program offers a higher frequency of games targeting executive functions (four out of six domains), while remaining games targeted processing speed and memory (ten Brinke et al., 2018). Details of the NIH Toolbox Cognition Battery can be found elsewhere (Weintraub et al., 2013), below we provide a short description of the tasks included in the current study:

Flanker inhibitory control and attention test

The Flanker test measures visuospatial inhibitory attention; in this test, participants are requested to as quickly as possible indicate the direction of a central arrow (target) within a row of arrows (i.e., flankers) (Weintraub et al., 2013) by touching one of two arrows at the bottom on the screen. In congruent trials, the target arrow is in the same direction as the flankers, while in incongruent trials the target arrow faces the opposite direction. Performance on the task was measured over 20 random trials.

Dimensional change card sort test

This task is a measure of set-shifting in which participants must match a series of bivalent test pictures (i.e., yellow balls and blue trucks) to a target picture according to one of two dimensions (i.e., color or shape) as quickly as possible. For each trial, the dimension by which they need to "sort" appears on the screen and participants touch the screen to select one of two pictures that match the correct target dimension. Performance on the task was measured over 30 trials.

Pattern comparison processing speed test

This task measures choice reaction time whereby participants must indicate whether two images presented side-by-side are identical by touching "yes" or "no" on the screen. The task lasts 85 s and participants are to complete as many trials as possible with a maximum of 130 trials.

Data cleaning

Raw reaction time data were extracted for all accurate trials from each of the three tasks included in the study. We trimmed accurate reaction time by removing latencies lower than 150 ms or 3 standard deviations (SD) above the mean for the same participant, task, and timepoint (Bielak & Anstey, 2019). Moreover, to conform with previous research (Bielak & Anstey, 2019; Brydges et al., 2020), we performed imputation of excluded data by applying a regression substitution procedure that creates individualized reaction time equations, which are then used to predict the missing values (Bielak & Anstey, 2019). Missing data were not imputed if a participant had more than 50% of data missing across trials in which case data for that participant were excluded. Only ~1.5% of raw data were imputed across all tasks and timepoints. As well, one participant had only two reaction time trials in the Pattern Comparison Processing Speed Test at baseline, this participant was not included in the analysis of this task.

Computation of intraindividual variability

The main measure of intraindividual variability applied in this study was residual intraindividual SD (residual ISD), which is an unbiased measure of variability that accounts for within (e.g., practice effects) and between participant (e.g., age differences) source of variation that could influence reaction time latencies (Bielak & Anstey, 2019; Hultsch et al., 2008). For each task and timepoint, we entered reaction time data for all participants in a regression model with reaction time trial, categorical age (i.e., 65–69, 70–74, 75–79, or 80–84), and an interaction term (trial × age) as model predictors (Bielak & Anstey, 2019). Next, we extracted residuals from each model and transformed these residuals into T scores. We then computed the SD of the transformed residuals (i.e., residual ISD) separately for each participant, task, and timepoint. In addition, we calculated the commonly used SD of raw reaction time latencies (raw-score ISD) and intraindividual coefficient of variation (ICV, defined as raw-score ISD/mean) (Haynes, Bauermeister, et al., 2017). Although raw-score ISD and ICV are not considered entirely robust measures of intraindividual variability (Bielak & Anstey, 2019), we included these measures as secondary outcomes in our analysis given their common use (Haynes, Bauermeister, et al., 2017). All intraindividual variability measures were log-transformed prior to analysis.

Lastly, we computed intraindividual variability metrics separately for the congruent and incongruent conditions in the Flanker task, and then derived the Flaker cost (i.e., interference score) subtracting the incongruent from the congruent intraindividual variability metrics after log-transformation. The Flanker cost is a robust index of inhibitory attention in which performance is unbiased by differences in response time (Kramer et al., 1994). Data derived from the Flanker congruent condition and Flanker cost were used in the analysis.

Statistical analysis

We applied multilevel modeling to determine differences between groups at 8 weeks on residual ISD, raw-score ISD, and ICV measures. Specifically, we applied linear mixed models with restricted maximum likelihood estimation including random intercepts, and fixed effects of group, task, and group-by-task interaction. Baseline performance, age, and MoCA were included as fixed effects covariates in each model. In total, three models were conducted for each intraindividual variability measure (i.e., residual ISD, raw-score ISD, and ICV).

Differences between groups were determined via post hoc, Bonferroni-corrected pairwise comparisons. Using BAT as the reference group, we extracted estimated mean difference between groups along with 95% confidence interval. In all post hoc analyses, two-sided, Bonferroni-corrected p values < 0.05 were considered as statistically significant.

Data preparation, cleaning, and analysis were performed in R version 4.2.0 (https://www.R-project.org/) using the *tidyverse*

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(version 1.3.1), *lme4* (version 1.1-32), *lmerTest* (version 3.1-3), *emmeans* (version 1.7.4-1), *knitr* (version 1.39), and *patchwork* (version 1.1.1) packages within RStudio version 2023.06.1+524 (RStudio Team, 2023).

Results

Participant clinical and demographic characteristics

Descriptive characteristics and baseline intraindividual variability parameters are presented in Table 1 (see Supplementary Material for log-transformed intraindividual variability data at baseline). Overall, study participants were highly educated and mostly female. Adherence and adverse events have been reported previously (ten Brinke et al., 2020). Briefly, all groups achieved >90% compliance on all elements of the interventions administered in the current study, and there were 7 dropouts across the whole study sample.

Differences between groups in study outcomes

Results for between-group differences are reported in Table 2. Compared with the control group (BAT), Ex-FBT significantly reduced attention intraindividual variability indexed as lower residual ISD in the Flanker congruent task (mean difference [95% confidence interval] −0.130 [−0.242 to −0.017], $p < 0.05$, Figure 1). Similarly, Ex-FBT significantly reduced Flanker congruent raw-score ISD (−0.124 [−0.239 to −0.009], $p < 0.05$) compared with BAT

Both experimental groups also significantly reduced processing speed intraindividual variability measured with the Pattern Comparison Processing Speed Test. These changes were seen as reduction in residual ISD in FBT (−0.144 [−0.255 to −0.034], $p < 0.01$) and Ex-FBT (−0.113 [−0.225 to −0.001], $p < 0.05$) compared with BAT. Also, for processing speed, both FBT (−0.170 [−0.282 to −0.058], $p < 0.01$) and Ex-FBT (−0.125 [−0.239 to −0.011], $p < 0.05$) groups showed greater reduction in raw-score ISD compared with BAT, while only FBT reduced ICV for this task (−0.108 [−0.200 to −0.017], $p < 0.05$).

There were no differences between the intervention groups compared with BAT in set-shifting (Dimensional Change Card Sort Test) in any of the studied intraindividual variability measures. As well, despite intraindividual variability reductions in the Flanker congruent following Ex-FBT reported above, we did not notice any changes in any of the intraindividual variability measures for the Flanker cost.

Discussion

This exploratory study investigated the effects of an 8-week computerized cognitive training with or without aerobic exercise in intraindividual variability measures in community-dwelling older adults aged 65 to 85 years old. Our findings indicated that computerized cognitive training improved intraindividual variability on a processing speed task relative to an 8-week sham exercise and cognitive training program. Moreover, a 15-min brisk walk prior to computerized cognitive training also conferred benefits to intra-individual variability on tasks measuring attention and processing speed. These findings expand upon the parent study results (ten Brinke et al., 2020) showing that improvements in cognition following computerized cognitive training, with or without additional aerobic exercise, may result from increased consistency on task performance.

Our investigation shows novel findings suggesting improvements in intraindividual variability parameters following a computerized cognitive training with or without additional aerobic exercise in otherwise healthy older adults. Reduced

Table 2. Log-transformed estimated marginal means and differences between groups after the 8-week intervention period

Outcomes[a]	Estimated marginal means at 8 weeks, log-transformed (95% CI)						Adjusted between-group contrast, log-transformed (95% CI)	
	BAT	*N*	FBT	*N*	Ex-FBT	*N*	FBT vs BAT	Ex-FBT vs BAT
DCCS								
Residual ISD	0.660 (0.587 to 0.733)	40	0.640 (0.567 to 0.713)	39	0.604 (0.531 to 0.676)	38	−0.020 (−0.130 to 0.091)	−0.056 (−0.168 to 0.055)
Raw-score ISD	−0.538 (−0.607 to −0.468)	40	−0.557 (−0.628 to −0.486)	39	−0.612 (−0.684 to −0.539)	38	−0.019 (−0.132 to 0.093)	−0.074 (−0.187 to 0.039)
ICV	−0.514 (−0.570 to −0.457)	40	−0.529 (−0.587 to −0.472)	39	−0.516 (−0.574 to −0.458)	38	−0.016 (−0.108 to 0.076)	−0.002 (−0.095 to 0.090)
Flanker congruent								
Residual ISD	0.568 (0.499 to 0.637)	40	0.487 (0.417 to 0.556)	39	0.439 (0.369 to 0.508)	38	−0.082 (−0.192 to 0.029)	**−0.130 (−0.242 to −0.017)***
Raw-score ISD	−0.735 (−0.811 to −0.658)	40	−0.824 (−0.904 to −0.745)	39	−0.858 (−0.947 to −0.770)	38	−0.090 (−0.202 to 0.023)	**−0.124 (−0.239 to −0.009)***
ICV	−0.726 (−0.787 to −0.664)	40	−0.780 (−0.843 to −0.717)	39	−0.784 (−0.854 to −0.715)	38	−0.054 (−0.146 to 0.038)	−0.059 (−0.152 to 0.035)
Flanker, cost								
Residual ISD	0.108 (0.019 to 0.197)	40	0.124 (0.025 to 0.222)	39	0.097 (0.007 to 0.187)	38	0.015 (−0.096 to 0.127)	−0.011 (−0.122 to 0.100)
Raw-score ISD	−0.256 (−0.340 to −0.172)	40	−0.197 (−0.276 to −0.119)	39	−0.199 (−0.281 to −0.117)	38	0.059 (−0.054 to 0.172)	0.057 (−0.056 to 0.171)
ICV	−0.245 (−0.320 to −0.169)	40	−0.207 (−0.278 to −0.137)	39	−0.194 (−0.268 to −0.120)	38	0.038 (−0.055 to 0.130)	0.051 (−0.042 to 0.143)
PACPS								
Residual ISD	0.796 (0.721 to 0.871)	40	0.651 (0.576 to 0.727)	39	0.683 (0.608 to 0.759)	37[b]	**−0.144 (−0.255 to −0.034)****	**−0.113 (−0.225 to −0.001)***
Raw-score ISD	−0.326 (−0.397 to −0.255)	40	−0.496 (−0.567 to −0.425)	39	−0.451 (−0.523 to −0.379)	37[b]	**−0.170 (−0.282 to −0.058)****	**−0.125 (−0.239 to −0.011)***
ICV	−0.591 (−0.648 to −0.534)	40	−0.699 (−0.758 to −0.641)	39	−0.659 (−0.720 to −0.599)	37[b]	**−0.108 (−0.200 to −0.017)***	−0.068 (−0.162 to 0.025)

Note: CI = confidence interval; DCCS = Dimensional Change Card Sort; PACPS = Pattern Comparison Processing Speed; BAT = balanced and toned group; FBT = Fit Brains® training group; Ex-FBT = exercise plus Fit Brains® training group; ISD = intraindividual standard deviation; ICV = intraindividual coefficient of variation.

[a]All intraindividual variability data presented are log-transformed. All models were adjusted for baseline performance, age, and Montreal Cognitive Assessment scores.

[b]Data removed for one participant with only two reaction time trials at baseline.

*Significant between-group differences at Bonferroni-corrected $p < 0.05$.

**Significant between-group differences at Bonferroni-corrected $p < 0.01$.

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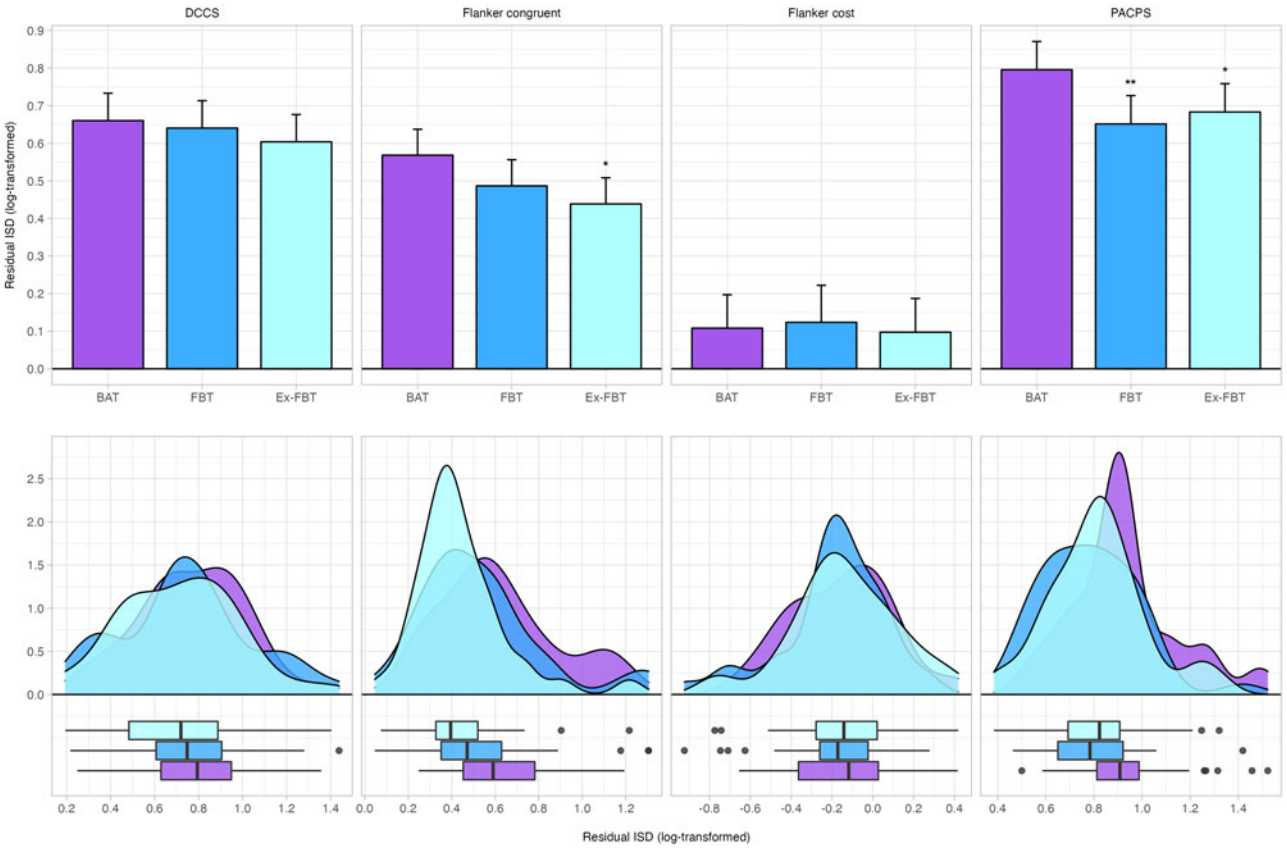

Figure 1. Comparisons between groups in residual ISD after the 8-week intervention period.
Note: Lower values indicate reduced variability and thus better performance. Upper panel shows estimated marginal means at 8 weeks, lower panel shows distribution of data across groups. DCCS = Dimensional Change Card Sort; PACPS = Pattern Comparison Processing Speed; BAT = balanced and toned group; FBT = Fit Brains® training group; Ex-FBT = exercise plus Fit Brains® training group; ISD = intraindividual standard deviation. *Significant differences compared with the BAT group at Bonferroni-corrected $p < 0.05$. **Significant differences compared with the BAT group at Bonferroni-corrected $p < 0.01$.

variability in our study suggests preserved integrity of neurobiological processes underlying performance on processing speed tasks (Hultsch et al., 2008). We also noted intervention effects in raw-score ISD and ICV on processing speed and attention tasks, suggesting agreement between the distinct measures employed in our investigation.

Our results partially support the findings from the main study in this sample (ten Brinke et al., 2020) where effects on cognition were seen in the combined computerized cognitive training with aerobic exercise group (Ex-FBT). Specifically, the Ex-FBT group improved response inhibition and set-shifting compared with the control group, as measured via neuropsychological tests independent from the ones used in the current study (i.e., Stroop Test and Trail-Making Test, respectively). The previous study also found improvements in the Dimensional Change Card Sort Test and Flanker overall scores (combined congruent and incongruent) favoring computerized cognitive training with additional aerobic exercise, while the computerized cognitive training group (FBT) only improved on the Stroop Test. Therefore, our results suggest that healthy older adults benefit from computerized cognitive training not only on mean cognitive performance but also on indices of cognitive variability. Although our investigation was not powered to detect differences between intervention groups, the additional aerobic training seemed to confer additional benefits to intraindividual variability of attention measured with the Flanker congruent condition, while computerized cognitive training alone did not.

Notwithstanding, our results showed no intervention effects of computerized cognitive training with or without exercise on intraindividual variability for the Dimensional Change Card Sort Test task, which does not align with the results in the main trial (ten Brinke et al., 2020). It is plausible that as a complex set-shifting task (Zelazo et al., 2014), the neurobiological substrates related to intraindividual variability in the Dimensional Change Card Sort Test are differently influenced by computerized cognitive training with aerobic exercise. This would be in contrast with simpler tasks like the Flanker congruent condition (Zelazo et al., 2014) and the Pattern Comparison Processing Speed Test (Weintraub et al., 2013). This conjecture can be supported by our results showing a lack of intervention effects on intraindividual variability in the Flanker cost (i.e., incongruent minus congruent), despite changes in the original Flanker congruent score. The Flanker cost theoretically comprises a more robust index of inhibitory attention, reflecting performance unbiased by differences in base response time. In this context, our findings indicate that the combined intervention effects seem to primarily impact performance on cognitive domains of less complexity such as processing speed and attention, with little effect on set-shifting.

The literature assessing the impact of interventions on intraindividual variability as an outcome measure is still developing, with recent studies showing mixed results (Bielak & Brydges, 2019; Brydges & Bielak, 2019; Brydges et al., 2021, 2020; Vrinceanu et al., 2021). Brydges and Bielak reported no significant intraindividual

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variability changes in inhibitory attention (measured with Flanker) in older adults following 15 weeks of either productive cognitive engagement or passive engagement interventions (Brydges & Bielak, 2019). A study investigating changes in intraindividual variability following resistance exercise compared with exergaming in healthy older adults also showed no intraindividual variability differences between groups in response inhibition (Meneghini et al., 2022). As well, little improvement in intraindividual variability in an inhibitory attention task was reported in older adults following a 2-year physical activity program compared with an education control group (Bielak & Brydges, 2019). In contrast, reductions in intraindividual variability for response inhibition have been reported in older adults following a 2-year program of combined physical, cognitive, and social engagement (Brydges et al., 2021). A 12-week RCT also reported improvements in intraindividual variability on a dual-task paradigm following computerized cognitive training, but not resistance exercise or gross-motor abilities training, in healthy older adults (Vrinceanu et al., 2021). Considering these mixed findings and the findings of the current study, cognitively engaging interventions with or without additional exercise might elicit similar changes in intraindividual variability, with additional aerobic exercise potentially expanding cognitive benefits; however, the different types, length of interventions, outcome measures, and population in previous studies limit our ability to draw definitive conclusions.

We consider lower intraindividual variability as marker of cognitive improvement. This notion stems from several cross-sectional and longitudinal investigations linking high intra-individual variability to poor cognitive performance in younger and older adults, as well as cognitive decline in older individuals. For instance, in healthy younger adults, increasing task difficulty results in decline in task accuracy (i.e., worse performance) and a linear increase in intraindividual variability measured with residual ISD (Garrett et al., 2014). Older individuals showing greater neurofunctional adaptability (measured with task-based fMRI) also show better cognitive performance and lower intraindividual variability across a series of cognitive tasks (Garrett et al., 2020). Compared with healthy age-matched controls, older individuals with mild cognitive impairment show higher intraindividual variability on executive functions and poorer cognitive performance (Chow et al., 2022). Longitudinally, higher intraindividual variability at baseline in older adults has been associated with steeper cognitive decline, increased dementia risk, and overall higher mortality risk (Haynes, Bauermeister, et al., 2017). A recent meta-analysis further corroborates these findings wherein greater intraindividual variability is longitudinally associated with risk of cognitive decline and conversion to mild cognitive impairment and dementia with a moderate effect size (Mumme et al., 2021). With substantial support in the previous literature, we can conclude that there is enough evidence to suggest that lower intraindividual variability of cognitive performance in older adults reflects healthier cognitive states. Although, we recognize that the field is evolving and there may very well be instances wherein lower intraindividual variability of cognitive performance may not be unequivocally better for all older individuals.

Limitations

One important limitation of the current study is that the reliability of intraindividual variability measures has not been fully established. However, the NIH Toolbox Cognitive Battery as a whole has good to excellent reliability across a large age range (Weintraub et al., 2013) and the methodology applied in the current study has been used in several other publications (Bauermeister & Bunce, 2016; Brydges & Bielak, 2019; Brydges et al., 2020; Chow et al., 2022), Further, as stated by Hultsch and colleagues, the systematic associations between intraindividual variability measures with personal traits such as cognitive status, age, and physical function provide compelling evidence for the reliability of intraindividual variability measures (Hultsch et al., 2008). Importantly, any differences in intraindividual variability related to measurement error would not bias study results for comparisons between groups, given that participants were randomly allocated at baseline. Additionally, we conducted an exploratory secondary analysis of intraindividual variability data and, given the potential for Type I error, our findings must be interpreted with caution. As well, we included highly educated individuals the majority of which were females. Our sample also may have included older adults with some degree of cognitive impairment as 61 (49.2%) individuals scored less than 26/30 on the MoCA, despite not having a formal diagnosis of cognitive impairment or dementia. To minimize the impact of baseline cognitive status on the study outcomes, we adjusted for MoCA scores in the models. Further, as research is still evolving in the field, it remains unclear what impact improving intraindividual variability would have on everyday activities such as driving or financial decision-making. Because of these reasons, future investigations are warranted to replicate our findings and establish whether intraindividual variability improvements reflect improvement in other aspects of health and everyday functioning. Finally, we did not record compliance data for homework completion in the control group (i.e., BAT), which hinders accurate comparison of hours spent working at home between control and computerized cognitive training groups.

Conclusions

In community-dwelling older adults without dementia, computerized cognitive training improved intraindividual variability on a processing speed task. Performing 15 min of brisk walking immediately prior to computerized cognitive training appeared to confer additive benefits on measures of processing speed and attention in this population. Overall, our findings strengthen the notion that a multidomain lifestyle intervention may promote cognitive health via reductions in indices of cognitive variability in otherwise healthy older adults.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1355617723000577

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