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A 24-Week Multi-Modality Exercise Program Improves Executive Control in Older Adults with a Self-Reported Cognitive Complaint: Evidence from the Antisaccade Task

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Abstract. Exercise programs involving aerobic and resistance training (i.e., multiple-modality) have shown promise in improving cognition and executive control in older adults at risk, or experiencing, cognitive decline. It is, however, unclear whether cognitive training within a multiple-modality program elicits an additive benefit to executive/cognitive processes. This is an important question to resolve in order to identify optimal training programs that delay, or ameliorate, executive deficits in persons at risk for further cognitive decline. In the present study, individuals with a self-reported cognitive complaint ($_S$CC) participated in a 24-week multiple-modality (i.e., the M2 group) exercise intervention program. In addition, a separate group of individuals with a $_S$CC completed the same aerobic and resistance training as the M2 group but also completed a cognitive-based stepping task (i.e., multiple-modality, mind-motor intervention: M4 group). Notably, pre- and post-intervention executive control was examined via the antisaccade task (i.e., eye movement mirror-symmetrical to a target). Antisaccades are an ideal tool for the study of individuals with subtle executive deficits because of its hands- and language-free nature and because the task's neural mechanisms are linked to neuropathology in cognitive decline (i.e., prefrontal cortex). Results showed that M2 and M4 group antisaccade reaction times reliably decreased from pre- to post-intervention and the magnitude of the decrease was consistent across groups. Thus, multi-modality exercise training improved executive performance in persons with a $_S$CC independent of mind-motor training. Accordingly, we propose that multiple-modality training provides a sufficient intervention to improve executive control in persons with a $_S$CC.

Keywords: Executive-control, exercise, mind-motor training, multiple-modality training, subjective cognitive complaint

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INTRODUCTION

Older adults (i.e., $\geq$55 years of age) with self-reported cognitive complaints or mild cognitive impairment (MCI) exhibit specific, yet subtle, cognitive deficits linked to the prodromal stages of Alzheimer's disease (AD) [1–4]. In particular, these individuals display executive deficits of perceptual speed [1], response inhibition [5, 6], strategic planning [7], and explicit memory [8]. These observations indicate that older adults reporting a subjective cognitive complaint or individuals meeting the MCI definition exhibit salient—and early—milestones for an increased risk of continuing cognitive decline and draws attention to the need to develop intervention strategies that ameliorate, or preclude, further decline in these groups.

One intervention shown to produce neurocognitive benefits and improve general physical and psychological well-being in non-demented older adults is the participation in long-term aerobic fitness training programs. For example, Colcombe et al.'s [9] seminal functional MRI study found that non-demented, but sedentary, older adults who participated in a 24-week walking program showed improved supervisory attentional control and task-appropriate modulation of executive-related cortical structures compared to a non-aerobic control group (i.e., 24-week "stretching and toning" group). Such findings indicate that aerobic training is causally linked to improved task-appropriate cortical activation (i.e., cortical efficiency) and enhanced transfer and quality of communication between and within cortical structures (i.e., cortical effectiveness). Moreover, exercise programs combining aerobic and resistance training (i.e., multiple-modality training) lead to greater cognitive benefits than single-modality training (i.e., aerobic or resistance), and multiple-modality programs engender the largest training-related benefit to high-level executive functioning [10, 11; cf. 12]. Indeed, because executive control reflects the ability to attend to task-relevant stimuli, the updating and monitoring of working memory, and the evocation of high-level inhibitory control [13], its improved function imparts an important benefit to activities of daily living [14].

Work involving persons with MCI and AD have reported conflicting findings related to the role of aerobic/resistance training programs and cognition. Gates and colleagues [15] meta-analysis concluded, "There is very limited evidence that exercise improves cognitive function in individuals with MCI" (p. 1086). In contrast, Öhman et al.'s [16] systematic review concluded that aerobic exercise improves global cognition, executive function, and memory in persons with MCI but not individuals with AD [see also 17,18]. Of course, the discrepancy most likely relates to the fact that many of the reviewed studies did not: (1) provide operational definitions for AD or MCI, (2) provide adequate samples sizes, (3) provide measures of participant compliance or adherence, or (4) provide objective measures of cognitive impairment with sufficient resolution to detect subtle executive deficits. Thus, the authors of the aforementioned meta-analysis and systematic reviews proposed that there is need for high-quality studies evaluating exercise effects in persons at risk, or experiencing, cognitive decline. Moreover, the majority of the studies examining the link between exercise and cognitive decline have relied on single-modality (i.e., aerobic) training programs—a training program type that may not maximize neurocognitive benefits. To highlight this point, recent randomized controlled trials involving persons experiencing cognitive decline (i.e., self-reported cognitive complaint or objective cognitive impairment) [19] and those recovering from stroke [20] have shown that multiple-modality training programs (>9 weeks of duration) elicit reliable post-intervention benefits to neurocognitive function. Accordingly, it has been proposed that the contextual variety and/or the biochemical consequences (i.e., neuroprotective factors responsible for neuronal growth and differentiation) associated with multiple-modality training provide an ideal environment for attaining exercise-related benefits in persons experiencing cognitive decline [21].

In addition to work reporting that multi-modality training enhances executive-related processes, some evidence from animal and human studies suggests that physical activity performed in a cognitively challenging environment elicits an additive benefit to executive/cognitive function. For example, Fabel and colleagues [22] reported that female mice that completed a wheel running task in an enriched environment showed greater neuronal proliferation than animals that performed in a standard wheel running task (i.e., no environmental enrichment). Moreover, the authors reported that their conjoint morphological, molecular, and behavioral data demonstrate that physical activity and cognitive training "... can be combined to obtain specific *additive* (italics added) regulatory effects" (p. 5). In addition, Oswald et al. [23] reported that cognitively healthy older adults who participants in a combined multi-modality physical activity and cognitive training program showed larger, and long-lasting, benefits to cognition (as assessed via memory and perceptual speed) than those who participated in multi-modality training alone. Notably, however, the salience of combined physical activity and cognitive training is tempered by evidence reporting that such an affect may not extend to populations with cognitive impairment. In particular, Law et al.'s [24] systematic review concluded that in populations with cognitive impairment "... well-designed studies are still needed to explore the potential benefits of this new intervention paradigm" (p. 61). As such, the primary objective of this study was to determine whether a cognitive-based visuo-spatial stepping task included in a multiple-modality exercise training program (i.e., multiple-modality, mind-motor intervention) renders an additive post-intervention benefit in executive control for persons self-reporting a cognitive complaint ($_{S}$CC). To that end, older adults with a $_{S}$CC were randomly assigned to one of two groups that completed a 24-week exercise training program. The first group completed a multiple-modality exercise program that involved resistance (as well as balance, range-of-motion, and breathing exercises) and moderate-to-vigorous intensity aerobic training [25] (65–85% maximum heart rate, for 20 min/d, 3x/wk) (i.e., the *multiple-modality intervention group*: M2). The second group completed the same aerobic and resistance training as the M2 group; however, in the place of balance, range of motion and breathing exercises a cognitively demanding task was performed (i.e., *multiple-modality, mind-motor intervention group*: M4). In particular, in each exercise session the M4 group performed 15 min of square-stepping exercises (SSE), a contextually varied visuo-spatial working memory task requiring that participants memorize and execute progressively more complex foot placement patterns that involve forward, backwards, lateral, and diagonal steps. The SSE was originally designed to improve balance for individuals at risk for falling [26]; however, it has also shown promise for improving cognition in non-demented older adults [27, 28]. As such, the M4 group provided a framework to determine whether multiple-modality, mind-motor training enhances executive control more than multiple-modality training alone. Moreover, we purpose-designed the M4 group based on Law and colleagues' [24] assertion that the empirical evaluation of an additive benefit of a cognitive-motor task in persons at risk for cognitive decline requires the direct comparison to an 'active' control group (i.e., the M2 group).

To address our primary objective, M2 and M4 group pre- and post-intervention executive control was examined via the antisaccade task. The antisaccade task requires a goal-directed eye movement (i.e., saccade) mirror-symmetrical to the location of a visual target. Notably, the task is cognitively 'challenging' and extensive behavioral and neuroimaging work in humans as well as single-cell recording work in non-human primates has shown that correct antisaccade performance is contingent upon premovement activity within the prefrontal cortex [29–33], a region supporting executive control [34] and known to be compromised in AD [35]. In particular, Munoz and Everling [33] proposed that the wealth of behavioral and neurophysiological evidence accumulated from the antisaccade task provides for specific predictions regarding the neural mechanisms impaired in clinical populations. Moreover, Peltsch et al. [36] demonstrated that persons meeting Petersen's et al.'s [37] definition for amnestic MCI (i.e., aMCI: cognitive complaint not normal for age, not demented, memory decline, essentially normal functional activities) exhibited antisaccade reaction time (RT) costs that were larger than cognitively healthy older adults. As well, Peltsch et al. reported that antisaccade metrics were more effective at differentiating executive function between controls and individuals with aMCI than standardized neuropsychological tests (i.e., California Verbal Learning Test, Wisconsin Card Sorting Task). Thus, the hands- and language-free nature of the antisaccade task coupled with the temporal and spatial resolution of eye-tracking provides an ideal tool for the assessment of subtle executive deficits/improvements in persons with a cognitive complaint/impairment [36, 38].

As a secondary research goal, we examined whether our exercise interventions differentially influenced executive control in persons with a selective $_{S}$CC and those meeting the definition for MCI. The basis for this question was motivated by evidence that persons meeting the MCI definition are progressed further along the continuum of cognitive decline than individuals with a selective $_{S}$CC [39]. As such, it is possible that persons with MCI may show an increased (or decreased) benefit to executive control following a 24-week multi-modality exercise training program than those with a selective $_{S}$CC. To accomplish our secondary goal, we dichotomized all the M2 and M4 $_{S}$CC participants included in our primary research goal into those: (1) having a selective $_{S}$CC, and (2) meeting the definition for MCI (i.e., an individual with a $_{S}$CC and an associated objective cognitive impairment as determined by a Montreal Cognitive Assessment (MoCA) score of less than 26) [40]. Subsequently, we evaluated whether persons with $_S$CC and MCI elicited differential executive-related oculomotor benefits following M2 and M4 interventions.

METHODS

Participants

Community-dwelling older adults (≥55 years of age) from the communities in and around Woodstock, ON, Canada, were recruited for this study. Study recruitment involved: (1) advertisement in local newspapers and partnership publications, (2) posters at local businesses, (3) health fairs, and (4) word of mouth. Individuals within the aforementioned age range were eligible for participation based on a self-reported cognitive complaint (i.e., answering yes to the question: "*Do you feel that your memory or thinking skills have gotten worse recently?*"), and preserved instrumental activities of daily living (i.e., Lawton-Brody Instrumental Activities of Daily Living, IADL scale > 6) [41]. Participants were excluded from participation based on: (1) probable dementia (i.e., self-reported diagnosis or Mini Mental State Exam (MMSE) score < 24) [42], (2) major depression (i.e., score ≥16 on the Center for Epidemiological Studies Depression scale) or the clinical judgment of the study physician (RJP), (3) diagnosis of other neurological or psychiatric disorders, (4) recent history of severe cardiovascular conditions, (5) significant orthopedic conditions (i.e., limiting the ability to exercise), (6) blood-pressure considered unsafe for exercise (i.e., >180/100 and/or <100/60 mm/Hg) [43], (7) severe sensory impairment, (8) unable to comprehend the study letter of information, (9) unable to commit to 80% of exercise sessions over the 24-week intervention period, and (10) any other factors that could limit the ability to fully participate in the intervention. In addition, we computed MoCA scores for all participants to address our secondary research goal (i.e., to contrast persons with a selective $_S$CC from those meeting the definition for MCI). Further, by including MoCA, MMSE, CES-D, and IADL scales we used a screening package identified by the Vascular Cognitive Disorders Harmonization Standards paper as providing a valid means for identifying individuals with a possible cognitive deficit but not meeting the definition for AD or other dementias [44].

A total of 179 individuals showed initial interest and 127 met the inclusion criteria and were enrolled in the full study. The study was conducted in four waves, with participants beginning the 24-week intervention in groups. The first 41 participants were excluded from the oculomotor analyses presented below due to technical difficulties with our eye-tracker. Of the remaining 86 participants, nine were excluded because the eye-tracker could not be calibrated to their eye movements, two did not have usable pre-intervention baseline data, eight dropped out of the study prior to their post-intervention assessment, and four produced an extensive number of saccade anticipation errors (see details below). Thus, 63 participants were used in our final analyses (see Table 1 for participant demographics). The Health Sciences Research Ethics Board, University of Western Ontario, approved this study and this work was conducted according to the ethical standards laid down in the Declaration of Helsinki. All participants provided written informed consent prior to taking part in any study procedures.

Exercise intervention

Participants were randomly allocated (1:1) to a: (1) multiple-modality exercise intervention group (i.e., M2 group) or (2) multiple-modality, mind-motor exercise intervention group (i.e., M4 group). As will be detailed below, the M2 group ($n = 32$) completed a 24-week multiple-modality training program, whereas over the same time range the M4 group ($n = 31$) completed a multiple-modality, mind-motor training program. Both M2 and M4 interventions involved group-based exercise classes in which individual participants completed three sessions per week over the course of the intervention period.

The multiple-modality exercise intervention: the M2 group

The M2 group participated in a 60-min group-based multiple-modality (i.e., M2) exercise classes, 3 days per week over 24 weeks. As shown in Table 2, each exercise session involved: (1) a 5-min warm up, (2) 20 min of moderate-to-vigorous intensity aerobic training (i.e., 65–85% maximum heart rate), (3) 5-min aerobic cool-down, (4) 10 min of resistance training, (5) 15 min of balance training, range of motion, and breathing exercises, and (6) 5 min of stretching. The balance, range of motion, and breathing exercises did not include the use of additional

Table 1
Baseline characteristics of 63 participants in the multi-modality (M2) and multiple-modality, mind-motor (M4) exercise groups

	M2 group ($n = 32$)	M4 group ($n = 31$)
Age, mean (SD), years	68.3 (8.1)	65.7 (6.6)
Female, No. (%)	24 (75)	23 (74)
White Race, No. (%)	32 (100)	30 (97)
Education, mean (SD), years	14.2 (2.8)	14.0 (2.7)
Memory worse[a], No. (%)	23 (72)*	29 (94)*
MMSE[b], mean (SD), /30	29.0 (1.1)	29.3 (0.9)
MoCA[c], mean (SD), /30	25.1 (2.2)	26.3 (2.6)
Fitness[d] (pVO_{2max}), score, mean (SD)		
Pre-intervention	27.4 (7.4)	29.2 (7.3)
Post-intervention	29.6 (7.0)	32.3 (8.2)
Body Mass Index, mean (SD)		
Pre-intervention	27.5 (4.7)	28.1 (3.8)
Post-intervention	27.5 (4.4)	28.0 (3.9)
Systolic Blood Pressure, mean (SD)[e]	137.8 (18.4)	131.3 (20.1)
Diastolic Blood Pressure, mean (SD)[e]	80.2 (10.9)	77.6 (12.6)
Medical History, No (%)		
Depression	2 (6)	5 (16)
Hypertension	12 (37)	17 (55)
Hypercholesterolemia	10 (31)	11 (35)
Type 2 diabetes	1 (3)	1 (3)
Myocardial infarction	0 (0)	3 (10)
Angina	1 (3)	0 (0)

[a]Participants were asked to rate their memory on a scale of 5 (from much better to much worse). [b]MMSE, Mini-Mental State Exam, scored out of 30. [c]MoCA, Montreal Cognitive Assessment, scored out of 30. [d]Predicated maximal oxygen uptake, via STEP™ tool [46]. [e]Average systolic and diastolic of last 2 of 3 seated clinic blood pressure readings. *Reports of worsening memory were statistically different at baseline, $p < 0.01$.

loading (i.e., hand weights or resistance bands) and were selected as suitable control exercises within the M2 group because they do not impart cognitive benefits [9]. Table 2 provides a complete description (and sequence) of the exercises performed during the 10-min resistance and 20-min aerobic components of each exercise session. As well, the design of our exercise program was based on: (1) extensive pilot work involving group-based exercise classes and feedback from participants indicating that they wished for exercise sessions to be completed within a 60-min timeframe, (2) physical activity guidelines published by the Public Health Agency of Canada and endorsed by the Canadian Society for Exercise Physiology stating that 150–180 min of moderate-to-vigorous intensity activity completed across three days per week promotes healthy aging [45].

The multiple-modality and mind-motor exercise intervention: the M4 group

The M4 group completed the same multiple-modality exercise training as the M2 group with one exception. In particular, the M4 group completed 15 min of mind-motor exercise (i.e., progressive square-stepping exercise: SSE) in place of the 15 min balance, range of motion, and breathing exercises. As such, the M2 and M4 groups completed the same duration of activity (60-min classes, 3 times per week) and were afforded the same amount of social interaction and attention from study personnel (see Table 2 for details).

As mentioned above, the SSE was used as the mind-motor training component of this study. The SSE is a simple, low-cost, indoor, and group-based exercise program for older adults [27]. The task required that participants memorize and execute progressively more complex foot placement patterns that involved forward, backwards, lateral, and diagonal steps using a gridded floor mat (250 cm by 100 cm, portioned into 10 rows of 4 equal-sized squares; for schematic see Fig. 1). The SSE involves over 200 stepping patterns (i.e., ranging from simple to complex) and the M4 group progressed across patterns over the duration of the training intervention with each exercise session beginning with the SSE pattern attained during the previous session. The goal for the M4 group was to progress as far as possible over the 24-week intervention period. At the beginning of each SSE session, the participants watched an instructor demonstrate a pattern and then attempted to repeat the pattern (i.e., via memory) on the SSE

Table 2
Description of the exercise interventions associated with the multi-modality (M2) and multiple-modality, mind-motor (M4) exercise groups

M2	M4
Warm-up (5 minutes)	Warm-up (5 minutes)
○ Light aerobics	○ Light aerobics
○ Dynamic range of motion of the major joints	○ Dynamic range of motion of the major joints
Aerobic Exercise (20 Minutes)	Aerobic Exercise (20 Minutes)
○ Large rhythmical endurance activities (e.g., walking, marching, sequenced aerobics)	○ Large rhythmical endurance activities (e.g., walking, marching, sequenced aerobics)
○ Keep HR continuously in target zone (i.e., not interval training)	○ Keep HR continuously in target zone (i.e., not interval training)
○ Moderate to vigorous intensity	○ Moderate to vigorous intensity
○ RPE: 5–8 on scale of 0–10	○ RPE: 5–8 on scale of 0–10
○ Participants to check HR ½ way through and at end of aerobic exercise.	○ Participants to check HR ½ way through and at end of aerobic exercise.
Aerobic Cool Down (5 minutes)	Aerobic Cool Down (5 minutes)
○ Safely bringing heart rates down	○ Safely bringing heart rates down
Resistance Training (10 minutes)	Resistance Training (10 minutes)
○ Therabands, wall or chair exercises, core strengthening	○ Therabands, wall or chair exercises, core strengthening
○ Day 1 – Upper body focus	○ Day 1 – Upper body focus
○ Day 2– Lower body focus	○ Day 2 – Lower body focus
○ Day 3 – Core focus	○ Day 3– Core focus
Balance, Range of Motion & Breathing (15 minutes)	Mind-Motor Training (15 minutes)
○ Keep HR BELOW target zone	○ Keep HR BELOW target zone
○ Dynamic, static and functional balance	○ Progressive, group-based, Square Stepping Exercise (SSE)
○ Breathing and relaxation exercises	
○ Finger exercises	
○ Range of motion (e.g., arm circles)	
Stretching (5 minutes)	Stretching (5 minutes)
TOTAL: 60 minutes	TOTAL: 60 minutes
60 minutes Multiple-Modality Exercise	45 minutes Multiple-Modality Exercise 15 minutes Mind-Motor Exercise

HR, heart rate; RPE, rating perceived exertion. Note: a version of Table 1 was previously published [45]. The table is reprinted here with the authors' permission and BioMed Central is duly identified as the original publisher.

mat. Participants worked in small groups ($N \leq 6$) on an individual SSE mat. To promote a positive social environment, participants were encouraged to assist each other during the SSE component of the group exercise class. To progress to the next SSE pattern, at least 80% of the group (i.e., class) was required to have successfully completed the pattern at least four times in a row in a reasonable period of time (i.e., 2-3 sessions). If the group did not successfully complete a specific pattern after three classes then the group would progress to the next pattern within the same difficulty level.

Instructor training, class size, and intensity

Two Seniors Fitness Instructors certified through the Canadian Centre for Activity and Aging led the exercise classes. The M2 and M4 exercise classes were held during morning time slots, with class sizes varying from eight to 23. At the start of the study, participants were provided an individualized target heart rate (65–85% of estimated maximum heart rate) determined via the Step Test and Exercise Prescription (STEP™) tool [46]. During the aerobic exercise component of each training session, participants were encourage to exercise at their prescribed training heart rate and/or at a rating of 5–8 on the 10-point modified Borg Rating of Perceived Exertion (RPE). During the balance/range-of-motion/breathing (i.e., M2 group) or the SSE (i.e., M4 group) components, participants were encouraged to keep their heart rates below their training heart rate to ensure that the aerobic exercise component was comparable between groups. At the end of each aerobic and each balance/range-of-motion or SSE component participants were instructed to record their heart rate and RPE. To ensure progression in aerobic training, individualized training heart rates were recalculated at the midpoint of the intervention (i.e., 12 weeks) via the STEP™ tool.

Oculomotor assessment

Antisaccades require a saccade mirror-symmetrical to a target stimulus. The task therefore requires the top-down (i.e., executive) and two-

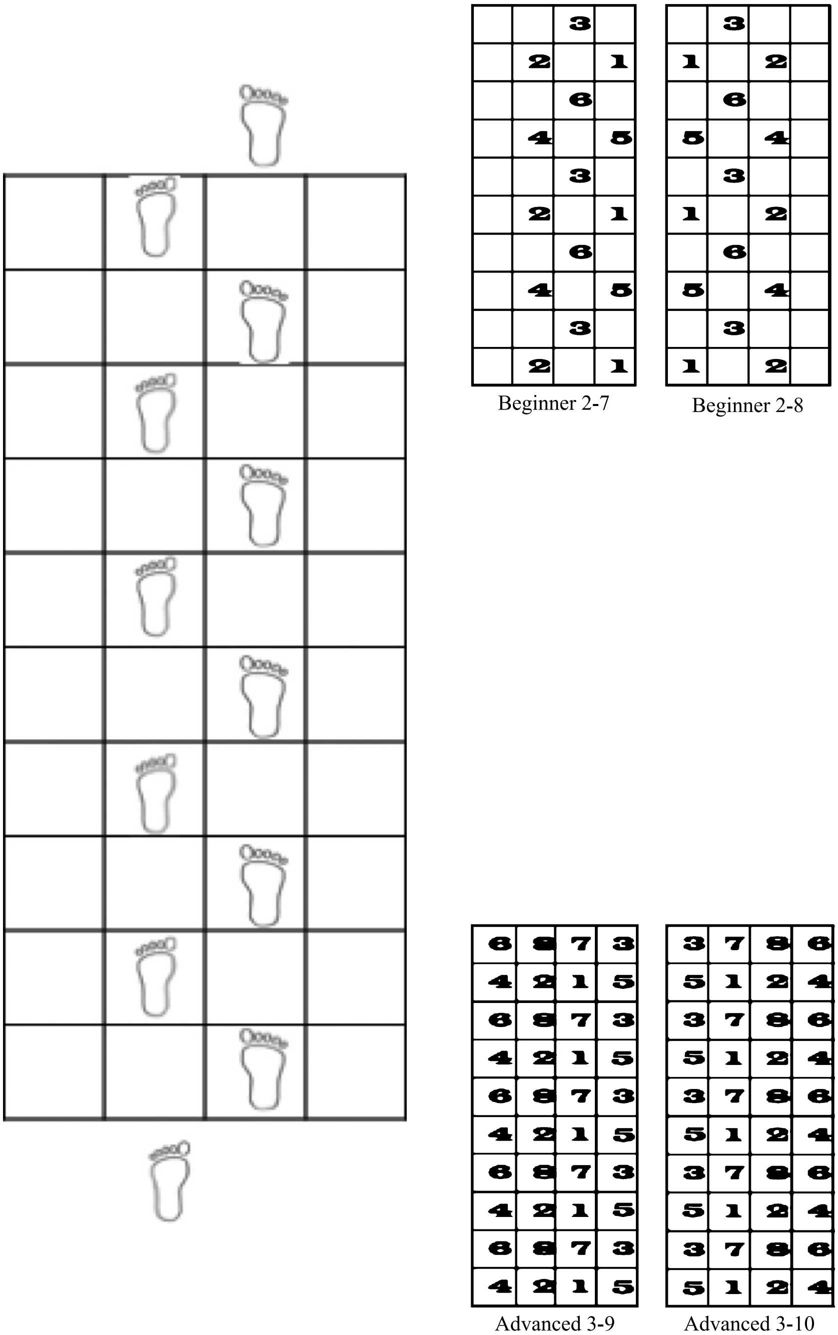

Fig. 1. Schematic of the square-stepping exercise (SSE) task. Participants were instructed to walk across a gridded floor mat while completing a pattern that involved, forward, backwards, lateral, and diagonal steps that were identical to a foot placement pattern demonstrated by an exercise leader. The patterns used for the SSE became gradually more complex within and between training sessions. Note: a version of Fig. 1 was previously published [45]. The figure is reprinted here with the authors' permission and BioMed Central is duly identified as the original publisher.

component processes of suppressing of a pre-potent response (i.e., suppression of a prosaccade) and inverting a target's spatial coordinates (180° spatial transformation: i.e., visual vector inversion) [33]. In contrast, a prosaccade requires a saccade to a target's veridical location, and the direct stimulus-response mapping associated with this task allows for motor output via direct retinotopic maps in the superior colliculus that operate largely independent of cortical mechanisms (i.e., the visual 'grasp' reflex) [47]. Indeed, by contrasting pro- and antisaccades our investigation provided a framework to determine whether our exercise interventions rendered a general improvement in oculomotor control per se, or imparted a selective benefit to an oculomotor response requiring high-level executive control (i.e., antisaccades only).

Pro- and antisaccades were completed pre- and post-intervention. The pre-intervention was completed on average 19.8 ± 13.0 days prior to the beginning of the exercise program and the post-intervention was completed on average 10.0 ± 5.5 days following the end of the exercise program. For each session, participants sat in a height-adjustable chair located in front of a tabletop (height 775 mm) with their head placed in a head-chin rest. A 30-inch LCD monitor (60 Hz, 8 ms response rate, 1,280 by 960 pixels; Dell 2007WFP, Round Rock, TX, USA) located at participants' midline and 600 mm from the front edge of the table-top was used to present visual stimuli. Visual stimuli were presented against a high contrast black background and included a white fixation cross (1°: 135 cd/cm^2) placed at the center of the monitor and yellow target crosses (1°: 135 cd/cm^2) located 11° and 14° left and right of the fixation and in the same horizontal axis. The gaze location of participants' left eye was measured via a video-based eye-tracking system (EyeLink 1000: SR Research, Mississauga, ON, Canada) sampling at 500 Hz. In addition, two monitors visible only to the experimenter provided: (1) real-time point of gaze information, (2) trial-to-trial information on saccade kinematics (i.e., displacement and velocity), and (3) information about the accuracy of the eye-tracking system (i.e., to permit a recalibration when necessary). All visual and computer events were controlled via MATLAB (ver 7.6: The MathWorks, Natick, MA, USA) and the Psychophysics Toolbox extensions (ver 3.0) [48]. The lights in the experimental suite were extinguished during data collection.

At pre- and post-intervention oculomotor assessments pro- and antisaccades were completed in separate and randomly ordered blocks. The beginning of each block provided a written instruction screen indicating the nature (i.e., pro- or antisaccade) of the upcoming series of trials. Participants were also provided five practice trials at the beginning of each block. All trials started with the appearance of the fixation cross which instructed the participant to direct their gaze to its location. Once a stable fixation was achieved (i.e.,±1.5° for 450 ms) a randomized foreperiod was introduced (i.e., 1,000–2,000 ms) after which time the fixation was extinguished (i.e., gap paradigm). After a 200 ms interval one of the target stimuli was briefly (i.e., 50 ms) presented and its onset served as the imperative to pro- (i.e., look to veridical target location) or antisaccade (i.e., look mirror-symmetrical to the target) as "quickly and accurately" as possible. The ordering of target eccentricity (i.e., 11° and 14°) and the visual field the target appeared (i.e., left or right of fixation) was randomized and presented 20 times within a block of trials (i.e., 80 pro- and 80 antisaccades within each pre- and post-intervention session). Last, and as noted above, we employed a gap paradigm because it is cognitively more challenging then its overlap counterpart (i.e., when fixation and target are visible at response onset), and as such served as a viable framework to examine exercised-induced changes in executive oculomotor control [33].

Data reduction and dependent variables

Pre- and post-intervention body mass index (BMI) and predicted maximal aerobic capacity (i.e., $_{\rm P}VO_2$ max determined via the STEP^{TM} tool) [46] were computed. Gaze position data were filtered offline using a dual-pass Butterworth filter employing a low-pass cut-off frequency of 15 Hz. Filtered displacement data were used to compute instantaneous velocities via a five-point central finite difference algorithm. Acceleration data were similarly obtained from the velocity data. Saccade onset was defined as the first frame wherein velocity and acceleration values respectively exceeded 30°/s and 8,000°/s^2. In turn, saccade offset was defined as the first frame wherein velocity fell below a criterion of 30°/s for 20 frames (i.e., 40 ms). Dependent variables for the oculomotor assessment included RT (time from target onset to saccade onset), the coefficient of variation (CV) of RT (standard deviation/mean × 100%), the percentage of directional errors (i.e., the completion of a prosaccade instead of an instructed antisaccade and vice versa) and saccade amplitude in the primary (i.e., horizontal) movement direction. Individual trial data were excluded from further analyses if RTs were less than 100 ms (i.e., an anticipatory or express saccade) [49] or were greater than two standard deviations above a participant-specific mean. In addition, data were excluded if saccade amplitude was less than 2.5° or greater than 24° [50]. Less than

8% of all experimental trials were removed due to the exclusion criteria and less than 4% of trials were removed due to signal loss (i.e., blinking). Further, and in line previous work, the RT and amplitude data used here involved only directionally correct trials because trials involving an antisaccade directional error are supported via planning and control mechanisms that are distinct from their directionally correct counterparts [31, 50–52].

RESULTS

Pre-intervention MMSE and MoCA scores

At baseline participants were an average age of 67.0 ± 1.5 years of age, 74% female, 98% white race, 14.2 ± 2.8 years of education, and had a blood pressure of 134.7 ± 19.4 / 78.9 ± 11.8 mmHg. The MMSE has been traditionally used to identify older adults with significantly progressed cognitive impairment and dementias [42], whereas the MoCA, which contains more complex tasks than the MMSE, has been used to identify individuals exhibiting the early stages of cognitive decline [40, 53]. We used the MMSE and MoCA to provide a general pre-intervention evaluation of the cognitive status of M2 and M4 groups. Results indicated that MMSE (M2:29.0, SD = 1.1; M4:29.3, SD = 0.9) and MoCA (M2:25.1, SD = 2.2; M4:26.3, SD = 2.6) values did not reliably differ between groups (all $t(61) = 1.08$ and 1.91 for MMSE and MoCA, respectively, ps = 0.28 and 0.07, d_z = 0.28 and 0.49).

Pre- and post-intervention BMI and $_{P}VO_2$ max

BMI and $_{P}VO_2$ max measures were examined via 2 (group: M2, M4) by 2 (time: pre-, post-intervention) mixed-groups ANOVA. Results for BMI showed that values for M2 (27.5 kg/m^2, SD = 4.7) and M4 (28.0 kg/m^2, SD = 3.8) groups did not reliably vary and that values did not reliably vary with time or elicit a group by time interaction, all $F(1,61)<1$. For $_{P}VO_2$, M2 (28.5 O_2/kg/min, SD = 7.6) and M4 (30.7 mL O_2/kg/min, SD = 3.8) groups did not reliably differ, $F(1,61)<1$; however, a main effect for time indicated that values for both groups increased from pre- to post-intervention, $F(1,61) = 36.90$, $p < 0.001$, $\eta_p{}^2 = 0.38$ (Table 1). Thus, pre-intervention fitness scores were comparable for M2 and M4 groups and both groups showed a post-intervention improvement in $_{P}VO_2$ max.

Square-stepping exercise (SSE) progression (M4 group only)

The SSE program is separated by difficulty: Beginner 1, Beginner 2, Intermediate 1, Intermediate 2, Intermediate 3, Advanced 1, Advanced 2, Advanced 3; with a range of 8–36 patterns in each difficulty level. All waves of M4 groups progressed to the Advanced 1 patterns, with one group progressing to the Advanced 2 patterns by the end of the 72 sessions. The level of progression varied between groups because of: (1) the waves progressing as a group rather then individually, (2) class size (i.e., smaller class sizes progressed faster), and 3) the cognitive level of some participants varied in the waves (e.g., a participant with a more advanced cognitive decline may have decreased a group's progression rate). Since all of the waves reached the Advanced 1 pattern, we are confident that each progressed at a similar rate and attained a comparable level of cognitive-motor training.

Attendance and exercise intensity compliance following aerobic and balance/range of motion/breathing (i.e., M2 group) and SSE (i.e., M4 group) training

All participants were requested to attend 72 exercise sessions across the 24-week intervention period. Table 3 shows the average number of classes attended by M2 (56/72 or 77%) and M4 (53/72 or 73%) participants. In addition, Table 3 presents the percentage of M2 and M4 participants that achieved their prescribed heart rate as assessed immediately following aerobic training. Table 3 shows the percentage of participants for which we did not obtain heart rate values (i.e., Absent) and participants' whose post-aerobic performance was below, at, or above, their prescribed heart rate. For M2 and M4 groups, the percentage of participants achieving their prescribed heart rate (M2 = 53%; M4 = 51%) was greater than any of the other categories and this compliance did not differ between groups ($\chi^2 = 1.69$, $p = 0.64$). In addition, we assessed heart rate immediately following the balance/range of motion/breathing (i.e., the M2 group) and SSE (i.e., the M4 group) components of each exercise session and found that 81% of M2 and 90% of M4 participants were below their prescribed heart rate during this time. Further, the frequency of participants who were below their prescribed heart rate did not vary between M2 and M4 groups ($\chi^2 = 1.98$, $p = 0.37$) (Note: no participant from M2 or M4 groups

Table 3
Compliance to prescribed interventions for 63 participants by randomization group

Compliance Variable	M2 group ($n=32$)	M4 group ($n=31$)
Attendance, mean(SD) /72 sessions	56.1 (11.2)	53.7 (13.7)
Heart rate[a] after aerobic exercise, No. (%)		
Absent	3 (9)	1 (3)
Below target heart rate	9 (28)	12 (3)
At target heart rate	17 (53)	16 (51)
Above target heart rate	3 (9)	2 (6)
Heart rate[a] after Balance and range of motion or mind-motor exercise, No. (%)		
Absent	4 (12)	1 (3)
Below target heart rate	26 (81)	28 (90)
At target heart rate	2 (6)	2 (6)
Above target heart rate	0 (0)	0 (0)
Rating of Perceived Exertion[b] after aerobic exercise, No. (%)		
Absent	2 (6)	1 (3)
Below target heart rate	2 (6)	2 (6)
At target heart rate	26 (81)	28 (90)
Above target heart rate	2 (6)	0 (0)
Rating of Perceived Exertion[b] after Balance and range of motion or mind-motor exercise, No. (%)		
Absent	4 (12)	1 (3)
Below target heart rate	23 (71)	28 (90)
At target heart rate	5 (15)	2 (6)
Above target heart rate	0 (0)	0 (0)

[a]Heart rates were taken by participants via radial or carotid pulse over ten seconds. For the aerobic exercise portion of each class, participants were given a prescribed heart rate; i.e., between 65–85% of heart rate maximum as derived from the STEP™ tool [46]. During the mind-motor or balance/range-of-motion/breathing components of M4 and M2 groups, respectively, participants were requested to exercise below their prescribed heart rate. [b]Rating of perceived exertion was from 1–10 on a modified Borg Scale, where 1 was very light activity and 10 was maximal effort. Participants were asked to work at a rating of 5–8 during aerobic exercise and 4 or less during the mind-motor or balance/range-of-motion/breathing components of M4 and M2 groups, respectively.

attained a heart rate above their prescribed level during balance/range of motion/breathing (i.e., M2 group) and SSE (i.e., M4 group) exercise components, thus our chi-squared test did not include the category "Above target heart rate"). As such, the SSE component did not result in M4 participants having a longer within-session prescribed aerobic heart rate than the M2 group.

Oculomotor planning and control pre- and post-intervention: reaction time, directional errors, and saccade amplitude

Figure 2 provides pro- and antisaccade RT percent frequency histograms for M2 and M4 groups separately for pre- and post-intervention assessments. We present the histograms to document the number of trials associated with our experimental conditions and to demonstrate the basic finding that antisaccade RTs were longer than prosaccades regardless of group and intervention time point. In terms of quantitative analyses, mean RT were examined via 2 (group: M2, M4) by 2 (time: pre-, post-intervention) by 2 (task: pro-, antisaccade) mixed-groups ANOVA. Results produced main effects for time, $F(1,61)=6.85$, $p<0.02$, $\eta_p{}^2=0.10$, task, $F(1,61)=534.47$, $p<0.001$, $\eta_p{}^2=.90$, and their interaction, $F(1,61)=24.52$, $p<0.001$, $\eta_p{}^2=0.29$. Figure 3 shows that prosaccade RTs did not vary from pre- to post-intervention ($t(62)<1$), whereas antisaccade RTs decreased from pre- to post-intervention ($t(62)=3.90$, $p<0.001$). As well, and in light of our primary research objective, we note that neither group nor any higher-order interactions involving group elicited a significant effect/interaction (all $F<1$).

Results for the CV of RT produced an effect for task, $F(1,61)=63.45$, $p<0.001$, $\eta_p{}^2=0.51$: the CV for prosaccades (21, SD = 8) was greater than antisaccades (15, SD = 6); however, neither group nor any higher-order interaction involving group elicited a significant effect (all $F<1$). We believe it important to highlight these null effects because they demonstrate that the post-intervention decrease in antisaccade RTs was not associated with a reliable change in its CV.

Figure 4 presents participant-specific pre- and post-intervention directional errors for M2 and M4

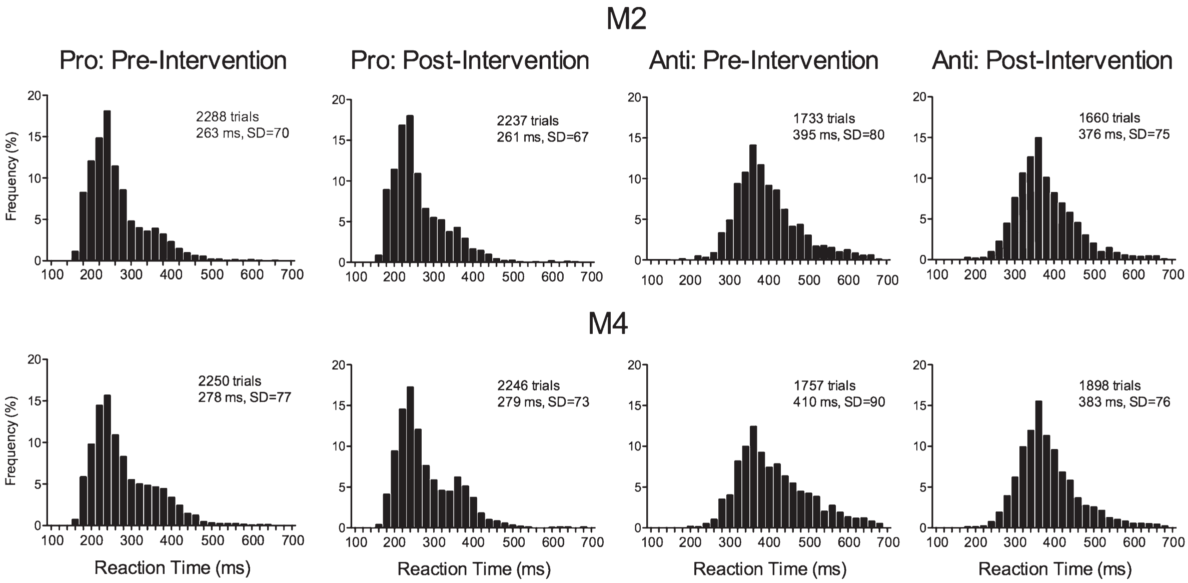

Fig. 2. Pro- and antisaccade reaction time (ms) frequency histograms for the multiple-modality (i.e., M2: see top panel) and multiple-modality, mind-motor (i.e., M4: see bottom panel) exercise groups at pre- and post-intervention assessments. Bin widths are 20 ms and the number of trials and descriptive statistics for each panel are included. The panels provide a graphic indication that antisaccade RTs were longer than prosaccades and is a result consistent with extensive evidence that antisaccades require the time-consuming suppression of a prepotent response (i.e., inhibit a prosaccade) and the inversion of a target's coordinates in mirror-symmetrical space.

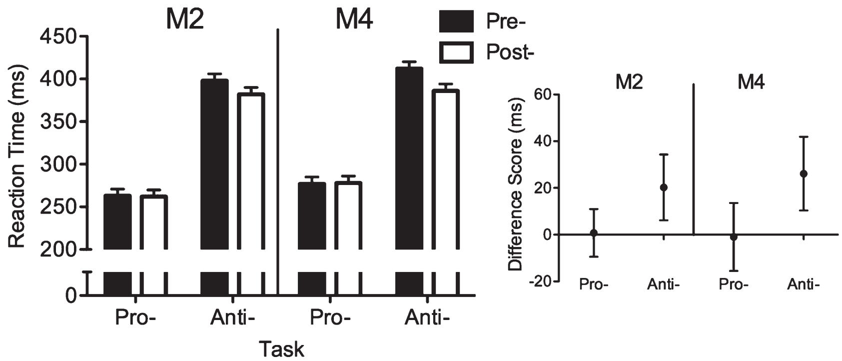

Fig. 3. The main panel presents mean pro- and antisaccade reaction times (ms) for the multiple-modality (i.e., M2) and multiple-modality, mind-motor (i.e., M4) exercise groups at pre- and post-intervention assessments. Error bars are 95% within-participant confidence intervals computed via the mean-squared error term for the time by task interaction separately for each group [70]. The smaller offset panel shows pre- and post-intervention difference scores (pre-intervention minus post-intervention) for M2 and M4 group pro- and antisaccades. Error bars are 95% between-participant confidence intervals and the absence of overlap between the error bars and zero indicates a reliable effect that can be interpreted inclusive to a test of the null hypothesis [71].

groups. The figure shows that for prosaccades a number of M2 ($n = 17$) and M4 ($n = 24$) participants produced error-free performance. The floor-level performance precluded examination via ANOVA model. As such, pro- and antisaccades were contrasted qualitatively and Fig. 4 shows that the former were associated with fewer directional errors across pre- and post-intervention sessions. In terms of antisaccades, directional errors were examined quantitatively via 2 (group: M2, M4) by 2 (time: pre-, post-intervention) mixed-groups ANOVA and results did not indicate reliable main effects or an interaction (all $F(1,61) < 1.13$, $ps > 0.29$, all $\eta_p^2 < 0.03$).

Saccade amplitude was examined via 2 (group: M2, M4) by 2 (time: pre-, post-intervention) by 2 (task: pro-, antisaccade) by 2 (target eccentricity: 11° [i.e., proximal] and 14° [i.e., distal] mixed-groups ANOVA. Results revealed a main effect for target eccentricity, $F(1,61) = 308.99$, $p < 0.001$, $\eta_p^2 = 0.83$, and a task by target eccentricity

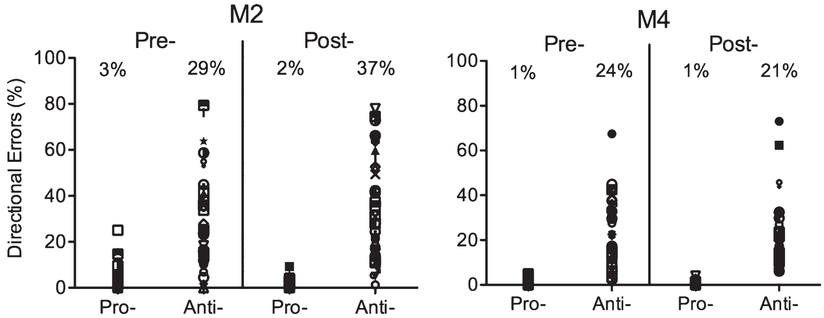

Fig. 4. Participant-specific percentage of pro- and antisaccade directional errors across multiple-modality (i.e., M2: see left panel) and multiple-modality, mind-motor (i.e., M4: see right panel) exercise groups at pre- and post-intervention assessments. Participant-specific data are presented to demonstrate that the majority of participants' prosaccade trials were error-free, whereas the percentage for antisaccades varied considerably. The value stated at the top of each column is the mean percentage of directional errors for a given experimental condition. As expected, the figure shows that antisaccade directional errors were significantly more than prosaccades and further demonstrates that pre- and post-intervention directional errors did not reliably vary between M2 and M4 groups.

interaction, $F(1,61) = 160.73$, $p < 0.001$, $\eta_p^2 = 0.72$. Pro- (9.8°, SD = 0.8) and antisaccade (10.4°, SD = 2.0) amplitudes to the proximal target were shorter than their distal target counterparts (prosaccade: 12.0°, SD = 0.9; antisaccade: 10.8°, SD = 1.7) (all $t(62) = 34.22$ and 3.03, for pro- and antisaccades, respectively, $ps < 0.01$). In other words, amplitude increased with increasing target eccentricity. To further decompose the interaction, we computed participant-specific target eccentricity difference scores (i.e., distal target minus proximal target) separately for pro- and antisaccades. Results showed that the difference score was larger for pro- (2.1°, SD = 0.4) than antisaccades (0.3°, SD = 1.0), $t(62) = 12.58$, $p < 0.001$ – a result evincing that prosaccade amplitudes scaled to veridical target eccentricity more than antisaccades. Notably, however, no further effects/interactions were reliable (all $Fs < 1$). Thus, the accuracy of saccades was consistent across M2 and M4 groups and did not vary pre- to post-intervention.

Oculomotor control in persons with a selective $_S$CC and those meeting the definition for MCI

Recall that the secondary goal of this investigation was to determine whether our exercise interventions differentially influenced executive control in persons with a selective $_S$CC and those meeting the definition for MCI. To address that goal, we identified individual M2 and M4 participants with an objective cognitive impairment; in other words, we classified individuals as meeting the definition for MCI from those with a selective $_S$CC. The identification of an objective cognitive impairment was based on a MoCA score of less than 26. For the M2 and M4 groups, 17 (53%) and 20 (65%) participants were classified as meeting the MCI definition, respectively. Notably, the frequency of individuals identified with a MCI or $_S$CC did not vary between M2 and M4 groups ($\chi^2 = 1.98$, $p = 0.16$). Further, we employed 2 (group: M2, M4) by 2 (MoCA classification: $_S$CC, MCI) mixed-groups ANOVA to contrast antisaccade RT difference scores (i.e., pre-intervention minus post-intervention). The basis for this analysis was to determine whether the magnitude of the post-intervention antisaccade benefit differed as a function of M2 and M4 participants classified as meeting the $_S$CC and MCI definitions. Figure 5 presents the difference scores and results did not yield any reliable effects or interactions (all $F < 1$). Thus, the magnitude of the post-intervention antisaccade benefit reported in our general analysis (see *Oculomotor planning and control pre- and post-intervention: Reaction time, directional errors, and saccade amplitude*) did not vary across M2 and M4 participants with MCI or $_S$CC. Moreover, the above analyses demonstrate that the absence of an additive post-intervention antisaccade benefit for the M4 group reported in our general analysis cannot be attributed to group-based differences in the frequency of MCI.

DISCUSSION

The primary objective of this study was to determine whether persons with a self-reported cognitive complaint ($_S$CC) who completed a 24-week multiple-modality, mind-motor exercise training program

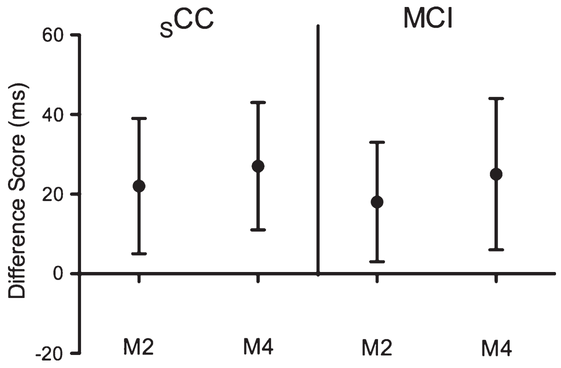

Fig. 5. Mean antisaccade difference scores (pre-intervention minus post-intervention) for individuals meeting the definitions for mild cognitive impairment (MCI) and individuals with a selective self-reported cognitive complaint ($_S$CC) in each of the multiple-modality (M2) and multiple-modality, mind-motor (M4) exercise intervention groups. Error bars are 95% between-participant confidence intervals and the absence of overlap between the error bars and zero indicates a reliable effect that can be interpreted inclusive to a test of the null hypothesis [71].

(M4 group: i.e., aerobic and resistance training with a cognitive-motor component) show an additive post-intervention benefit to executive-related oculomotor control than counterparts involved in multiple-modality training only (M2 group: i.e., aerobic and resistance training). Before discussing our primary objective, we first provide a general description of the difference between pro- and antisaccades. In particular, prosaccades had shorter RTs, produced fewer directional errors, and were more accurate than antisaccades. Results for prosaccades evince that saccades with spatial overlap between stimulus and response are mediated via direct retinotopic projections within the superior colliculus [54], and operate with minimal top-down cortical control [47]. In turn, the longer RTs, more errorful and less accurate performance of antisaccades has been tied to the time-consuming demands of suppressing a prepotent response and evoking a saccade to a mirror-symmetrical location [33, 55, 56]. Further, ample evidence has attributed the longer RTs of directionally correct antisaccades to the activation of executive networks within the prefrontal cortex [32]. Thus, the behavioral properties associated with the antisaccades studied here demonstrate a cognitively challenging task providing a framework to evaluate whether multiple-modality or multiple-modality, mind-motor exercise training programs differentially influences executive-related training benefits in persons with a $_S$CC.

Pre- and post-intervention pro- and antisaccade performance

At the pre-intervention oculomotor assessment, M2 and M4 groups exhibited comparable pro- and antisaccade performance. The comparable antisaccade performance in combination with null group differences in general clinical assessment measures (i.e., MMSE and MoCA) demonstrate similar pre-intervention executive and cognitive status for M2 and M4 groups. As well, our pre-intervention assessment of body mass index and predicted VO_2 max indicated comparable values for M2 and M4 groups—a result indicating similar group fitness levels.

In terms of pre- and post-intervention differences, prosaccade planning (i.e., RT and directional errors) and control (i.e., amplitude) did not reliably vary for M2 or M4 groups. This is an expected finding and as indicated above is attributed to prosaccade evocation via retinotopic projections within the superior colliculus [54]. In other words, the subcortical mediation of prosaccade renders their control independent of cortically based modifications associated with an exercise intervention [10]. More notably, results for antisaccades showed that post-intervention RTs were shorter than their pre-intervention counterparts and the magnitude of this reduction did not reliably differ between M2 and M4 groups. M2 and M4 groups showed a 20 ms and 26 ms post-intervention RT reduction, respectively. Moreover, when we decomposed our M2 and M4 participants based on those with a selective $_S$CC and those meeting the definition for MCI (see secondary research objective) we found that the post-intervention antisaccade benefit did not vary across M2 and M4 sub-groups. In other words, exercise training elicited a global benefit to persons reporting a $_S$CC regardless of an accompanying objective cognitive impairment.

In outlining the salience of our antisaccade RT findings we highlight four points. First, antisaccade directional errors and endpoint accuracy did not differ from pre- to post-exercise intervention. These findings demonstrate that participants did not 'improve' their antisaccade planning times at the cost of increased directional errors and endpoint accuracy (i.e., speed-accuracy trade-off). Second, it is unlikely the improved post-intervention RTs are tied to a 'learning event' as work involving healthy young and older adults has reported that antisaccade RTs are stable when tested in deliberate practice sessions completed over a 4-week period [57–59].

Third, the magnitude of the post-intervention antisaccade RT reduction is in line with a previous study by our group showing a similar magnitude training effect (i.e., 30 ms) for individuals with objective cognitive impairments who completed a 24-week aerobically based gait training program [60]. Moreover, in the extant antisaccade literature, the RT reduction observed here can only be described as 'large' in magnitude [33] and is a finding that has been directly tied to the improved efficiency and effectiveness of executive-related oculomotor mechanisms. Fourth, Peltsch et al. [36] proposed that antisaccade metrics are more effective at differentiating executive function between controls and individuals with aMCI than standardized neuropsychological tests (i.e., California Verbal Learning Test, Wisconsin Card Sorting Task). Thus, accumulating evidence indicates that the antisaccade task, and associated temporal resolution (i.e., 500 Hz) of eye-tracking technology, provides a viable tool for identifying executive deficits/improvements in persons experiencing cognitive decline [38]. Accordingly, we believe that a parsimonious interpretation for the post-intervention RT reduction is that exercise training improves executive-related oculomotor control in persons with a $_S$CC. Although we do not have a direct mechanism to account for our finding, it may be that exercise benefits functional connectivity of fronto-parietal structures associated with high-level executive control [61].

M2 and M4 group post-intervention RT performance

Recall that the M4 group performed that same aerobic and resistance exercise-intervention as the M2 group, but also completed a SSE task to provide a cognitively challenging training environment. The motivation for including the M4 group was based on animal and human work (cognitively healthy participants) reporting that aerobic/resistance training programs including a cognitive training component enhance cerebral blood flow and render additive neurocognitive benefits than aerobic/resistance training alone [22, 23, 62, 63]. Notably, however, the present results provide no evidence that the M4 group elicited enhanced executive-related oculomotor benefits. Of course, we recognize that the M4 group's cognitive-training was limited to 15 minutes per exercise session, and as such it could be argued that the duration was not sufficient to elicit a reliable effect. As well, our conclusion is restricted to executive-related cognitive processes; that is, from our results it is unclear whether the M4 group would produce additive benefits to visuo-spatial skills, memory, and general cognition. That being said, Law et al.'s [24] systematic review has argued that the conclusions drawn from the four previous studies reporting a beneficial effect of a multiple-modality, mind-motor training in persons experiencing cognitive decline may not relate to a cognitive training component per se. For example, Coehlo et al. [64] reported that persons with AD demonstrated improved cognitive performance following 16 weeks of multi-modality, mind-motor training (i.e., the active group) compared to an inactive control group. Kounti et al. [65] and Suzuki et al. [66] employed a similar inactive control group when examining multi-modality, mind-motor training benefits in persons with MCI. The use of inactive control groups in all three cases raises concern as to whether improved cognition is related to the inclusion of cognitive training or reflects the general (and documented) benefit of aerobic/resistance training. Moreover, Schwenk et al. [67] examined the effect of multiple-modality, mind-motor training in persons with confirmed AD relative to a control group that performed "unspecific low-intensity exercise". Because moderate-to-vigorous intensity exercise is more beneficial to executive/cognitive processes [10], it is possible that the between-group differences reported by Schwenk et al. reflect an effect of exercise intensity. It is also worthy to note that cognitive training in each of the aforementioned studies (as well as the current study) was distinct from the clinical scales and/or experimental tools used to assess cognitive/executive functioning. For example, we used the SSE as the cognitive training program and employed the antisaccade task to determine exercise-related changes in executive control. Thus, the absence of a transfer from the SSE to the antisaccade task may speak to the fact that cognitive training is task-specific and does not generalize across global cognitive/executive processes (i.e., specificity of practice hypothesis) [68]. That said, and regardless of the specificity of cognitive training, we believe that our work adds importantly to the literature insomuch as it provides the first demonstration that when equated for exercise-intensity a multiple-modality, mind-motor training program does not engender an additive executive-related cognitive benefit than multiple-modality training alone.

Study limitations

The pre-intervention oculomotor assessment was completed from 19.8 ± 13.0 days prior to onset of the exercise intervention. The basis for the extended timeframe was scheduling conflict for the individual participants prior to their beginning in one of the four intervention waves used here. It is therefore possible that the extended time-frame of the pre-intervention assessment may have introduced within-groups variability in antisaccade performance. A second limitation to our conclusions is that the group-based training for M2 and M4 groups afforded an interactive social environment, and as a result we cannot directly disentangle the beneficial neurocognitive effects of social engagement and physical activity [69]. That being said, we structured the present investigation on the basis of overwhelming evidence that group-based exercise programs elicit global benefits to physical and mental health. Further, and although pre- and post-exercise intervention antisaccade RT difference scores did not produce reliable correlations with pre- and post-intervention BMI and $_{\mathrm{P}}VO_2$ max difference scores (all $r<0.02$), $_{\mathrm{P}}VO_2$ max values for M2 and M4 groups increased from pre- to post-intervention assessments. Thus, our results provide evidence that our exercise interventions improved aerobic physical fitness. A third limitation identified in the review process was whether we captured data regarding the frequency of a self-reported cognitive complaint at the end of our exercise intervention. This is an interesting issue and unfortunately we treated self-reported cognitive complaints as an inclusion criterion and not as an outcome measure. Future work should consider this issue and evaluate whether an individual participant's post-exercise intervention improvement in executive control (e.g., the antisaccade task) is linked to a perceived improvement in their subjective cognitive abilities. Indeed, if a participant exhibits a conjoint objective and subjective improvement to executive/cognitive processes then it may impart increased confidence and efficiency in their ability to carryout activities of daily living.

CONCLUSIONS

The present findings demonstrate that executive-related oculomotor processing in persons with a $_{\mathrm{S}}$CC is improved following a 24-week multiple-modality training program. Moreover, we show that improved executive control is unrelated to whether multiple-modality training involves a concurrent cognitive training component.

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REFERENCES

[1] Bennett DA, Wilson RS, Schneider JA, Evans DA, Beckett LA, Aggarwal NT, Barnes LL, Fox JH, Bach J (2002) Natural history of mild cognitive impairment in older persons. *Neurology* **59**, 198-205.

[2] Jessen F, Wolfsgruber S, Wiese B, Bickel H, Mösch E, Kaduszkiewicz H, Pentzek M, Riedel-Heller SG, Luck T, Fuchs A, Weyerer S, Werle J, van den Bussche H, Scherer M, Maier W, Wagner M (2014) German Study on Aging, Cognition and Dementia in Primary Care Patients, AD dementia risk in late MCI, in early MCI, and in subjective memory impairment. *Alzheimers Dement* **10**, 76-83.

[3] Morris JC, Cummings J (2005) Mild cognitive impairment (MCI) represents early-stage Alzheimer's disease. *J Alzheimers Dis* **7**, 235-239.

[4] Schmand B, Jonker C, Hooijer C, Lindeboom J (1996) Subjective memory complaints may announce dementia. *Neurology* **46**, 121-125.

[5] Balota DA, Tse CS, Hutchison KA, Spieler DH, Duchek JM, Morris JC (2010) Predicting conversion to dementia of the Alzheimer's type in a healthy control sample: The power of errors in Stroop color naming. *Psychol Aging* **25**, 208-218.

[6] Traykov L, Raoux N, Latour F, Gallo L, Hanon O, Baudic S, Bayle C, Wenisch E, Remy P, Rigaud AS (2007) Executive functions deficit in mild cognitive impairment. *Cogn Behav Neurol* **20**, 219-224.

[7] Takeda N, Terada S, Sato S, Honda H, Yoshida H, Kishimoto Y, Kamata G, Oshima E, Ishihara T, Kuroda S (2010) Wisconsin card sorting test and brain perfusion imaging in early dementia. *Dement Geriatr Cogn Disord* **29**, 21-27.

[8] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E (199) (1999) Mild cognitive impairment: Clinical characterization and outcome. *Arch Neurol* **56**, 303-308.

[9] Colcombe SJ, Kramer AF, Erickson KI, Scalf P, McAuley E, Cohen NJ, Webb A, Jerome GJ, Marquez DX, Elavsky S (2004) Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci U S A* **101**, 3316-3321.

[10] Colcombe S, Kramer AF (2003) Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychol Sci* **14**, 125-130.

[11] Scherder E, Scherder R, Verburgh L, Königs M, Blom M, Kramer AF, Eggermont L (2014) Executive functions of sedentary elderly may benefit from walking: A systematic review and meta-analysis. *Am J Geriatr Psychiatry* **22**, 782-791.

[12] 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.

[13] Norman DA, Shallice T (1986) *Attention to Action, Springer*, New York.

[14] Bell-McGinty S, Podell K, Franzen M, Baird AD, Williams MJ (2002) Standard measures of executive function in predicting instrumental activities of daily living in older adults. *Int J Geriatr Psychiatry* **17**, 828-834.

[15] Gates N, Fiatarone Singh MA, Sachdev PS, Valenzuela M (2013) The effect of exercise training on cognitive function in older adults with mild cognitive impairment: A meta-analysis of randomized controlled trials. *Am J Geriatr Psychiatry* **21**, 1086-1097.

[16] Öhman H, Savikko N, Strandberg TE, Pitkälä KH (2014) Effect of physical exercise on cognitive performance in older adults with mild cognitive impairment or dementia: A systematic review. *Dement Geriatr Cogn Disord* **38**, 347-365.

[17] Heyn PC, Johnson KE, Kramer AF (2008) Endurance and strength training outcomes on cognitively impaired and cognitively intact older adults: A meta-analysis. *J Nutr Health Aging* **12**, 401-409.

[18] Groot C, Hooghiemstra AM, Raijmakers PG, van Berckel BN, Scheltens P, Scherder EJ, van der Flier WM, Ossenkoppele R (2016) The effect of physical activity on cognitive function in patients with dementia: A meta-analysis of randomized control trials. *Ageing Res Rev* **25**, 13-23.

[19] Liu-Ambrose T, Donaldson MG (2009) Exercise and cognition in older adults: Is there a role for resistance training programmes? *B J Sports Med* **43**, 25-27.

[20] Marzolini S, Oh P, McIlroy W, Brooks D (2012) The feasibility of cardiopulmonary exercise testing for prescribing exercise to people after stroke. *Stroke* **43**, 1075-1081.

[21] Kramer AF, Bherer L, Colcombe SJ, Dong W, Greenough WT (2004) Environmental influences on cognitive and brain plasticity during aging. *J Gerontol A Biol Sci Med Sci* **59**, 940-957.

[22] Fabel K, Wolf S, Ehninger D, Babu H, Galicia P, Kempermann G (2009) Additive effects of physical exercise and environmental enrichment on adult hippocampal neurogenesis in mice. *Front Neurosci* **3**, 50.

[23] Oswald WD, Gunzelmann T, Rupprecht R, Hagen B (2006) Differential effects of single versus combined cognitive and physical training with older adults: The SimA study in a 5-year perspective. *Eur J Ageing* **3**, 179-192.

[24] Law LL, Barnett F, Yau MK, Gray MA (2014) Effects of combined cognitive and exercise interventions on cognition in older adults with and without cognitive impairment: A systematic review. *Ageing Res Rev* **15**, 61-75.

[25] Tremblay MS, Warburton DE, Janssen I, Paterson DH, Latimer AE, Rhodes RE, Kho ME, Hicks A, LeBlanc AG, Zehr L, Murumets K (2011) New Canadian physical activity guidelines. *App Physiol Nutr Metab* **36**, 36-46.

[26] Shigematsu R, Okura T (2006) A novel exercise for improving lower-extremity functional fitness in the elderly. *Aging Clin Exp Res* **18**, 242-248.

[27] Gill DP, Gregory MA, Zou GY, Shigematsu R, Hachinski V, Fitzgerald C, Petrella RJ (2016) The Healthy Mind, Healthy Mobility Trial: A novel exercise program for older adults. *Med Sci Sports Exerc* **48**, 297-306.

[28] Shigematsu R, Okura T, Nakagaichi M, Nakata Y (2014) Effects of exercise program requiring attention, memory and imitation on cognitive function in elderly persons: A non-randomized pilot study. *J Gerontol Geriat Res* **3**, 2.

[29] Heath M, Weiler J, Marriott K, Welsh TN (2011) Vector inversion diminishes the online control of antisaccades. *Exp Brain Res* **209**, 117-127.

[30] Hussein S, Johnston K, Belbeck B, Lomber SG, Everling S (2014) Functional specialization within macaque dorsolateral prefrontal cortex for the maintenance of task rules and cognitive control. *J Cogn Neurosci* **26**, 1918-1927.

[31] Weiler J, Heath M (2014) Oculomotor task switching: Alternating from a nonstandard to a standard response yields the unidirectional prosaccade switch-cost. *J Neurophyiol* **112**, 2176-2184.

[32] Everling S, Johnston K (2013) Control of the superior colliculus by the lateral prefrontal cortex. *Philos Trans R Soc Lond B Biol Sci* **368**, 20130068.

[33] Munoz DP, Everling S (2004) Look away: The anti-saccade task and the voluntary control of eye movement. *Nat Rev Neurosci* **5**, 218-228.

[34] Goldman-Rakic PS (1996) The prefrontal landscape: Implications of functional architecture for understanding human mentation and the central executive. *Philos Trans R Soc Lond B Biol Sci* **351**, 1445-1453.

[35] Braak H, Braak E (1991) Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol* **82**, 239-259.

[36] Peltsch A, Hemraj A, Garcia A, Munoz DP (2014) Saccade deficits in amnestic mild cognitive impairment resemble mild Alzheimer's disease. *Eur J Neurosci* **39**, 2000-2013.

[37] Petersen RC, Roberts RO, Knopman DS, Boeve BF, Geda YE, Ivnik RJ, Smith GE, Jack CR (2009) Mild cognitive impairment: Ten years later. *Arch Neurol* **66**, 1447-1455.

[38] Kaufman LD, Pratt J, Levine B, Black SE (2012) Executive deficits detected in mild Alzheimer's disease using the antisaccade task. *Brain Behav* **2**, 15-21.

[39] Di Carlo A, Lamassa M, Baldereschi M, Inzitari M, Scafato E, Farchi G, Inzitari D (2007) Italian Longitudinal Study on Aging Working Group, CIND and MCI in the Italian elderly: Frequency, vascular risk factors, progression to dementia. *Neurology* **68**, 1909-1916.

[40] Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* **53**, 695-699.

[41] Lawton MP, Brody EM (1969) Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist* **9**, 179-186.

[42] Folstein MF, Folstein SE, McHugh PR (1975) Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr* **12**, 189-198.

[43] Thompson WR, Gordon NF, Pescatello LS (2010) *American College of Sports Medicine*, ACSM's Guidelines for Exercise Testing and Prescription, Lippincott Williams & Wilkins, Philadelphia.

[44] Hachinski V, Iadecola C, Petersen RC, Breteler MM, Nyenhuis DL, Black SE, Powers WJ, DeCarli C, Merino JG,

Kalaria RN, Vinters HV (2006) National Institute of Neurological Disorders and Stroke–Canadian stroke network vascular cognitive impairment harmonization standards. *Stroke* **37**, 2220-2241.
[45] Gregory MA, Gill DP, Shellington EM, Liu-Ambrose T, Shigematsu R, Zou G, Shoemaker K, Owen AM, Hachinski V, Stuckey M, Petrella RJ (2016) Group-based exercise and cognitive-physical training in older adults with self-reported cognitive complaints: The Multiple-Modality, Mind-Motor (M4) study protocol. *BMC Geriatr* **16**, 17.
[46] Petrella RJ, Koval JJ, Cunningham DA, Paterson DH (2001) A self-paced step test to predict aerobic fitness in older adults in the primary care clinic. *J Am Geriatr Soc* **49**, 632-638.
[47] Pierrot-Deseilligny C, Rivaud S, Gaymard B, Müri R, Vermersch AI (1995) Cortical control of saccades. *Ann Neurol* **37**, 557-567.
[48] Brainard DH (1997) The Psychophysics Toolbox. *Spat Vis* **10**, 433-436.
[49] Wenban-Smith MG, Findlay JM (1991) Express saccades: Is there a separate population in humans? *Exp Brain Res* **87**, 218-222.
[50] Weiler J, Heath M (2012) The prior-antisaccade effect influences the planning and online control of prosaccades. *Exp Brain Res* **216**, 545-552.
[51] DeSimone JC, Weiler J, Aber GS, Heath M (2014) The unidirectional prosaccade switch-cost: Correct and error antisaccades differentially influence the planning times for subsequent prosaccades. *Vis Res* **96**, 17-24.
[52] Weiler J, Hassall CD, Krigolson OE, Heath M (2015) The unidirectional prosaccade switch-cost: Electroencephalographic evidence of task-set inertia in oculomotor control. *Behav Brain Res* **278**, 323-329.
[53] Hanzevacki M, Ozegovic G, Simovic I, Bajic Z (2011) Proactive approach in detecting elderly subjects with cognitive decline in general practitioners' practices. *Dement Geriatr Cogn Dis* **1**, 93-102.
[54] Wurtz RH, Albano JE (1980) Visual-motor function of the primate superior colliculus. *Annu Rev Neurosci* **3**, 189-226.
[55] Heath M, Gillen C, Weiler J (2015) The antisaccade task: Vector inversion contributes to a statistical summary representation of target eccentricities. *J Vis* **15**, 4.
[56] Zhang M, Barash S (2000) Neuronal switching of sensorimotor transformations for antisaccades. *Nature* **408**, 971-975.
[57] Klein C, Berg P (2001) Four-week test-retest stability of individual differences in the saccadic CNV, two saccadic task parameters, and selected neuropsychological tests. *Psychophysiology* **38**, 704-711.
[58] Roy-Byrne P, Radant A, Wingerson D, Cowley DS (1995) Human oculomotor function: Reliability and diurnal variation. *Biol Psychiatry* **38**, 92-97.
[59] Heath M, Weiler, J, Shoemaker K (2014) Antisaccade planning times do not differ for older adults with and without cardiovascular disease. Paper presented at the Annual Meeting of the *Canadian Society of Psychomotor Learning and Sport Psychology*.
[60] Heath M, Weiler J, Gregory MA, Gill DP, Petrella RJ (2016) A six-month cognitive-motor and aerobic exercise program improves executive function in persons with an objective cognitive impairment: A pilot investigation using the antisaccade task. *J Alzheimers Dis* **54**, 923-931.
[61] Voss MW, Erickson KI, Prakash RS, Chaddock L, Malkowski E, Alves H, Kim JS, Morris KS, White SM, Wójcicki TR, Hu L (2010) Functional connectivity: A source of variance in the association between cardiorespiratory fitness and cognition? *Neuropsychologia* **48**, 1394-1406.
[62] Fabel K, Kempermann G (2008) Physical activity and the regulation of neurogenesis in the adult and aging brain. *Neuromolecular Med* **10**, 59-66.
[63] Fabre C, Chamari K, Mucci P, Masse-Biron J, Prefaut C (2002) Improvement of cognitive function by mental and/or individualized aerobic training in healthy elderly subjects. *Int J Sports Med* **23**, 415-421.
[64] Coelho FG, Andrade LP, Pedroso RV, Santos-Galduroz RF, Gobbi S, Costa JL, Gobbi LT (2013) Multimodal exercise intervention improves frontal cognitive functions and gait in Alzheimer's disease: A controlled trial. *Geratric Gerontol Int* **13**, 198-203.
[65] Kounti F, Bakoglidou E, Agogiatou C, Lombardo NB, Serper LL, Tsolaki M (2011) RHEA, a nonpharmacological cognitive training intervention in patients with mild cognitive impairment: A pilot study. *Top Geriatr Rehabil* **27**, 1-12.
[66] Suzuki T, Shimada H, Makizako H, Doi T, Yoshida D, Tsutsumimoto K, Anan Y, Uemura K, Lee S, Park H (2012) Effects of multicomponent exercise on cognitive function in older adults with amnestic mild cognitive impairment: A randomized controlled trial. *BMC Neurol* **12**, 128.
[67] Schwenk M, Zieschang T, Oster P, Hauer K (2010) Dual-task performances can be improved in patients with dementia A randomized controlled trial. *Neurology* **74**, 1961-1968.
[68] Proteau L, Marteniuk RG, Lévesque L (1992) A sensorimotor basis for motor learning: Evidence indicating specificity of practice. *Q J Exp Psychol A* **44**, 557-575.
[69] Wang HX, Karp A, Winblad B, Fratiglioni L (2002) Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: A longitudinal study from the Kungsholmen project. *Am J Epidemiol* **155**, 1081-1087.
[70] Loftus GR, Masson ME (1994) Using confidence intervals in within-subject designs. *Psychon Bull Rev* **1**, 476-490.
[71] Cumming G (2013) Understanding the New Statistics: Effect sizes, Confidence Intervals, and Meta-Analysis, Routledge, New York.