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Original Research Article

Thinking-While-Moving Exercises May Improve Cognition in Elderly with Mild Cognitive Deficits: A Proof-of-Principle Study

Casper de Boer[a, b] Holly V. Echlin[a] Alica Rogojin[a] Bianca R. Baltaretu[a] Lauren E. Sergio[a]

[a]School of Kinesiology and Health Science, Centre for Vision Research, York University, Toronto, ON, Canada; [b]VUmc Alzheimercentrum, Amsterdam, The Netherlands

Keywords

Cognition · Motor functions · Training · Neurology · Geriatrics · Elderly

Abstract

Background: Noninvasive interventions to aid healthy cognitive aging are considered an important healthcare priority. Traditional approaches typically focus on cognitive training or aerobic exercise training. In the current study, we investigate the effect of exercises that directly combine cognitive and motor functions on visuomotor skills and general cognition in elderly with various degrees of cognitive deficits. ***Subjects and Methods:*** A total of 37 elderly, divided into four groups based on their level of cognition, completed a 16-week cognitive-motor training program. The weekly training sessions consisted of playing a videogame requiring goal-directed hand movements on a computer tablet for 30 minutes. Before and after the training program, all participants completed a test battery to establish their level of cognition and visuomotor skills. ***Results:*** We observed an overall change in visuomotor behavior in all groups, as participants completed the tasks faster but less accurately. More importantly, we observed a significant improvement in measures of overall cognition in the subaverage cognition group and the mild-to-moderate cognitive deficits group. ***Conclusion:*** Our findings indicate that (1) cognitive-motor exercises induce improved test scores, which is most prominent in elderly with only mild cognitive deficits, and (2) cognitive-motor exercises induce altered visuomotor behavior and slight improvements in measures of general cognition.

Casper de Boer
VUmc Alzheimercentrum
P.O. Box 7057
NL–1007 MB Amsterdam (The Netherlands)
E-Mail c.deboer2@vumc.nl

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Introduction

An important healthcare need in our aging society is the development of easily applicable, noninvasive strategies to aid the functional independence of elderly with cognitive complaints. From a neuropathological standpoint, this implies that methods should be developed that stimulate those neural networks that are most vulnerable in the early stages of cognitive decline. Accumulating evidence is emerging pointing to early-stage dementia, the most prevalent cause of cognitive decline among elderly, as a network failure syndrome. Hence, strengthening of neural network integrity is considered a prime target for intervention strategies [1]. However, traditional noninvasive approaches such as training of specific cognitive functions [2] or aerobic exercise [3] may not be sufficient by themselves, since these methods do not necessarily target large networks. In the current study, we investigated the effect of a newly developed intervention method aimed at improving whole brain neural network integrity through exercises that require direct integration of both cognitive and motor functions.

Various forms of dementia are increasingly considered neural network disorders, emphasizing the importance of while matter dysfunction as a prime aspect of early-stage disease pathology [4]. Especially in Alzheimer's disease, the most common dementia etiology, it is emerging that diminished neural integrity in large whole brain functional networks may precede the manifestation of traditional clinical symptoms such as hippocampal atrophy and memory loss [1]. Recent investigations have even started to question the presumed temporal causality between abnormal accumulation of amyloid-beta and tau proteins and gray matter atrophy, suggesting instead that failure in the posterior default mode network is the driving force behind the cascade of neurodegenerative events in the Alzheimer brain [5]. These advances in our knowledge on the pathophysiological processes in Alzheimer's disease, and in abnormal cognition in general, underline the importance of neural network integrity as a prime target for functional interventions to combat cognitive decline in the elderly.

In the current study, we implement a visuomotor exercise paradigm designed to simultaneously recruit networks involved in cognition and motor action, i.e., thinking and moving at the same time. This type of task was developed based on years of research on the neural underpinnings of cognitive-motor integration as well as on deficits in neurological populations in such behavior. Integration of cognitive and motor functions involves large neural networks, including frontoparietal connections [6, 7]. There is considerable overlap between these neural networks and the networks at risk in the (pre)clinical stages of Alzheimer's disease [5]. In previous work, we not only showed that outcome measures of processing speed and accuracy in cognitive-motor integration tasks are altered in Alzheimer patients [8–10] and even in asymptomatic subjects at high risk of developing dementia [11], but also that such deficits are correlated with decreased frontoparietal network integrity as measured by diffusion tensor imaging [12] and decreased resting stating activity [13]. Given the clear brain-behavior relationship in cognitive-motor integration tasks, we hypothesize that repetitive cognitive-motor integration training may strengthen the involved neural networks and consequently have beneficial effects on cognitive and functional abilities. Here, we investigated the effect of a 16-week cognitive-motor training program on behavioral measures of cognition and visuomotor skills in a group of community-dwelling elderly with various levels of cognitive deficits.

Subjects and Methods

Subjects

A total of 53 community-dwelling elderly were recruited for the study in collaboration with local community senior centers. After initial screening of exclusion criteria, i.e., the presence of neurological comorbidities (e.g., recent stroke or transient ischemic attack, recent period of delirium, other psychiatric disorders) or any upper limb motor deficits that might interfere with task performance, 4 participants were excluded. Another 12 participants failed to complete the intervention program for various reasons, including loss of motivation, hospital admission during the intervention program, and moving to a different city during the program. The remaining 37 participants who completed the study were classified in one of four groups (controls with normal cognition [n = 12], subaverage cognition [n = 8], mild-to-moderate cognitive deficits [n = 6], severe cognitive deficits [n = 11]) based on comparison of their scores on cognitive tests against normative data [14]. None of the participants were using cholinesterase inhibitors during the intervention program.

Study Design

An intervention study design was used, consisting of a preintervention test battery, a 16-week intervention period, and a postintervention test battery. Pre- and postintervention tests were performed 14 days prior to and after the intervention period, respectively. All data collection sessions were performed on site at the community senior centers.

Pre- and Postintervention Tests

To test for cognitive functioning, all participants completed the Dementia Rating Scale (DRS) [14] and the Montreal Cognitive Assessment (MoCA) [15] questionnaires. Classification of participants was based on age-corrected DRS score [14] during the preintervention test. To test for cognitive-motor functioning, all subjects completed the Brain Dysfunction Indicator (BrDI™) test, developed at York University. An elaborate description of this test as well as its data processing steps and outcome parameters are provided in a previous publication (see online suppl. Fig. 1 for a graphical representation of the task instructions; for all online suppl. material, see www.karger.com/doi/10.1159/000490173) [9]. In short, all subjects completed a maximum of four conditions of the BrDI test (Direct, Direct Reversal, Plane Change, Plane Change Reversal; see online suppl. Fig. 2). The outcome measures of task performance were path length (distance travelled by finger between targets), reaction time, movement time, movement precision, movement accuracy, trial success rate, and number of trials where the initial direction was opposite to the target [11].

For descriptive purposes, the Disability Assessment for Dementia (DAD) [16] questionnaire, a test of independence of instrumental activities of daily living (IADL), was administered with a spouse or close family member prior to the intervention program. No exclusion criterion based on the DAD was applied.

Cognitive-Motor Exercises (Intervention Program)

All participants completed a 16-week cognitive-motor intervention program using a tablet-based video game. This game contains a clear visuomotor component, as players are instructed to slice moving objects on the screen by sliding their finger through it. Points are awarded for each object sliced, and bonus points can be earned by slicing multiple objects in a single motion. In the current study, participants played two versions of the game: (1) the Zen version, in which the player has to slice as many objects as possible in 90 s, and (2) the Classic version, in which the player has to slice as many objects as possible while avoiding no-go objects (contact with which would end the trial). In addition, all participants played these game versions across three settings: (1) the Direct setting, in which the viewing and movement planes are the same, (2) the Plane Change setting, in which the viewing plane and the movement plane are dissociated (i.e., the player watches a vertical monitor while moving their finger on a horizontal screen), and (3) the Plane Change Reversal setting, in which the viewing and moving plane are dissociated and the movement plane is reversed (i.e., left =

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Table 1. Demographics and clinical descriptors of all study participants prior to the intervention program

Group	n (M/F)	Age, years	DRS	MoCA	DAD
Controls	12 (0/12)	77.0±1.8	142.0±0.5	27.7±0.6	100.0±0.0
Subaverage	8 (2/6)	78.8±1.6	134.6±0.8	25.5±1.1	96.8±1.9
Mild-to-moderate	6 (2/4)	77.8±3.0	125.5±1.2	22.0±0.7	96.8±2.0
Severe	11 (7/4)	80.4±2.2	95.6±4.5	11.5±2.3	47.9±5.2

Data are expressed as group mean ± standard error. DAD, Disability Assessment for Dementia (range 0–100); DRS, Dementia Rating Scale (range 0–144); MoCA, Montreal Cognitive Assessment (range 0–30).

right and up = down). During each training session, participants played each of the six conditions (version × setting) at least twice. The highest score in each condition was used for analysis of training progression.

The video game was played in the recreational rooms of the partnering community senior centers, under guidance by a researcher form York University. The videogame was played on a 13-inch ASUS tablet using an 18-inch external MagicTouch™ USB touchscreen (Keytek, USA; 100 Hz sampling rate, 3.1 mm resolution) for the Plane Change and Plane Change Reversal conditions. Each participant completed one session per week for a total of 16 weeks. Each session lasted approximately 20–30 min.

Statistical Analysis

To compare demographics, measures of cognition, IADL functioning, and cognitive-motor functioning between all groups at baseline, one-way ANOVA with Bonferroni-corrected post hoc tests was used.

To test for training progression on the video game, data were pooled into four blocks of four sessions for each participant. The mean score of each block was used for analysis. A repeated-measures ANOVA was performed with the mean block score of each condition as dependent variable and the training block as within-subject variable. In addition, group was added as between-subjects variable to analyze differences between training groups. Bonferroni-corrected post hoc tests were used to analyze differences between individual training blocks.

To test for effects of the intervention program on measures of cognition, paired-samples t tests were performed for each group separately. To test for effects of the intervention program on outcome measure of the BrDI task, all outcome parameters were first normalized by calculating their relative change after the program. Consequently, the average relative change in measures of performance, timing, and accuracy was calculated. This data set was tested against a value of zero using one-sample t tests.

All statistical analyses were performed using the IBM SPSS statistics software. A p value of 0.05 was used. In all statistical tests normality of distribution was confirmed, and consequently the appropriate parametric tests could be used.

Results

Demographic and Clinical Characteristics at Baseline

Table 1 describes the demographic and clinical characteristics of all groups at baseline. No effect of group on age was found ($F_{(3, 33)} = 0.539$, $p = 0.659$). At baseline, significant group

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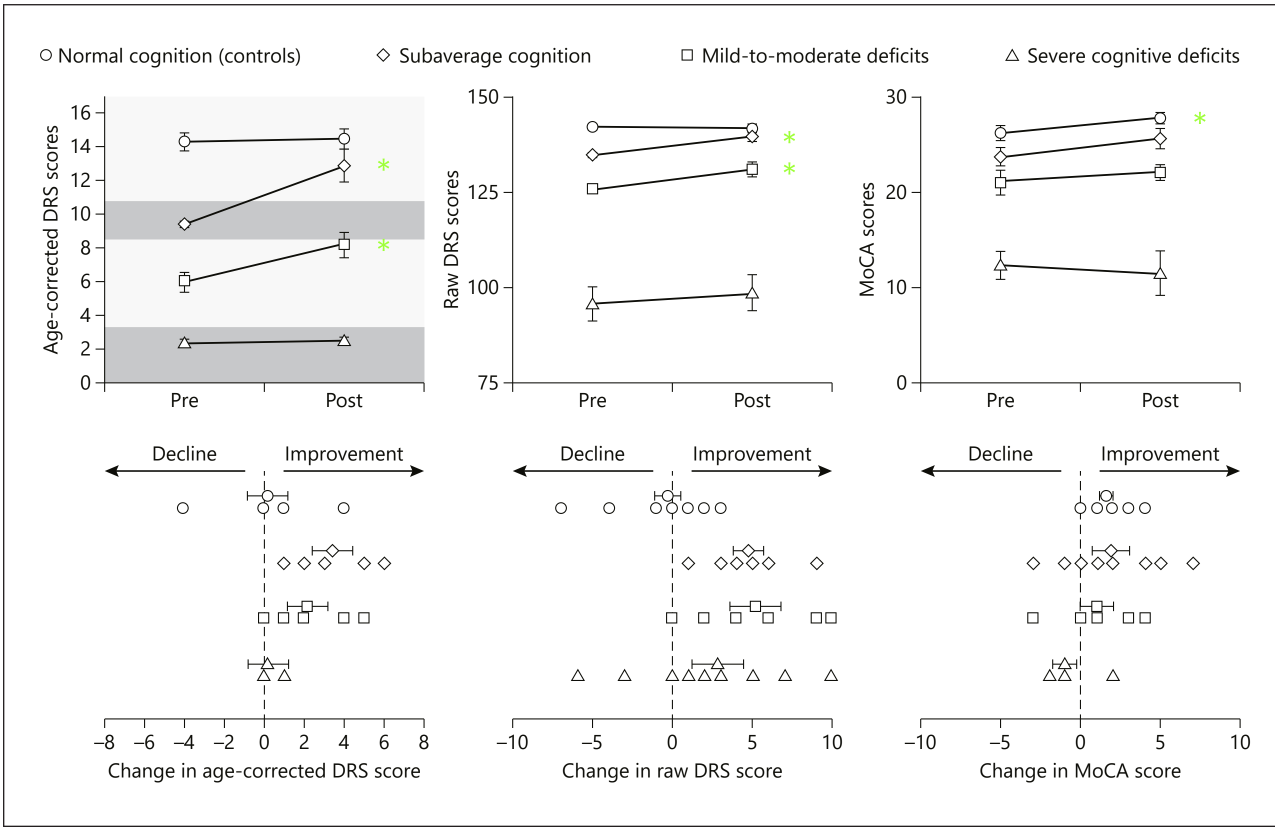

Fig. 1. Effects of the intervention program on outcome measures of cognition. All data are represented as mean ± standard error. Significant differences are indicated by green asterisks. DRS, Dementia Rating Scale; MoCA, Montreal Cognitive Assessment.

effects on raw DRS score ($F_{(3, 33)} = 65.361$, $p < 0.001$), MoCA score ($F_{(3, 33)} = 33.543$, $p < 0.001$), and DAD score ($F_{(3, 18)} = 60.118$, $p < 0.001$) were found. Overall, post hoc tests indicated the expected gliding scale on measures of cognition from the control group down to the severe cognitive deficits group. Regarding IADL functioning as indicated by the DAD scale, the severe deficits group displayed a lower score than all other groups.

Effects of the Intervention Program on Measures of Cognition

Our most striking finding was a significant improvement in the DRS scores (raw and age-corrected) and the MoCA scores of the subaverage cognition and mild-to-moderate deficits groups before and after the intervention program. We also observed an improvement in the neuropsychological measures of the control group following training. Lastly, we found no changes in the DRS or MoCA scores in the severe deficits group over the course of the cognitive-motor training intervention. Put differently, over the 5 months of our intervention, we observed no decline in their cognitive and IADL measures as might be expected. Rather, they remained stable. Figure 1 displays the age-corrected DRS scores, the raw DRS scores, and the MoCA scores of each group before and after the intervention program. Specific findings are as follows:

In the control group, no changes were observed in the age-corrected DRS score (pre: 14.2 [0.6], post: 14.4 [0.6], $t_{(11)} = -0.353$, $p = 0.731$) and in the raw DRS score (pre: 142.0 [0.5], post: 141.7 [0.8], $t_{(11)} = 0.407$, $p = 0.692$). However, this group displayed a significant increase in

MoCA score after the training program (pre: 26.1 [0.7], post: 27.7 [0.6], $t_{(11)} = -3.800$, $p = 0.003$).

In the subaverage cognition group, a significant increase in age-corrected DRS score (pre: 9.4 [0.2], post: 12.9 [0.9], $t_{(6)} = -4.076$, $p = 0.007$) and raw DRS score (pre: 134.9 [0.9], post: 139.6 [1.3], $t_{(6)} = -4.994$, $p = 0.002$) was observed. A 1.9 point increase in MoCA score was found (pre: 23.6 [0.9], post: 25.5 [1.1], $t_{(7)} = -1.600$, $p = 0.154$), but this findings was not statistically significant.

In the mild-to-moderate deficits group, a significant increase in age-corrected DRS score (pre: 6.0 [0.6], post: 8.2 [0.7], $t_{(5)} = -2.745$, $p = 0.041$) and raw DRS score (pre: 125.5 [1.2], post: 130.7 [2.0], $t_{(5)} = -3.228$, $p = 0.023$) was observed. No change in MoCA score was found (pre: 21.0 [1.3], post: 22.0 [0.7], $t_{(5)} = -1.000$, $p = 0.363$).

In the severe deficits group, no change were observed in age-corrected DRS score (pre: 2.4 [0.2], post: 2.5 [0.2], $t_{(10)} = -1.491$, $p = 0.167$), raw DRS score (pre: 95.6 [4.5], post: 98.5 [4.7], $t_{(10)} = -1.807$, $p = 0.101$), or MoCA score (pre: 12.4 [1.4], post: 11.5 [2.3], $t_{(4)} = 1.291$, $p = 0.266$).

Progression in Training Scores during the Intervention Program

Online supplementary Figure 4 displays the video game training scores during the intervention program across all groups. A multivariate repeated-measures ANOVA with training month as within-subject variable and group as between-subjects variable indicated no training month × group interactions. This finding suggests that the data of all groups followed a similar pattern and warrants an analysis of training scores within each group separately.

Significant training effects within the control group were found in the Direct Zen condition ($F_{(3)} = 4.421$, $p = 0.010$), the Plane Change Reversal condition ($F_{(3)} = 3.302$, $p = 0.032$), the Direct Classic condition ($F_{(3)} = 4.540$, $p = 0.009$), and the Plane Change Classic condition ($F_{(3)} = 4.753$, $p = 0.007$). Post hoc tests exclusively showed an increase in training scores in each of these conditions.

Significant training effects within the subaverage cognition group were found in the Direct Zen condition ($F_{(3)} = 4.125$, $p = 0.019$), the Plane Change Zen condition ($F_{(3)} = 7.443$, $p = 0.001$), and the Plane Changer Reversal Zen condition ($F_{(3)} = 7.805$, $p = 0.001$). Post hoc tests exclusively showed an increase in training scores in each of these conditions.

Significant training effects within the mild-to-moderate deficits group were found only in the Plane Change Reversal Zen condition ($F_{(3)} = 4.014$, $p = 0.028$). Post hoc tests showed an increase in training scores from the first to the last month of training in this condition.

Significant training effects within the severe deficits group were found only in the Direct Classic condition ($F_{(3)} = 3.889$, $p = 0.031$). Post hoc tests showed an increase in training scores from the first to the last month of training in this condition.

Effects of the Intervention Program on Measures of the BrDI Task

Figure 2 displays the mean relative change in measures of performance, timing, and accuracy in the BrDI task. Overall, we observed an improvement in measures of timing (difference: 5.9% [2.3%], $t_{(110)} = 2.572$, $p = 0.011$) and a decline in measures of accuracy (difference: –41.9% [2.2%], $t_{(110)} = -18.995$, $p < 0.001$).

Even though a one-way ANOVA indicated no effects of task condition or testing group on any of the outcome measures, we performed an exploratory analysis of the data by running one-sample *t* tests on the data split by condition and group (see online suppl. Tables 1 and 2). When splitting the data by task condition, we found a significant improvement in timing in the Plane Change Reversal condition. Furthermore, a significant decline in accuracy was found in all four task conditions. When splitting the data by testing group, we found a significant improvement in timing in the control group. All groups also showed a significant decline in accuracy.

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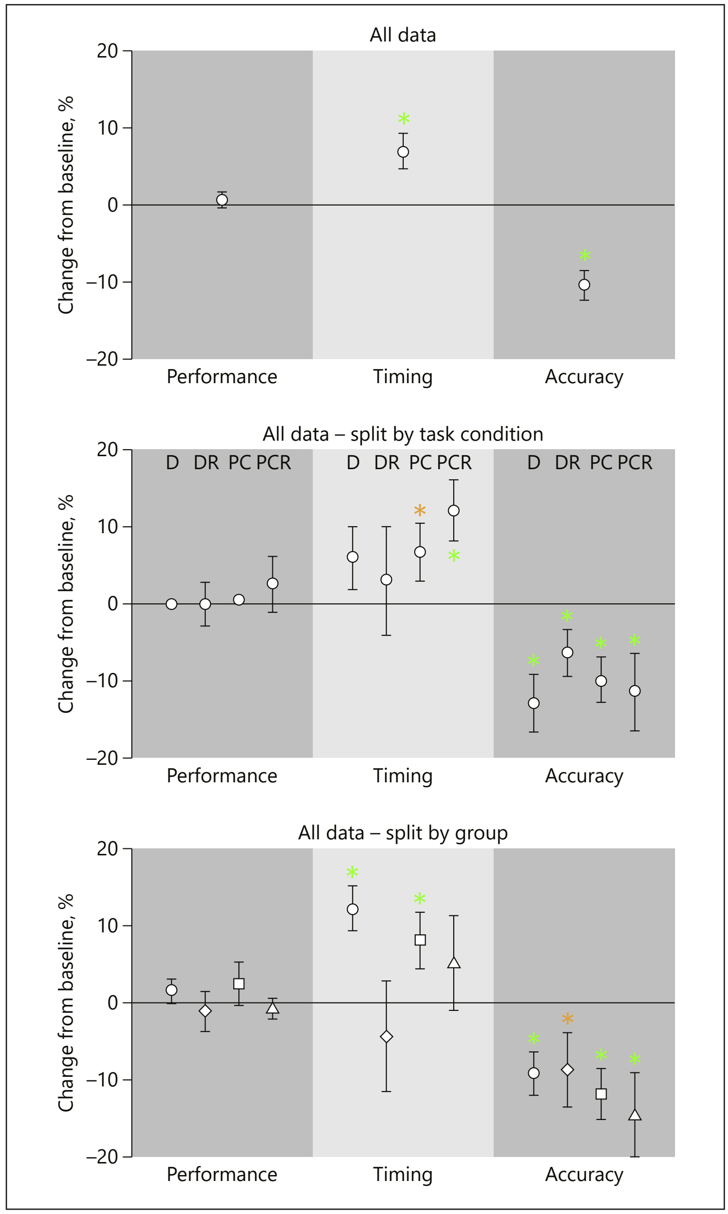

Fig. 2. Effects of the intervention program on outcome measures on the BrDI task. All data are represented as mean ± standard error. Significant differences are indicated by green asterisks, while trends towards significance (*p* values between 0.05 and 0.01) are indicated by orange asterisks. For group symbols see Figure 1. BrDI, Brain Dysfunction Indicator; D, Direct; DR, Direct Reversal; PC, Plane Change; PCR, Plane Change Reversal.

Discussion

The overall goal of this study was to investigate the effect of exercises that directly combine cognitive and motor skills on visuomotor functioning and general cognition in community-dwelling elderly. Our findings indicate that (1) improved test scores were obtained, which were most prominent in older adults with a level of cognition in between the spectra of healthy aging and dementia, and (2) the intervention program induces altered visuomotor behavior and slight improvements in measures of general cognition in elderly with mild cognitive deficits, suggesting a possible relationship between these two behavioral measures.

Neuroplasticity in Elderly with Mild Cognitive Deficits

It is well established that the brain's neuroplasticity abilities diminish with age. This occurs at all levels, ranging from formation of new synaptic connections on a molecular level to getting acquainted with new cognitive concepts on a behavioral level [17]. This phenomenon is regarded as a major contributing factor to the increase in prevalence of cognitive disorders, such as dementia, with age. A large body of literature is available on the effects of noninvasive interventions on neuroplasticity in the brain, both in normal and abnormal cognitive aging [18]. Even though a wide variety of intervention paradigms have been described, the majority of methods can be classified either as cognitive training, with the goal of improving specific cognitive functions that are functionally relevant for the group at hand, or as aerobic exercise training, with the goal of improving overall cardiovascular health and cerebral blood flow. A consensus is emerging that beneficial effects can be obtained through such programs, although improvements cannot always be deemed clinically relevant, nor have they been found to transfer to other cognitive domains [19–21]. Interestingly, relatively strong training effects are often found in older adults with only mild cognitive deficits, while those with severe cognitive deficits, such as in dementia disorders, seem to profit less [22]. These findings suggest that, in general, an aging brain in the earliest stages of neurodegeneration still possesses the functional capacities to form sufficient new synaptic connections to induce relevant changes on a systems level. Our findings support this notion, since the improvements in general cognition that we observed were limited to those older adults who displayed subaverage cognition or mild-to-moderate cognitive deficits at baseline. It is important to realize though that our finding in the severe cognitive deficits group, which consisted solely of older adults with a diagnosed form of dementia, can be interpreted as a positive result. On average, we found a stabilization of cognitive scores in this group. However, since dementia is a progressive neurodegenerative disorder, these patients are typically expected to show a measurable decline in cognition over the course of 5 months. Even though no longitudinal data on the DRS in dementia patients are available, this effect has been well documented in other, comparable, cognitive questionnaires [23]. We thus propose that even patients with more advanced levels of neurodegenerative dementia could still profit from cognitive-motor exercises. However, exploring the factors that may determine why some dementia patients seem to profit from such exercises while others do not remains a very important topic for future study.

Cognitive-Motor Exercises

As opposed to pure cognitive training or pure aerobic exercise training, several studies have incorporated interventions that combine both elements with the aim of inducing cumulative effects [24]. However, it is important to note that these studies still employed separate cognitive and motor exercises. The number of intervention studies that designed exercises that directly combine aspects of cognitive and motor functioning is very limited. To our knowledge, only one study has applied a similar intervention approach in a small group of dementia patients [25]. Their findings are in line with our study, as they found no significant changes in cognition in their testing group, which was interpreted as a positive finding. The apparent lack of intervention studies that use integrated cognitive-motor exercises is striking, especially considering the functional relevance of "thinking-while-moving" in daily life. Since dementia is, by definition, a disorder that interferes with daily life abilities [1], our present findings suggest that more interventions should be designed with this concept in mind.

A novel finding of the current study is that improvements in rule-based visuomotor skills (e.g., slide the finger right to move the cursor left in our feedback reversal condition) appear to transfer to other domains such as general cognition, particularly in older adults with only mild cognitive deficits. This suggests that our intervention may induce neuronal changes on the level of networks that are not only relevant for the task at hand, but also for more general abilities of the brain. The design of our intervention tasks is based on extensive research on the neural representations of cognitive-motor behavior [6, 12, 13, 26]. These investigations have indicated that performance in such tasks is highly dependent on functional connectivity, particularly in frontoparietal networks [6, 7]. When considering cognition, the (pre)frontal lobe is highly involved in a variety of executive functions which includes, but is not limited to, response inhibition, updating of working memory, and rule integration [27]. In addition, the parietal lobe, particularly the precuneus region, is highly involved in generating accurate spatial representations of our environment to facilitate goal-directed behavior [28]. Both executive functioning and visuospatial skills are highly important aspects of overall cognition. The hypothetical overlap between the frontoparietal networks that are presumably targeted with our intervention exercises and the functional relevance of these networks for general cognitive abilities may explain why the beneficial effects of our exercises were not limited to visuomotor skills alone. This theoretical association is partially confirmed by the profile of cognitive improvement, as expressed by subscales of the DRS questionnaire, that we observed in the subaverage cognition group and the mild-to-moderate deficits group (see online suppl. Fig. 3). A visual inspection of these profiles suggests that the study participants in these groups improved particularly in the domains of initiation/perseveration, conceptualization, and, to a lesser degree, memory. These cognitive subdomains are generally considered executive functions and could thus be linked to structural and functional integrity of (pre)frontal networks [27]. To this end, direct examination of brain network changes with cognitive-motor training is currently a topic of study in our laboratory.

Unexpected Findings

As the intervention paradigm we chose for this study has a very strong visuomotor component, we anticipated that the outcome measures with the largest improvements would be those related to visuomotor behavior. Even though we did find an overall relative improvement in measures of timing, this appeared to arise at the expense of an overall relative decline in measures of accuracy. However, upon closer inspection of the data, we observed that this decline in accuracy could not be deemed clinically relevant (see online suppl. Tables 1 and 2). Even though, on average, after the intervention program participants made less accurate movements to the targets (i.e., they were further from the center of the target and needed a longer path length), this behavior did not negatively influence their correct task completion rate. On the other hand, all groups displayed large improvements of up to several hundreds of milliseconds in response times and task completion times. These changes may be deemed clinically more relevant, since previous studies have described differences of the same magnitude in these outcomes between neurologically normal and abnormal populations [9, 10]. Overall, we conclude that our study participants did therefore display a relevant improvement in visuomotor behavior.

Another unexpected finding was that our normal cognition group displayed an improvement in overall cognition as measured by the MoCA questionnaire. We emphasize, however, that this change occurred well within the range of normal cognitive functioning. We suspect that this finding may be due to a small learning effect within this group, since both test time points were only 5 months apart. Even though the MoCA questionnaire is a highly practical bedside test for cognitive (dys)functioning, the relatively low resolution (score range 0–30) makes it sensitive to incidental findings. This explanation is confirmed by the fact that the same normal cognition group displayed no change in cognition as measured by the more elaborate DRS questionnaire.

Limitations and Future Directions

The current study provides behavioral evidence that may suggest a generalized positive effect of cognitive-motor exercises on frontoparietal neural network integrity in elderly with mild cognitive deficits. We are aware that these findings should be interpreted with caution.

Our results may serve as a proof of principle, but do not yet provide conclusive evidence for this claim. Going forward, it is important to repeat these findings in studies that go beyond behavioral measures and include network-based structural and functional neuroimaging techniques such as diffusion tensor imaging, resting-state functional magnetic resonance imaging, and arterial spin labeling. Furthermore, we consider it highly important for future studies to include control groups that receive either no intervention or a purely cognitive intervention. Furthermore, several improvements regarding the study design should be incorporated, including increasing the sample size and balancing the male-female ratio. Finally, to confirm the clinical significance of our findings, we consider it very important to include more elaborate measures of IADL, such as the Amsterdam IADL questionnaire [29], in future studies.

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Statement of Ethics

All participants signed informed consent prior to the start of the study. In the case of participants with a diagnosed form of dementia, which was only the case in the severe cognitive deficits group, consent was obtained from a caregiver. The study was approved the by human participants ethics board at York University.

Disclosure Statement

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