Featured Article

Virtual reality-based cognitive-motor training for middle-aged adults at high Alzheimer's disease risk: A randomized controlled trial

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Abstract

Introduction: Ubiquity of Alzheimer's disease (AD) coupled with relatively ineffectual pharmacologic treatments has spurred interest in nonpharmacologic lifestyle interventions for prevention or risk reduction. However, evidence of neuroplasticity notwithstanding, there are few scientifically rigorous, ecologically relevant brain training studies focused on building cognitive reserve in middle age to protect against cognitive decline. This pilot study will examine the ability of virtual reality (VR) cognitive training to improve cognition and cerebral blood flow (CBF) in middle-aged individuals at high AD risk due to parental history.

Methods: The design is an assessor-blind, parallel group, randomized controlled trial of VR cognitive-motor training in middle-aged adults with AD family history. The experimental group will be trained with adaptive "real-world" VR tasks targeting sustained and selective attention, working memory, covert rule deduction, and planning, while walking on a treadmill. One active control group will perform the VR tasks without treadmill walking; another will walk on a treadmill while watching scientific documentaries (nonspecific cognitive stimulation). A passive (waitlist) control group will not receive training. Training sessions will be 45 minutes, twice/week for 12 weeks. Primary outcomes are global cognition and CBF (from arterial spin labeling [ASL]) at baseline, immediately after training (training gain), and 3 months post-training (maintenance gain). We aim to recruit 125 participants, including 20 passive controls and 35 in the other groups.

Discussion: Current pharmacologic therapies are for symptomatic AD patients, whereas nonpharmacologic training is administrable before symptom onset. Emerging evidence suggests that cognitive training improves cognitive function. However, a more ecologically valid cognitive-motor VR setting that better mimics complex daily activities may augment transfer of trained skills. VR training has benefited clinical cohorts, but benefit in asymptomatic high-risk individuals is unknown. If effective, this trial may help define a prophylactic regimen for AD, adaptable for home-based application in high-risk individuals.

1. Introduction

Dementia prevalence roughly doubles every 4–5 years from age 65, so that more than one-third of individuals over 85 will likely have dementia [1,2]. The World Health Organization (WHO) estimated 35.6 million people with dementia in 2010 and expects 65.7 million in 2030 and 115.4 million in 2050 [3]. Alzheimer's disease (AD), the most common cause of dementia, is a progressive neurodegenerative disorder characterized by gradual cognitive decline, with eventual loss of independent function. Amyloid β plaque deposition, a precursor to neurodegeneration, begins up to 20 years before clinical manifestations [4], and an intervention delaying symptom onset in AD by only 5 years would reduce the prevalence of clinical disease by 50%, dramatically moderating the enormous emotional, economic, and societal burden [5].

Current pharmacologic treatments for AD include cholinesterase inhibitors donepezil, rivastigmine, and galantamine, as well as glutamate antagonist memantine. Although cognitive decline continues, sustained treatment may be somewhat beneficial. However, available medications have limited efficacy and do not alter the disease course. Recent phase 3 clinical trials aimed to directly eliminate the most predominant pathologies of AD, amyloid plaques and neurofibrillary tangles, have failed to improve clinical outcomes, suggesting that once symptoms appear, the brain is already substantially affected by neuronal death and neuropathology, significantly limiting efficacy of these drugs [6–8]. In this context, treatment administered to preclinical patients, when prevention may still be possible, is of great potential. Indeed several major pharmacologic and nonpharmacologic trials in individuals at high AD risk are underway investigating how to delay onset of cognitive decline.

The Alzheimer's Association's "Maintain Your Brain" campaign recommends mental activity as a key component of a "brain-healthy" lifestyle [9]. Further, the Alzheimer's Association has partnered with the Centers for Disease Control and Prevention to develop the "Healthy Brain Initiative", which recommends studying the effects of behavioral interventions on maintaining brain health and preventing cognitive decline [10]. Cognitive exercise may stimulate neuroplastic changes, drawing upon the brain's cognitive reserve [11–13]. Indeed, animal studies suggest the brain is highly plastic even in advanced age, generating new synaptic connections and neurons in enriched environments, as evidenced by increased brain weight, cortical thickness, and neurotrophic factors [14],

all associated with better cognitive function in humans [15–17]. These neural mechanisms provide the rationale for cognitive benefits afforded by cognitive interventions [18–20]. Critically, such behavioral interventions are free from adverse side effects common to pharmacological interventions. Recently, computerized training programs have been used, with tasks focused on particular cognitive functions [21]. Although these programs are more convenient and offer greater precision than training tasks requiring human intervention, the computerized paradigms show limited transfer of gains to performance of everyday activities [22].

Virtual reality (VR) training offers the potential for more engaging and effective training with higher likelihood of transfer of training gains to daily life [23]. VR technology facilitates the creation of a multisensory, dynamic, interactive virtual environment with greater similarity to real life (i.e., ecological validity). Notably, feasibility of VR has been demonstrated in healthy older individuals and those with dementia [24]. A recent systematic review of computerized and VR cognitive training for individuals with mild cognitive impairment (MCI) and dementia found the most consistent improvements in the cognitive domains of attention, executive function, and memory (visual and verbal), as well as significant reductions in depressive symptoms and anxiety [25]. The authors conclude that VR (together with computerized cognitive training) is effective in delaying the progression of cognitive impairment (see also [26]). Finally, a VR format may promote training adherence, as suggested by a study showing that individuals with MCI and dementia patients preferred the VR format of a task over the paper version [27]. To our knowledge, there has not been a study of VR training in cognitively normal middle-aged individuals at high AD risk.

On the assumption that more engaging training should be more effective, combining cognitive VR training with treadmill walking should augment training efficacy, given the greater cognitive demands of combined physical and cognitive activity [28], particularly in a dual-tasking context [29], as it requires greater allocation of attention in healthy and neurologically impaired individuals [30]. Moreover, a paradigm combining cognitive tasks with simultaneous walking mirrors key complex activities of daily living (e.g., shopping), boosting ecological validity and potential for transfer of these activities to "real life" [31]. VR training with walking also exploits growing evidence of synergism between motor and cognitive systems [32]. Notably, our

experimental intervention is designed to improve cognitive rather than motor function, and the simultaneous walking is intended to be incidental to the cognitive training tasks.

The study will include a primary cognitive outcome with prominent contributions from memory and executive function, the domains most affected by AD. The study also includes a primary neurobiological outcome, cerebral blood flow (CBF), as it has shown sensitivity to cognitive training in healthy seniors [13], and hypoperfusion has been found in individuals with AD family history [33]. As below, this pilot study aims to quantify treatment gain in these outcomes and hypothesizes the greatest gains in an experimental group completing a 12-week VR cognitive-motor training program relative to active and passive control groups in a randomized controlled trial.

2. Methods

2.1. Study setting and design

The current trial is an assessor-blind prospective parallel group, randomized controlled trial of intensive VR cognitive training combining lifelike cognitive tasks with simultaneous treadmill walking in adults ages 40 to 65 with a family history of AD. The overall study design and flow of the trial is shown in Fig. 1.

Table 1 illustrates the factorial design of the four intervention groups. The experimental group will be trained with a set of "real-world" VR cognitive tasks while walking on a treadmill (Group 1, VR + T). Design features of this training scheme expected to enhance training efficacy are (1) cognitive challenge, (2) ecological context, and (3) cognitive-motor interaction. One active control group will perform the VR tasks without treadmill (Group 2, VR − T); this group controls for the contribution of cognitive-motor interaction relative to the experimental group. For Groups 1 and 2, we developed adaptive VR tasks that simulate complex activities of daily living and challenge such cognitive functions as selective attention, working memory, and planning. Another active control group will walk on a treadmill while watching scientific documentaries (Group 3, TV + T); this group controls for the contribution of the VR environment and tasks relative to the experimental group. A passive control group will not receive training (Group 4); this group serves as a comparison to participants' routine activities and controls for nonspecific impact of any intervention.

Training sessions will be 45 minutes, twice/week for 12 weeks. Each training session is attended by an experimenter who instructs and encourages the participant, and a VR operator to perform the technical functions of running the training tasks and treadmill. At the conclusion of each training session, experimenter and operator independently rate participant effort on a 1 to 10 scale (10 = maximum effort). The study will be conducted in the Center of Advanced Technologies in Rehabilitation at

Sheba Medical Center, Israel. Magnetic resonance imaging (MRI) will be at the Sheba Functional Neuroimaging Laboratory and positron emission tomography amyloid imaging at the Department of Nuclear Medicine. All participants provide informed consent before participation, and ethics approval has been obtained from the Helsinki Committee of the Sheba Medical Center (protocol #2988-16-SMC).

2.2. Participants

Recruitment is currently ongoing. Participants are being recruited from the community via a research database of potentially eligible participants at the Joseph Sagol Neuroscience Center, advertisements on the websites of Israel's major health funds, and email campaigns to recipients interested in health-related topics. Potential participants are contacted by phone/email to provide additional details and screen for basic inclusion criteria. If deemed eligible, participants are invited for a baseline assessment. Participants also receive a training schedule with the dates of the 24 twice-weekly training sessions they must attend (unless later randomized to the passive control group; see Section 2.5). The importance of adherence to the training schedule is emphasized.
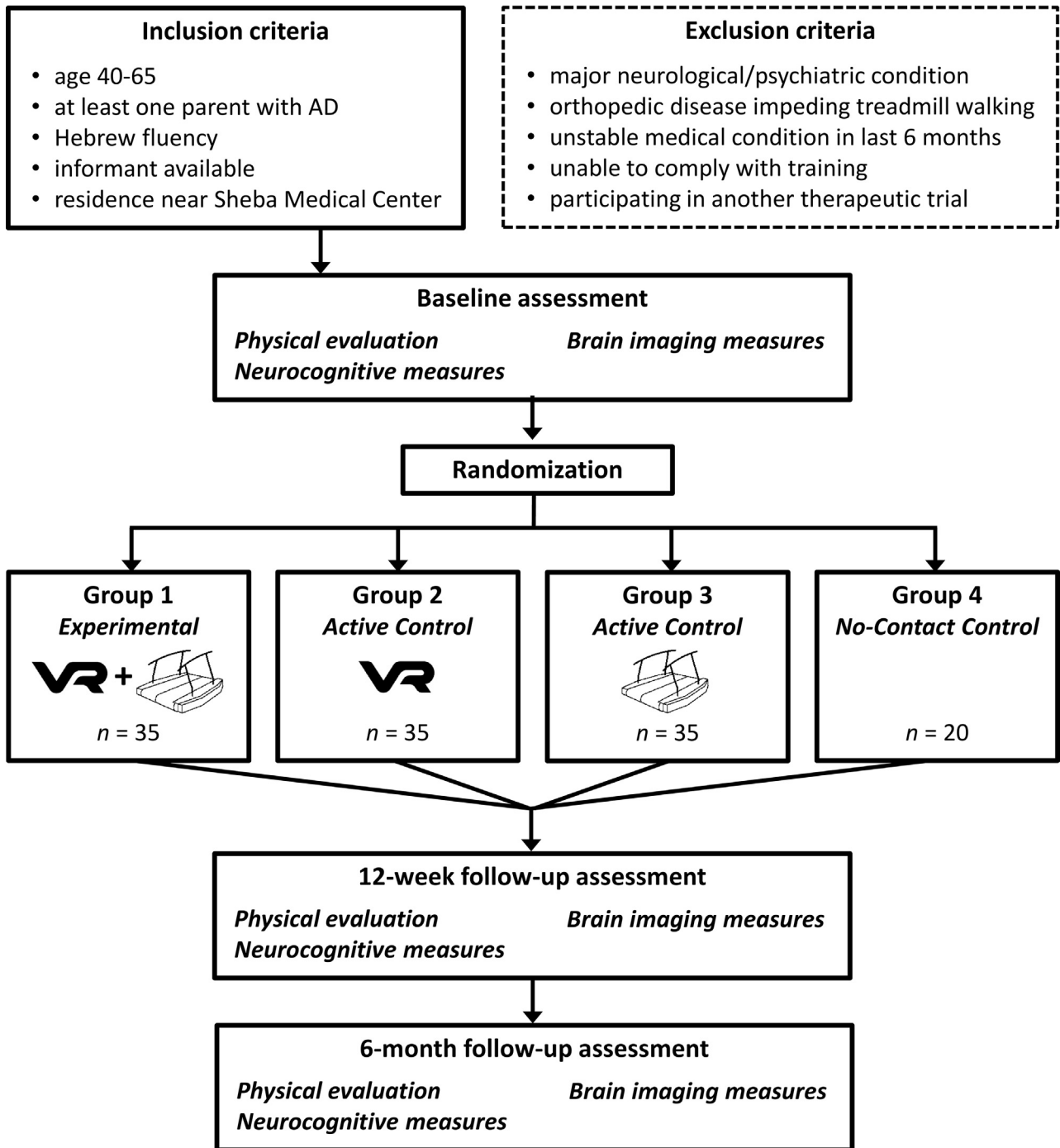
2.2.1. Inclusion criteria

Participants are required to (1) be between the ages of 40 and 65 and have at least one parent (alive or deceased) with AD; (2) be fluent in Hebrew; (3) have an informant (typically a family member) available; and (4) be living in central Israel in close proximity to the Sheba Medical Center.

2.2.2. Exclusion criteria

Participants are ineligible to enroll in the trial if they (1) have major neurological or psychiatric conditions that may affect cognition (e.g., Parkinson's disease, stroke, schizophrenia); (2) have acute orthopedic diseases that impede treadmill walking; (3) have had an unstable medical condition in the previous 6 months; (4) are unable to comply with the training regimen; or (5) are concurrently participating in another therapeutic trial.

2.2.3. Sample size calculations

Sample size calculations were estimated using G*Power (Version 3.1.9.2) and were based on small to medium effects in studies of cognitive training in cognitively healthy older adults and individuals with MCI [19,26]. As effect sizes are expected to be smaller for studies with an active control condition, we made a conservative assumption of a small effect (F = 0.10) for group differences on the primary cognitive outcome; we also make a conservative assumption of a small effect for the CBF primary outcome. To detect a small effect in a four-group design with a 5% risk of type 1 error (α), 90% power, and an estimated correlation of r = 0.8 between repeated measurements of the primary cognitive outcome, a total

Inclusion criteria

- age 40-65
- at least one parent with AD
- Hebrew fluency
- informant available
- residence near Sheba Medical Center

Exclusion criteria

- major neurological/psychiatric condition
- orthopedic disease impeding treadmill walking
- unstable medical condition in last 6 months
- unable to comply with training
- participating in another therapeutic trial

Baseline assessment

Physical evaluation *Brain imaging measures*
Neurocognitive measures

Randomization

Group 1
Experimental

VR + 🚶

n = 35

Group 2
Active Control

VR

n = 35

Group 3
Active Control

🚶

n = 35

Group 4
No-Contact Control

n = 20

12-week follow-up assessment

Physical evaluation *Brain imaging measures*
Neurocognitive measures

6-month follow-up assessment

Physical evaluation *Brain imaging measures*
Neurocognitive measures

VR virtual reality cognitive tasks   🚶 treadmill walking

Fig. 1. Study design and flow. The design is an assessor-blind, parallel group, randomized controlled trial of a cognitive-motor virtual reality (VR) training program in middle-aged adults with a parental family history of Alzheimer's disease (AD). Participants meeting inclusion/exclusion criteria will complete a baseline assessment including cognitive and neurobiological measures (Supplementary Table 1). Following randomization, participants in the experimental and active control groups will complete 24 training sessions over 12 weeks (45 minutes/session). Participants will repeat the assessment following the training period and again after an additional 3 months. Primary outcomes will be global cognition and cerebral blood flow (CBF) from magnetic resonance imaging (MRI) arterial spin labeling (ASL). For an exploratory analysis, participants will also undergo positron emission tomography amyloid imaging once during the study.

Table 1
Factorial design of intervention groups

		Treadmill walking	
		Yes	No
VR cognitive tasks	Yes	Group 1 (VR + T) [experimental]	Group 2 (VR − T) [active control]
	No	Group 3 (TV + T) [active control]	Group 4 [no-contact control]

Abbreviation: VR, virtual reality.

sample size of 120 is required. The target total sample size was set to 125. To account for a dropout rate of ∼15%, we may recruit up to 150 participants. Given the importance of detecting a difference among the active conditions and anticipated smaller differences among them, target sample size was set to 35 participants in each of the three active conditions and 20 in the passive control condition.

2.3. Assessments

The assessment schedule is summarized in Supplementary Table 1. All measures are collected at baseline, 12 weeks (immediately following completion of the training sessions), and after an additional 3 months. Primary outcomes are a global cognitive score and CBF from MRI arterial spin labeling (ASL). Secondary outcomes are detailed in Section 2.4. Informed consent is obtained before the baseline assessment, which is conducted on 2 days—one for the MRI measures and another for all other measures (Supplementary Table 1). All baseline assessment measures are obtained within 3 weeks of initiation of training. The first follow-up assessment is conducted within 3 weeks of the conclusion of training. The second follow-up assessment is conducted 3 months after the first follow-up assessment. Throughout the study, assessors of the outcome measures are blind to group assignment, and participants are blind to the experimental condition associated with their assigned group. Training session experimenters and operators are not blinded. To minimize likelihood of breaking the blind, participants, experimenters, and operators are instructed to refrain from discussing the study design.

2.3.1. Neurocognitive measures

As in Supplementary Table 1, the neurocognitive battery completed at each assessment consists of traditional neuropsychological tests focusing on memory and executive function, the cognitive domains most affected in AD.

2.3.2. Brain imaging procedures and measures

Participants will undergo MRI scanning on a 3 tesla (3T) Philips Ingenia scanner (Philips Medical Systems, Best, The Netherlands) using a 32-channel radio frequency coil. The scanning session will include anatomical and functional imaging. Structural sequences include ASL, T1-weighted imaging, T2-weighted-fluid-attenuated inversion recovery

(T2-FLAIR), and diffusion weighted imaging (DWI). Functional sequences include a functional MRI (fMRI) scan during an n-back working memory task, and a resting-state functional connectivity scan. As above, the identical MRI sequences will be acquired at the conclusion of the 12-week training period and after an additional 3 months. Participants will be asked to refrain from caffeine for 3 hours and nicotine for 1.5 hours before the scanning session. Details on the structural and functional imaging protocols, the n-back working memory task, as well as image postprocessing and quality control are provided in Supplementary Material 1.

Participants will also undergo positron emission tomography amyloid imaging once during the study. Amyloid positivity status is not an outcome measure. We will explore whether participants positive for amyloid have larger treatment-related gains [34], which may help refine the design of large-scale follow-up studies.

2.4. Outcomes

2.4.1. Primary cognitive outcome

The primary cognitive outcome is a global cognitive score computed by averaging the z-scores from all traditional neuropsychological tests [35]. The reference sample for the z-scores will be baseline data from all participants.

2.4.2. Secondary cognitive outcomes

Secondary outcomes will be memory and executive function domain scores computed by averaging the z-scores from relevant traditional neuropsychological tests (see Supplementary Table 2). The approach of combining individual scores to give a more robust domain measure has been adopted in large-scale trials [35–37].

2.4.3. Primary neurobiological outcome

The primary neurobiological outcome is CBF from ASL. CBF has evidenced hypoperfusion in individuals with a maternal history of AD [33] and has shown sensitivity to cognitive training in healthy seniors [13].

2.4.4. Secondary neurobiological outcomes

Secondary neurobiological outcomes include hippocampal volume, frontal inferior cortex volume, white matter hyperintensity burden, diffusion tensor imaging (DTI) measures (fractional anisotropy, mean diffusivity), functional activity (fMRI frontoparietal network associated with working memory), and resting-state functional connectivity (in such known networks as the default mode network). Notably, neuroplastic change in hippocampal and parahippocampal DTI measures has been shown following only 2 hours of cognitive training [38]. As an important exploratory analysis, we will evaluate the correlation between amyloid positivity and gains on our primary outcome measures. This is based on growing

evidence that amyloid-positive individuals show cognitive decline and are at the highest AD risk [4,34].

Exploratory outcomes to be collected at each of the three study time points are detailed in Supplementary Material 1.

2.5. Interventions

Following the baseline assessment, participants are assigned to one of the four intervention groups (Fig. 1), as determined by an automated randomization algorithm [39]. Randomization sequences are concealed from study personnel by a researcher unrelated to the study who provides participant group assignment to the study coordinator on request. Participants are unaware of the trial design and hypotheses and are told only that they have been assigned to a particular study group.

2.5.1. Group 1 (experimental): VR cognitive training with treadmill (VR + T)

Participants in Group 1 are trained with a set of "real-world" tasks presented on a large monitor while walking on an instrumented treadmill (R-Mill; ForceLink, The Netherlands). A VR system (V-Gait; Motek Medical, The Netherlands) synchronizes the treadmill (i.e., including embedded force plates) with the visual scene, and a motion capture system (Vicon, Oxford, UK) covering the space occupied by the treadmill captures kinematic data (sampling

Fig. 2. Virtual reality (VR) training setup. The experimental group (Group 1, VR + T) is trained with a set of "real-world" tasks presented on a large monitor while walking on an instrumented split-belt treadmill (R-Mill; ForceLink, The Netherlands). A VR system (V-Gait; Motek Medical, The Netherlands) synchronizes the treadmill (i.e., including embedded force plates) with the visual scene, and a motion capture system (Vicon, Oxford, UK) covering the space occupied by the treadmill captures kinematic data (sampling rate: 120 Hz) via a set of cameras and passive markers affixed to the top of the participant's right and left hands, respectively. One active control group (Group 2, VR − T) stands rather than walks on the treadmill, and the other active control group (Group 3, TV + T) views an episode of a scientific documentary rather than completing the VR tasks. Green arrows represent data flow; black arrows indicate system components.

rate: 120 Hz) via custom cameras and passive markers affixed to the top of the participant's right and left hands, respectively (Fig. 2). The five main training tasks are set in a virtual supermarket (Table 2; Fig. 3) and train sustained attention, selective attention, working memory, covert rule deduction, and planning. In all supermarket tasks, the participant collects products from the shelf while walking down an endless supermarket aisle. Products to be collected are on the middle shelf on right and left sides. To collect a product, the participant moves the corresponding virtual hand on the screen so that it is directly over the product to be collected (Fig. 4).

Each 45-minute training session typically consists of two different supermarket training tasks with a virtual road task between them. In this road task, participants hit virtual balls bouncing in space as they walk rapidly down a virtual road (Table 2; Fig. 3). The road task, which focuses on psychomotor speed and coordination, serves primarily to offer participants a respite from the more cognitively intensive supermarket tasks, with the goal of enhancing efficacy of the supermarket tasks.

As the participant improves on a given task, progressively more difficult levels are presented in an effort to continuously challenge him/her. Greater difficulty is introduced by making the task more demanding (e.g., longer list of products to remember in Task 3) or increasing the treadmill speed. Treadmill speeds range from 0.4 to 0.8 m/s in an effort to minimize physical exertion and accentuate the cognitive demands of the training tasks.

Additional details on the design of the VR training tasks are provided in Supplementary Material 2. Click <here> for a brief video demonstrating the tasks.
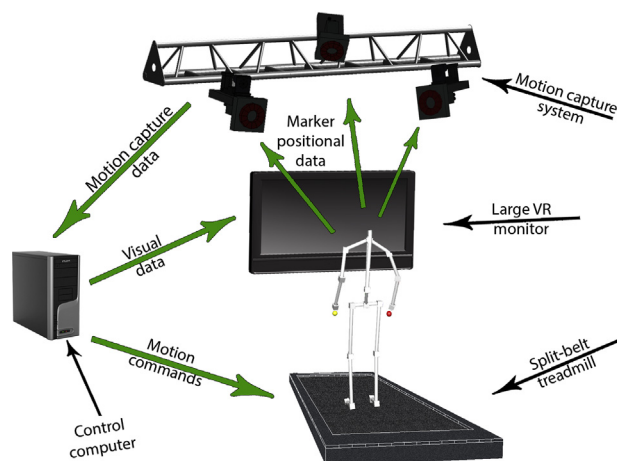
Heart rate is monitored throughout each session. If heart rate exceeds 65% of maximum capacity (calculated as 220 minus age; [40]) consistent with aerobic exercise, the participant provides a subjective rating of physical exertion on the Borg Scale of Perceived Exertion [41], a categorical scale ranging from 6 for no feeling of exertion to 20 for "very, very hard" exertion.

2.5.2. Group 2 (active control): VR cognitive training without treadmill (VR − T)

Participants in Group 2 are trained with the identical set of VR tasks and experimental setup as Group 1 but while standing rather than walking on a treadmill. This active control group is designed to evaluate whether combining treadmill walking with the visually presented VR tasks in Group 1 enhances training-related gains.

2.5.3. Group 3 (active control): Scientific TV documentary with treadmill (TV + T)

Participants in Group 3 view an episode of a science-related documentary while walking on a treadmill (Table 2). Experimental setup is otherwise identical to Group 1. Throughout the episode, three questions related

Table 2
Description of the VR training tasks

Task	Description
Supermarket	
Task 1: Sustained attention	Participant must collect as many products as possible.
Task 2: Selective attention	Participant must collect only products that conform to particular criteria displayed throughout the task (e.g., have a 15% sale sticker).
Task 3: Working memory	Participant is briefly shown a virtual shopping list and must then collect the items on the list.
Task 4: Covert rule deduction	Participant must deduce a covert rule related to product characteristics (e.g., location, appearance, contents) by collecting products and obtaining positive or negative auditory feedback for each product. Once deduced, only products conforming to the rule are to be collected.
Task 5: Planning	Participant is shown a list of products with prices and instructed to select products according to certain criteria so that the total cost is exactly 100 shekels (Israeli currency).
Road	Participants catch virtual balls bouncing in space as they walk rapidly down a virtual road.

Abbreviation: VR, virtual reality.

to the content of the episode are displayed beneath the screen. When the participant has an answer to a question, the treadmill and episode are paused while s/he records the answer on a response sheet. The participant responds to two additional content questions immediately following the episode. Provision of the questions and collection of responses is intended to parallel the periodic interaction with the experimenter during VR training in Groups 1 and 2. This active control group is designed to evaluate whether when combined with treadmill walking, the VR tasks result in greater training-related gains than the nonspecific cognitive stimulation associated with intently watching educational television.

2.5.4. Group 4 (no-contact control): Usual activities

Participants in Group 4 engage in their usual activities during the 12 weeks following the baseline assessment. Thus, this (waitlist control) group will allow comparison of the interventions to the natural course of cognitive and neural changes.

Following the study, if the results indicate significantly greater improvement in cognitive or CBF primary outcomes in one of the active groups, participants in the other groups will be offered the respective intervention as a courtesy for their participation.

2.6. Statistical analyses

Using mixed regression models, we will compare change in primary and secondary outcomes from baseline to 12 weeks (training gain) and from baseline to 6 months (maintenance gain) for the four study groups (Table 1). If the groups differ in age, gender, or years of education, these variables will be entered as control variables in the mixed regression. The hypotheses are that the experimental group (Group 1, VR + T) will show the largest gains in cognition and CBF relative to the active control groups (Group 2, VR − T; Group 3, TV + T) and the no-contact control group (Group 4). To minimize selection bias, data will be analyzed in accord with the intention-to-treat (ITT) principle [42]. Separate per-protocol analyses will be run including only

compliant participants with complete data. Analysis procedures for the neuroimaging data are described in Supplementary Material 1.

3. Discussion

The goal of this study is to assess the effectiveness of a VR cognitive training program on cognition and CBF in middle-aged individuals at high risk for developing AD due to a parental family history. Growing prevalence of AD, coupled with disappointing progress toward a pharmacologic intervention administrable prophylactically or early in the disease course, highlights the need for effective non-pharmacologic alternatives. The design of the present study addresses many pitfalls of past and ongoing studies: First, participants will be offspring of AD patients—individuals at high risk of developing the disease, yet middle-aged and asymptomatic, providing an opportunity for prevention. This, combined with the promise of fortifying the brain's cognitive reserve and stimulating neuroplasticity, makes middle-aged individuals at risk for AD (given the prominent role of genetics in the disease) the ideal population for evaluating the impact of our VR-based cognitive-motor training. Ultimately, it is our contention that by boosting cognitive function before AD onset, it may be possible to delay or even prevent the disease. Second, the intervention is behavioral rather than pharmacological, so eligibility criteria can be less stringent, making results more generalizable and diminishing screen fails. Third, the study is based on VR technology, enhancing ecological validity and thus likelihood of transfer to daily life. And finally, recent evidence of distinct behavioral and CBF benefits for cognitive and physical training suggests that combined cognitive-motor training may be more effective than cognitive or motor training alone [43]. Gait training using a treadmill in a VR setting has been shown to result not only in improved gait (e.g., faster gait, reduced dual-task gait variability) but also in cognitive gains, though it remains unclear whether these gains are greater for VR-based training as compared with a treadmill alone [44].

Supermarket Training Tasks

Task 1: Sustained Attention

Task 2: Selective Attention

Task 3: Working Memory

Task 4: Covert Rule Deduction

Task 5: Planning

Road Training Task

Fig. 3. The virtual reality (VR) training tasks. The training tasks developed for the current trial were designed to mimic the complex demands of everyday life. Five tasks are set in a virtual supermarket where the participant must collect products from the middle shelf (see Fig. 4). The products to be collected vary depending on the particular task. In the road task, participants hit virtual balls bouncing in space as they walk rapidly down a virtual road. Task difficulty is manipulated by incrementally adjusting the load/complexity of the cognitive task or the speed of the visual flow/treadmill. For details on the individual tasks, refer to Table 2 and Supplementary Material 2.

3.1. Benefits of cognitive training

In seminal work [45], degradation of myriad aspects of brain function in older adults and rats was reversed by brain training. In this regard, with a limited amount of training on a speeded, divided attention task, the older adult participants in the randomized controlled Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial showed a variety of long-term benefits, including many relevant to

driving performance (e.g., [46]), as well as everyday functional abilities (e.g., [19]), depression onset, self-rated health, quality of life [47,48], and most notably, dementia onset [49]. Specifically, speed of processing training conferred protection against dementia, such that these participants were 33% less likely than controls to develop dementia over 10 years [49]. Further, dementia risk was reduced in a dose-dependent manner, such that dementia incidence was 14% among controls, 12% among those
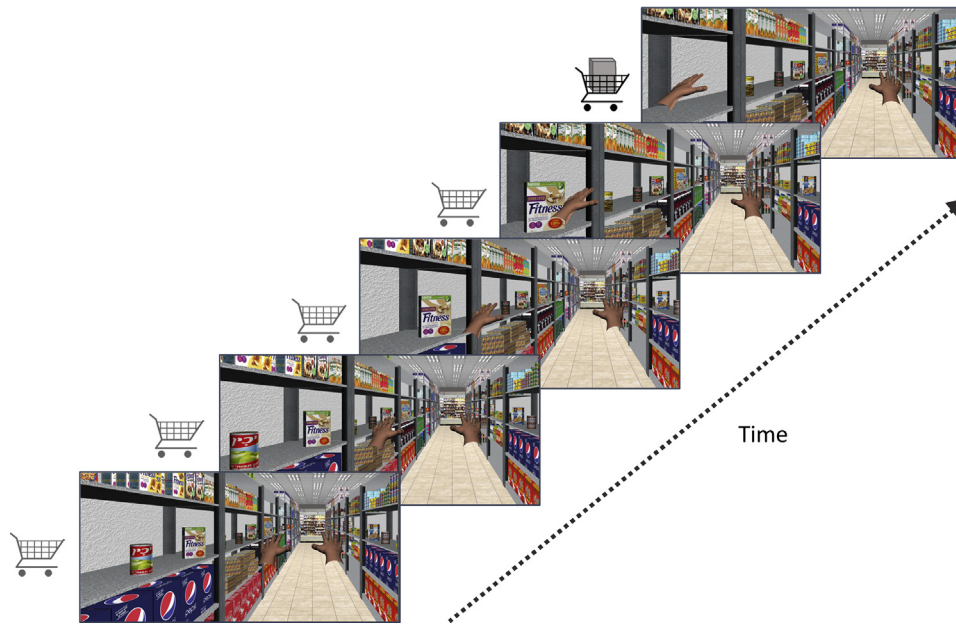
Fig. 4. Product collection process in supermarket virtual reality (VR) training tasks. To collect a product during the five supermarket VR training tasks (Table 2; Fig. 3), the participant moves the virtual hand until touching it (fourth frame), at which point the product disappears from the shelf (fifth frame), indicating that it has been successfully collected.

completing 10 or fewer sessions, and 8.2% among those who completed 11–14 training sessions, a reduction of 48% risk. This work is critical for demonstrating the prophylactic feasibility of brain training; more engaging and ecologically relevant VR training may lead to even greater risk reduction as well as broader and more robust transfer to everyday activities.

In the study by Chapman et al. [13], cognitive training in healthy older adults led to an increase of up to 12% in CBF. Interestingly, a subsequent study in healthy older adults (ages 56–75 years) found that cognitive training benefited executive function, whereas physical training benefited memory. Accordingly, the cognitive training group showed increased CBF in prefrontal and middle/posterior cingulate cortices, and those in the physical training group had higher hippocampal CBF, with no change in cerebral vascular reactivity [43]. As training in the present study is primarily cognitive (gait speed of 0.4–0.8 m/s to minimize physical exertion) and the tasks load primarily on executive functions, the prior work suggests that we may find significant benefit both behaviorally and in CBF. However, the concurrent treadmill walking in our study may confer additional or distinct benefit as compared with pure cognitive training, consistent with recent findings in adults at high fall risk with various motor and cognitive deficits, in which combined cognitive training and treadmill walking led to reduced fall rates and better obstacle avoidance (a task involving problem solving, response inhibition, and attention [50]) relative to cognitive and treadmill training separately [44].

We hypothesize that compared with the control groups, the experimental group (Group 1, VR + T) will show the most improvement in memory and the largest increase in CBF following training. Similarly, we expect more robust maintenance of these short-term gains in Group 1, the experimental group. Notably, the literature suggests that a training regimen like ours that is adaptive and consists of at least 10 intervention sessions is most likely to transfer to everyday functioning [20]. If effective, this trial may help define a new prophylactic paradigm for AD, adaptable for home-based application in high-risk individuals.

3.2. Unique advantages of VR training

Advances in computerized cognitive training and VR technology suggest that a VR-based approach to cognitive training may be promising, and a combined cognitive-motor approach may augment or accelerate improvement. VR can be operationalized as an interactive simulation that affords the user an opportunity to perform in an environment similar to a corresponding physical environment. VR uses computer technology to reproduce environments, situations, or objects that are comparable to those in the real world. Moreover, VR encompasses features of adaptability/personalization, ability to synchronously train motor and cognitive processes, multisensory feedback, real-time rewards, and enhanced motivation. As it mimics real life, VR training is ecologically valid (see Introduction), and the training is intensive in that the participant feels immersed in the VR environment (i.e., sense of presence) [51]. Greater engagement coupled with ecological validity makes VR training a prime candidate for transfer of training gains to daily activities [25]. Additional advantages of VR are improved

standardization and monitoring of participant responses, as well as ease of use and safety [24,52]. The suitability of VR for the assessment and treatment of cognitive and motor deficits has been demonstrated in a variety of patient groups [53]. Thus, VR may represent the frontier of cognitive training.

3.3. Virtual supermarket

The ecological validity of a virtual supermarket has been demonstrated by transfer of benefit to real-world functioning [54]. Tasks implemented in a daily functional environment like a virtual supermarket require the participant to plan, organize, problem solve, and multitask in a visual spatial context. Shopping is particularly relevant to autonomous daily living [55]; and in the context of aging, shopping may be regarded as one of the most important activities to maintain and/or regain independent daily functioning. Additional background supporting our choice of a VR supermarket is provided in Supplementary Material 2.

3.4. Limitations

As this is a relatively small pilot study to evaluate the efficacy of a novel VR-based cognitive-motor intervention, conclusions must be tempered and will require confirmatory full-scale clinical trials. Still, our sample size calculations are conservative and should allow detection of even small effects. By adopting an ITT approach, we hope to mitigate potential bias and loss of statistical power attributable to dropouts and noncompliance. At the same time, ITT may attenuate significant effects, and therefore, we will also run a per-protocol analysis limited to compliant participants with complete data. The intensive nature of the training and the extended duration of the training period may pose particular challenges to compliance. However, by recruiting participants who live in proximity to the training site and emphasizing the need for diligence in completing the assessments and training sessions, we aim to maximize compliance. Furthermore, the training is designed to encourage compliance and reduce fatigue by alternating among the various tasks, both within and across sessions. Also, training tasks are designed to promote incremental progression to more difficult levels, ensuring continuous task engagement, even for good performers. Potential experimenter bias is a limitation inherent in our design, though primary and secondary outcomes will be collected by blinded assessors. Despite our best efforts, scheduling constraints may require follow-up assessments to be administered at a different time of day than the baseline assessment, representing a potential confound. If necessary, we will attempt to control for such discrepancies in our statistical models. Prevalence of cybersickness during VR exposure is another potential limitation [56], but our VR tasks are nonimmersive and designed to involve slow-paced, level walking, which we expect to minimize

likelihood of cybersickness [57]. Possible technical issues with the apparatus (e.g., treadmill, motion capture cameras, and treadmill-VR synchronization) represent a limitation that we have mitigated by extensive field testing. In addition, the VR systems are stable and reliable in routine clinical use at our center. Poor effort during the training sessions represents yet another potential confound. To address this limitation, we collect effort ratings from the experimenter and operator that can be entered in the statistical models. Generally, the study is limited by a relatively brief follow-up period (i.e., 6 months) and no direct test of actual real-world function [31]. Provided that efficacy of our cognitive-motor training program is borne out by this initial study, follow-up studies should incorporate longer follow-up and measures of participant proficiency in daily activities (related and unrelated to the training tasks).

4. Summary

In conclusion, the design of the present trial builds on prior work in multiple disciplines, including cognitive training and VR, with the aim of devising and validating a protocol that heightens interventional efficacy, particularly by using a 12-week, 24-session multidomain, multimodal cognitive-motor regimen including treadmill walking. With engaging VR paradigms that mimic real life, we aim to leverage neuroplasticity to build cognitive reserve and enhance transfer of training gains to daily activities in a manner impossible with conventional cognitive training. The choice of cognitive and neurobiological (CBF) primary outcomes, coupled with immediate and longer-term follow-up, positions the study to make a significant contribution to addressing the urgent need for intervention in individuals at high risk for AD well before symptom onset. Indeed, if the results of the present trial substantiate the efficacy of a VR-based cognitive-motor training program, the regimen has the potential to become a standard of care, demonstrating the unique advantages of VR for staving off neurodegeneration characteristic of AD and the associated deterioration in daily functioning and quality of life.

authors have read and approved the final manuscript. The study data set will be made publicly available on completion of the study.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.trci.2018.02.005.

RESEARCH IN CONTEXT

1. Systematic review: Pharmacologic treatments in symptomatic Alzheimer's disease (AD) have had limited efficacy, spurring interest in nonpharmacologic potentially preventive therapies. Cognitive training shows promise but does not readily transfer to real life. Virtual reality cognitive-motor training mimicking daily activities is a viable alternative, but there are no trials in cognitively normal middle-aged individuals at high AD risk.

2. Interpretation: When completed, this randomized controlled trial will provide evidence for the ability of 12-week virtual reality cognitive-motor training to improve cognitive/neurobiological function in healthy middle-aged adults with an AD parental history. The design will facilitate evaluation of training and maintenance gains for combined virtual reality cognitive-motor relative to unimodal training.

3. Future directions: Findings will inform the design of full-scale trials to maximize potential improvement in cognitive/neurobiological function relevant to daily activities and the prospect of forestalling AD-related neurodegeneration. Ultimately a new standard of care may emerge—a prophylactic regimen adaptable for home-based application in high-risk individuals.

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