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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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Q2 **Abstract**

Background: 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 cerebral blood flow (from arterial spin labeling) at baseline, immediately after training (training gain), and 3 months after 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.

The authors declare that they have no competing interest.

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Q3 **Trial registration:** ClinicalTrials.gov Identifier: NCT02832921. Registered 7/11/2016.

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1. Background

Dementia prevalence roughly doubles every 4–5 years from age 65 years, so that more than one-third of individuals aged over 85 years 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]. Furthermore, 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 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 mild cognitive impairment 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