Cognitive remediation to enhance mobility in older adults: the CREM study

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Practice points

- Given the major medical and socioeconomic consequences of disability in seniors and the low compliance with recommended treatments such as physical exercise, investigation of alternate strategies to improve mobility is a vital need.
- We present a randomized clinical trial to test the efficacy of a computerized cognitive remediation program on improving mobility in sedentary seniors, a group at an especially high risk for disability.
- The primary outcome is postintervention change in gait speed measured during normal-pace walking (simple locomotion) and walking-while-talking (complex locomotion) conditions.
- This novel approach to improving mobility has the potential to shift treatment paradigms in the field of disability by introducing cognitive approaches to mobility that can be applied to prevention and rehabilitation in diverse settings.

Mobility disabilities represent the most prevalent disability among seniors. Emerging evidence indicates that executive functions play an important role in maintaining mobility. However, the use of cognitive remediation programs to enhance mobility has not been investigated in a full-scale randomized control trial. The CREM study is a single-blind randomized control trial to examine the effect of computerized cognitive remediation versus computer-based health education training on mobility in 420 seniors. The primary outcome is change in gait speed during normal walking and walking-while-talking conditions from baseline to postintervention. Secondary outcomes are change in mobility, mobility-related cognitive processes and neuroplasticity. Results of this study will fill an important gap in the efficacy and feasibility of cognitive remediation to improve mobility in seniors.

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Mobility disability, defined as severe difficulty or inability to walk a quarter of a mile or climb stairs, is associated with loss of independence and is an independent predictor of mortality in older adults [1,2]. While exercise is recommended to prevent mobility disability and improve gait speed [3], <10% of US seniors exercise at recommended levels [4] and 25% are inactive [1], necessitating exploration of new approaches to improve mobility.

Intact gait control requires efficient integration of many neural systems, namely motor, sensory and cognitive, including multiple cognitive subsystems (i.e., memory, attention and executive functions [EFs]). EFs are a set of higher cognitive processes that modulate behavior, facilitate allocation

KEYWORDS

- clinical trial protocol
- cognitive remediation
- executive function • gait velocity

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of attention during simultaneous tasks (divided attention) and afford adaptation to changing situations [5]. Impairments in EFs, particularly on measures of attention are associated with poor motor function [6]. Several pilot studies have shown that motor training with cognitive components improves mobility and balance in cognitively normal as well as impaired seniors [7–16]. Cognitive training of EF and attention has also been shown to improve both cognition and functional status in seniors [17]. In the ACTIVE study, attention and EF training resulted in improved activities of daily living and driving skills [17].

The term ‘cognitive training’ typically involves guided practice on a set of standard tasks designed to improve particular cognitive functions, such as memory, attention or problem solving [18]. The focus of training is on near transfer resulting in improved performance on the specific domain trained, and not on far transfer of effects to other behaviors or skills not directly trained, such as improving locomotion. The focus of cognitive remediation, as described in this clinical trial protocol, is to indicate cognitive exercises with an aim at improving attention and EFs where the expected result is a positive impact (far transfer) on mobility deficits affecting everyday life.

Results from our pilot study demonstrated for the first time that frail seniors who completed a computerized cognitive remediation program targeting EFs improved walking during simple (normal-pace walking [NPW]) and complex locomotion (walking-while-talking [WWT]) conditions compared with baseline (i.e., far transfer effects), as well as compared with frail seniors in a usual care group [19]. Our pilot results were independently replicated in several small pilot studies in frail seniors [20], Parkinson’s disease patients [21] and community-dwelling black older adults [22]. However, these studies were limited by small samples and focus on specific minority and disease groups [8–14,20,23]. To address this knowledge gap we are conducting a single-blind randomized control trial (RCT) over 5 years to test the effect of a commercially available internet-based cognitive training program (CogniFit Ltd; Israel), which offers programs specifically tailored for adults 55+ years as well as targeted training in EFs. Once complete, the RCT described in this protocol will provide a rigorous test of the efficacy of an innovative cognitive remediation approach to improving

mobility in vulnerable frail seniors as well as provide insights into the underlying biological mechanisms. Herein, we describe the protocol of our proposed clinical trial.

Hypothesis

Our hypothesis is that mobility and EFs are linked via frontal cortices, basal ganglia and their connections; and that neuroplasticity will occur in these areas in response to computerized cognitive remediation. The primary goal of the study is to compare the effect of an 8-week individualized computerized cognitive remediation program (experimental condition) versus interactive computerized health education program (control condition) on simple and complex locomotion measured by gait speed during NPW and WWT conditions in 420 seniors. As secondary outcomes, we will examine effects of the computerized cognitive remediation program on an expanded mobility battery and other quantitative gait variables during NPW and WWT conditions since mobility limitations other than gait speed [24] have been shown to increase risk of disability and falls [25]. Additional secondary outcomes include neuroplasticity measured by functional near-infrared spectroscopy (fNIRS), an innovative technology that enables cortical imaging during walking [26], and other mobility related cognitive processes such as speed of processing, attention and divided attention. We will also explore durability of cognitive remediation effects on these measures at 6 and 12 months postintervention.

Methods

• Study design

We are recruiting 420 sedentary seniors to participate in a single-blind RCT. Participants are randomly assigned to either an 8-week computerized cognitive remediation program or an interactive computerized health education program (210 per group). A computer familiarization session is administered to all participants prior to starting the RCT, regardless of group assignment.

• Screening, recruitment & randomization

Samples of individuals 70 years and over from Bronx and Westchester counties are being recruited using public records such as voter registration lists and through advertisements at local clinics and community organizations. Screening is conducted in two phases (telephone and clinic

visit). A letter explaining our study is sent followed by a structured telephone interview a few days later. Those expressing interest are screened with the Memory Impairment Screen [27] and AD8, a brief informant questionnaire [28], to exclude dementia. The Memory Impairment Screen is a brief four-item test which can be administered over the telephone and uses the same principles as the Free and Cued Selective Reminding Test [29]. It has a sensitivity of 85% and specificity of 86% for diagnosing dementia [27]. Potential recruits who meet eligibility criteria on the telephone are invited for in-person screening. Participants are randomized into control or experimental groups after completion of all baseline assessment measures and signing informed consent.

For the purpose of this study we chose to focus first on the efficacy of secondary prevention using a computerized cognitive remediation program in seniors at high-risk for disability. Eligible persons are 70 years and older; ambulatory with or without an assistive device; at high risk for disability defined using a short physical performance battery (SPPB) cut score of ≤ 9 [30] corresponding to frail range; and have a gait speed of ≤ 100 cm/s [31]. **Box 1** includes a full list of inclusion and exclusion criteria. Thus, final eligibility is determined based on performance on mobility tasks and questionnaires during the in-house screening visit. All study procedures have been approved by the Albert Einstein College of Medicine Institutional Review Board as well as the National Institute on Aging appointed Data and Safety Monitoring Board of this study. Prior to the onset of this RCT, all study staff and key personnel took the courses from the Collaborative Institutional Training Initiative.

• Study measures

A complete list of all evaluation tools conducted at baseline and follow-up visits is delineated in **Table 1**, and the primary outcomes are described below. These measures also serve to define the baseline characteristics of the groups, assess confounding and as covariates in analyses. To reduce bias, we have employed a number of methods in addition to randomization including concealing treatment allocation until the participants are enrolled into the trial [32]. Intervention and control programs are conducted at nonoverlapping times. Participants and study staff from different groups are kept

separate and instructed not to disclose group assignments or details of interventions.

• Primary outcomes

Normal pace walking

Gait speed was recommended by the US FDA as one of the two functional tests to be used as outcomes in pharmacological trials because of its good validity, reliability, sensitivity to change and predictive validity for multiple adverse outcomes [33]. Research assistants conduct gait evaluations using a computerized mat ($180 \times 35.5 \times 0.25$ inches) with embedded pressure sensors (GAITRite; CIR Systems, PA, USA). Participants are asked to walk on the mat at their 'normal walking speed' in a quiet and well-lit room. Our primary outcome is gait speed (cm/s). However, multiple gait parameters are obtained and available for analyses [34]. We have reported excellent test–retest reliability of gait speed on GAITRite ($\kappa > 0.9$) [35].

Walking-while-talking

The WWT paradigm has been widely studied as a real world test of divided attention to examine cognitive-motor interactions. The WWT test is a novel, reliable and ecologically valid mobility measure developed by our group [36–38]. Our studies have established the incremental validity of WWT over NPW speed for predicting adverse outcomes such as falls, frailty and disability [36,37]. Participants are instructed to walk on the mat, as described above, while performing a cognitive interference task, which is reciting alternate letters of the alphabet starting with the letter 'A'. They are instructed to pay equal attention to walking and talking to minimize task prioritization effects [36,38]. The number of errors and correctly recited alternate letters are recorded. There was good inter-rater reliability in our previous studies ($r = 0.602$) [36].

• Other study outcomes

Secondary outcomes include the SPPB, mobility-related cognitive processes assessed by a battery of validated tests, quantitative gait variables other than speed and neuroplasticity measured by fNIRS. Details regarding fNIRS are provided in our recent publications [39,40]. In brief, fNIRS measures change in cortical hemodynamic response by monitoring changes in light intensity within near-infrared range [39]. fNIRS can detect brain activation changes during walking in the

Box 1. Eligibility criteria.**Inclusion criteria**

- Adults aged 70 years and older, residing in the community
- Plan to be in area for next year
- Able to speak English at a level sufficient to undergo our cognitive assessment battery
- Ambulatory. Participants are classified as 'nonambulatory' if they are unable to leave the confines of their home and attend a clinic visit
- Gait speed during normal-pace walking ≤ 100 cm/s
- Short physical performance battery score less than or equal to nine

Exclusion criteria

- Presence of dementia identified by any one of the following: Memory Impairment Screen of less than 5, Alzheimer's disease-8 greater than or equal to 2 or dementia diagnosed by baseline cognitive assessment
- Serious chronic or acute illness such as cancer (late stage, metastatic or on active treatment), chronic pulmonary disease on ventilator or continuous oxygen therapy or active liver disease
- Mobility limitations solely due to musculoskeletal limitation or pain (e.g., severe osteoarthritis), which prevent subjects from completing mobility tests. Presence of arthritis will not be used to exclude subjects if they can complete the mobility tasks
- Any medical condition or chronic medication use (e.g., neuroleptics) that will compromise safety or affect cognitive functioning or terminal illness with life expectancy < 12 months
- Presence of progressive, degenerative neurologic disease (e.g., Parkinson's disease or amyotrophic lateral sclerosis)
- Hospitalized in the past 6 months for severe illness or surgery that specifically affects mobility (e.g., hip or knee replacement) and that prevents subjects from completing mobility tests or plans for surgery affecting mobility in the next 6 months
- Severe auditory or visual loss
- Active psychoses or psychiatric symptoms (such as agitation) noted during the clinic visit that will prevent completion of study protocols
- Living in nursing home
- Participation in other intervention trial or observational studies

prefrontal cortical regions and handle motion artifacts [41,42]; overcoming limitations of conventional imaging [43]. Oxygenated hemoglobin (HbO_2) and deoxygenated hemoglobin have characteristic optical properties in visible and near-infrared light range allowing the change in concentration of these molecules during neurovascular coupling to be measured using optical methods. fNIRS measure changes in the ratio of HbO_2 to blood volume in order to assess brain activity through intact skulls in adults [44]. The objective is to identify patterns of activations and alterations following the cognitive remediation program to provide insights into neuroplasticity. Initially, the fNIRS device used in our setting was successfully implemented in a walking experiment demonstrating a differential pattern of increased HbO_2 levels in the prefrontal cortex (PFC) in WWT compared with NPW in young and old participants [26]. In subsequent fNIRS studies, we have demonstrated that internal consistency of HbO_2 measurements, determined by split-half intraclass correlations, was excellent

for NPW (0.830) and WWT (0.849) [39]. Furthermore, we have replicated the original finding demonstrating increased activation levels in the PFC in WWT compared with NPW in a large cohort of older adults [39], elucidated the role of the PFC in cognitive control of attention-demanding locomotion in groups stratified by the presence of peripheral and central gait abnormalities [45] and reported on the effect of mild Parkinsonian symptoms on the involvement of the PFC in balance [46].

The durability of the cognitive remediation program effects on gait speed during NPW and WWT conditions measured at 6 and 12 months postintervention will also be recorded. Additional secondary and tertiary outcomes are presented in Table 1.

• Study interventions

Computerized cognitive remediation program CognitoFit, a commercially available internet-based cognitive training software, provides specialized training across multiple domains

Table 1. Outcome assessment schedule.

Assessments	Preintervention	Postintervention		
	Baseline	Week 9	6 months	12 months
Primary outcomes				
NPW gait speed (cm/s) [†]	x	x	x	x
WWT gait speed (cm/s) [†]	x	x	x	x
Secondary outcomes				
Short physical performance battery (range: 0–12) [†]	x	x	x	x
Quantitative gait performance other than speed [†]	x	x	x	x
Stair climbing [§]	x	x	x	x
Disability scale [§]	x	x	x	x
Functional near-infrared spectroscopy [‡]	x	x	–	–
Trail-Making Task Forms A and B [§]	x	x	x	x
Control Oral Word Association Test [†]	x	x	x	x
WAIS [¶] Digit Symbol Substitution Test [†]	x	x	x	x
Flanker task [‡]	x	x	x	x
Tertiary outcomes				
Geriatric Depression Scale (30 item) [§]	x	x	x	x
Falls self-efficacy [§]	x	x	x	x
12-Item Short Form Health Survey [†]	x	x	x	x
Fall history (number of falls) [§]	x	x	x	x
Additional neuropsychological measures ^{##}	x	x	x	x
Other study measures				
Demographic information	x	–	–	–
Memory Impairment Screen [†]	x	–	–	–
Ascertain dementia 8-item informant questionnaire [§]	x	x	x	x
Blessed Orientation-Memory-Concentration Test [§]	x	x	x	x
Medical history and medication inventory	x	–	–	–
Physical examination ^{††}	x	x	x	x
Unipedal stance [†]	x	x	x	x
Knee extensor [†]	x	x	x	x
Grip strength [†]	x	x	x	x
CogniFit assessment [†]	x	x	x	x
Transtheoretical model	x	–	–	–
Beck Anxiety Inventory [§]	x	x	x	x
Brief Fatigue Inventory [§]	x	x	x	x
Big 5	x	–	–	–
Medical Outcomes Study Social Support Survey [†]	x	–	–	–
Alcohol/Smoking Consumption Inventory	x	–	–	–
Medical Outcomes Study Pain Measures [§]	x	x	x	x
Activity Balance Confidence Scale [†]	x	x	x	x
Instrumental activities of daily living [§]	x	x	x	x
Duke Activity Status Index [†]	x	–	–	–
General mobility questionnaire	x	x	x	x
Marlowe–Crown Scale	x	–	–	–
[†] Higher scores indicate better performance. [‡] Depends on condition and/or variable. [§] Lower scores indicate better performance. [¶] Wechsler Adult Intelligence Scale. ^{##} Repeatable battery for assessment of neuropsychological status figure copy and delay figure copy measures; Wide Range Achievement Test & Wechsler Test of Adult Reading; Hopkins Verbal Learning Test; Boston Naming Tests (15-item). ^{††} Physical examination includes height, weight, blood pressure, auditory and visual measurement. NPW: Normal pace walking; WWT: Walking-while-talking.				

Table 1. Outcome assessment schedule (cont.).

Assessments	Preintervention	Postintervention		
	Baseline	Week 9	6 months	12 months
<i>Other study measures (cont.)</i>				
Rosenberg Self-Esteem Scale ⁵	x	–	–	–
CHAMPS [†]	x	x	x	x
Physical activity monitoring – accelerometer [‡]	x	–	–	–
⁵ Higher scores indicate better performance. [†] Depends on condition and/or variable. [‡] Lower scores indicate better performance. [§] Wechsler Adult Intelligence Scale. [¶] Repeatable battery for assessment of neuropsychological status figure copy and delay figure copy measures; Wide Range Achievement Test & Wechsler Test of Adult Reading; Hopkins Verbal Learning Test; Boston Naming Tests (15-item). ^{**} Physical examination includes height, weight, blood pressure, auditory and visual measurement. NPW: Normal pace walking; WWT: Walking-while-talking.				

including naming, memory, attention, perception and coordination, to a name a few. While Cognifit offers a wide array of specialized training, for the purposes of our study, we employed two specific training programs tailored for adults of age 55+ years as well as a targeted training in EFs. As described previously [19,47], each participants' individualized training plan is dependent on their performance on a baseline evaluation, which assesses cognitive processes including, but not limited to psychomotor skills, dual tasking, sustained attention, naming and working memory [47]. Based on the distribution of cognitive-test scores from the baseline CogniFit assessment, participants' cognitive abilities are divided into three categories: abilities on which the participant performed well, abilities performed in the medium range of the norm and abilities on which the participant performed low. The participant begins training on the tasks that reflect its weakest scoring ability in each category. The system is designed to calibrate the difficulty level of each task in order to moderate how challenging each subsequent task becomes. Then the system begins rotating the training tasks from a pool of tasks defined by the type of training in a way that maximizes the exposure to tasks that train the participants' weakest areas first. If a category of abilities has no new tasks, new tasks are taken from another category with the next lowest performance. This form of practice allocation continues throughout the program, so that a new task is introduced every session. It is a complex and sophisticated system, which ensures that the participant is always working within its comfort zone while simultaneously practicing its weakest abilities. Each training session includes two cognitive training tasks and one cognitive training

assessment task, which is used to choose the training tasks for the next session.

After a participant has completed three training sessions, a fourth session, which specifically targets EFs, is assigned irrespective of the baseline cognitive evaluation to ensure adequate training on EFs and related cognitive functions. Tasks in this session are designed to test areas of EF, which include but are not limited to divided attention, inhibition, updating, planning and shifting. One example of a task for areas of divided attention, response time and visual perception is the 'Traffic Manager' game. In this task, participants are shown an aerial view of several intersections with vehicles moving around the screen. They are instructed to control the traffic at different intersections by switching traffic lights from red to green by clicking on them with the mouse to avoid collisions and traffic jams. A second task called 'Cube Foundry', is a hand-eye coordination task that involves planning and spatial perception. This task instructs participants to assemble blocks of various shapes to create continuous layers in a 3D environment by moving and rotating the blocks.

Frequency & duration

Participants attend 24 training days over a period of 8 weeks for a total of 20 training hours. Each training day consists of three cognitive remediation sessions for adults 55+ years and one specialized concentration training session. Each training session is comprised of three tasks and requires about 12 min to complete; thus, total training time is on average 50 min per day. Over the 24 days, each participant will complete approximately 72 cognitive training sessions and 24 targeted EF training sessions. Noteworthy, by

the end of the 8 weeks all participants enrolled in the cognitive remediation program will complete the same number and types of scheduled and additional EF training sessions and tasks.

Interactive computerized health education program

The control program was guided by four principles: optimize participant recruitment and retention; minimal effect on outcomes as there is no evidence that health education alone improves mobility; control for computer exposure; and older adults are less inclined to continue participation if they perceive a lack of benefit.

Participants complete one 150-min session per week for a total of 8 weeks. Each session is divided into two sections: an interactive computer-based health education program; and low-intensity computer-based games that contrary to the experimental group, do not increase in intensity or complexity in order to match computer exposure time and intensity of interactions in the experimental group. Health education topics come from a large library of interactive multimedia tutorials from the Patient Education Institute [48], and include topics such as ‘Sleep Apnea in Elderly Adults’ and ‘Adult Self Care for Colds and Flu’. Participants randomized to the health education program complete the same baseline CogniFit assessment as the experimental group; however, their performance does not influence the complexity or intensity of the future low-intensity computer games, also developed by CogniFit, to avoid confounding of potential cognitive benefits of these programs. Sessions are completed on the same computer workstations as the experimental group on nonoverlapping days; one participant per computer.

Frequency & duration

The health education group attends a total of eight sessions in 8 weeks. Each session lasts 150 min, for a total of 20 h over the 8 weeks, identical in duration to the experimental group. The individualized computer-based interactive health education and low-intensity computer game classes are balanced with the intervention group in computer exposure time and amount, and quality of social contacts.

• Statistical plan

Baseline distribution of covariates will be compared with assess adequacy of randomization

of participants using appropriate graphical procedures and summary statistics.

We will employ linear mixed effects model to compare the changes in gait speed immediately postintervention (week 9) as well as at 6 and 12 months postintervention in experimental versus controls. The variance will be allowed to differ between experimental and control groups. The primary test of the effectiveness of the intervention will be change in mean pre- and postintervention gait speed during NPW and WWT conditions between the two groups. For WWT, we will also consider the change in WWT speed from normal walking (dual task cost). We will define improvers on NPW and WWT by using a cut score of 4 cm/s on these measures as described in our pilot study [19], and compare proportion of improvers versus nonimprovers in the two groups using linear mixed effects models [49].

The primary hypothesis examines change in gait speed during NPW and WWT conditions. Improvement in speed has been reported to be approximately 10 cm/s after 8–12 weeks physical exercise interventions [15]. In contrast, gait speed in the nonintervention controls shows minimal improvement [15], unchanged [3] or declined [50]. Based on these effects and results from our pilot study [19], we conservatively estimate a 5 cm/s improvement in the experimental group postintervention, which is approximately 50% of the mobility effect in physical exercise trials and less than that achieved in our pilot study (8 cm/s). This magnitude of change also corresponds to that recommended as small, but clinically meaningful change in gait in aging studies [51].

The sample size ($n = 420$) provides >80% power to detect clinically meaningful differences at significance level of 0.05. The Bonferroni correction for multiple testing was used in sample size calculations. Based on conservatively estimated standard deviations of 12 and 20 cm/s for NPW and WWT, respectively, to detect clinically meaningful differences of 5 cm/s for NPW and 10 cm/s for WWT with 80% power, at least 169 subjects per group are needed. To take into account the projected 20% dropout rate at end of intervention, 210 subjects will be enrolled per group. Assuming cumulative dropout rates of 25% at 6 months, with 210 participants per group, we will have 92 and 99% power for detecting differences of 5 and 10 cm/s in NPW and WWT, respectively. At 1 year of follow-up, assuming 30% cumulative dropout, we will have

90 and 98% power for detecting differences of 5 and 10 cm/s in NPW and WWT, respectively.

We will use intention to treat analysis, which includes all randomized participants in the groups assigned, regardless of adherence with entry criteria, whether the intervention was received, and subsequent withdrawal or deviation from the protocol [52]. Intention to treat analysis is pragmatic because it admits non-compliance and protocol deviations, and gives an unbiased estimate of the intervention effect. The linear mixed effects model is good at handling missing data due to dropout assuming a missing at random mechanism [49,53]. Mediation analysis (product of coefficients method) will be conducted to examine whether depression, psychosocial measures (mood, self-esteem and self-efficacy) as well as changes in proximal cognitive outcomes (attention and EF) mediate the effect of cognitive remediation on gait speed in NPW and WWT conditions. In addition, we will assess dose-response effects by tracking attendance and session duration for each participant.

All secondary outcomes including quantitative gait variables and gait domains, as well as SPPB scores and cognitive processes, will be analyzed using linear mixed effects models as described above [49]. In addition to PFC oxygenation levels on fNIRS, alternative measures such as areas activated, bilateral versus unilateral activation, and any reduction in activation will be considered simultaneously using linear mixed effects model. As discussed earlier, internal consistency of fNIRS measurements for both NPW and WWT is excellent [39].

A prespecified set of baseline covariates was selected to determine their influence on the treatment and include age, gender, education, chronic illnesses, cognitive test performance, pain, arthritis and cardiac fitness measured using the Duke Activity Status Index [54]. This method is preferred to adjusting for covariates that are imbalanced between treatment groups using significance testing, because it is possible for a covariate to have a strong confounding effect even if the difference in the average value of that variable between the parallel arms is not significant. We will conduct assessments on many of these covariates postintervention and monitor any change over the intervention period and analytically account for their effects by including these measures (baseline levels as well as change) in linear mixed effect models to control for possible confounding.

• Data management & quality control

The information collected from each participant at their screening and baseline visits, as well as at their postintervention visits at 9 weeks, 6 and 12 months is entered by trained research assistants and maintained in a Database Manager System programmed using Microsoft Access 2010 relational database software. The system is designed with automated checks for ranges of values and logical validity of data entered and imports data directly from the computerized assessment files. Imported data files are checked for data integrity and flagged in the event of inconsistent or missing data. Weekly progress reports are generated to track the number of participants that have been screened and enrolled as well as how many have dropped and the reasons for dropping. Analyses and data monitoring reports are performed and developed by the designated study statistician for the Data and Safety Monitoring Board meetings on a biannual basis.

Discussion

To our knowledge, this is the first full scale RCT proposed to test the efficacy of EF-targeted cognitive remediation on mobility, specifically gait speed during simple and complex locomotion. Our cognitive remediation approach is corroborated by independent pilot studies in small samples of older adults and Parkinson's disease patients [20–22]. The computerized cognitive remediation approach is also supported by studies that have shown that cognitive-motor training as well as dual-task training improves mobility and balance [10,15–16]. If successful, this approach will help shift paradigms in the disability field by introducing cognitive approaches to mobility that can be applied to prevention and rehabilitation. Even if negative, important insights will be gained on the effect of computerized cognitive remediation on a wide array of secondary mobility and cognitive measures, test feasibility of a computerized cognitive remediation program, as well as offer the potential to conduct future biological and genetic investigations of neuroplasticity.

Other investigators have shown that training older adults on similar WWT tasks translates into clinically relevant outcomes such as reduced falls, better balance or improved function [7,14]. Hence, establishing the effects of cognitive remediation on our co-primary outcome of WWT speed alone could be of high clinical

impact and relevance, irrespective of its effect on NPW speed.

Mobility disability is the most prevalent type of disability in older Americans [55]. The computerized cognitive remediation approach may be an effective, accessible and low-risk method to improve mobility-related cognitive functions in vulnerable seniors. Demonstrating mobility gains with computerized cognitive remediation will open new or supplemental treatment options for the majority of US seniors who do not engage in physical exercise due to physical, motivational or socioeconomic reasons. This 'proof of concept' RCT will provide scientific and biological support for a future multicenter RCT to examine the combined effect of computerized cognitive remediation and physical exercise on mobility, as well as the long-term

impact of computerized cognitive remediation programs on falls and cognition in healthy, frail and Mild Cognitive Impairment patient populations.

Disclosure

The CREM study has been registered on www.clinicaltrials.gov – identifier: NCT02567227.

Financial & competing interests disclosure

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