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Web-enabled Conversational Interactions as a Means to Improve Cognitive Functions: Results of a 6-Week Randomized Controlled Trial

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Abstract

INTRODUCTION—Increasing social interaction could be a promising intervention for improving cognitive function. We examined the feasibility of a randomized controlled trial to assess whether conversation-based cognitive stimulation, through personal computers, webcams, and a user-friendly interactive Internet interface had high adherence and a positive effect on cognitive functions among older adults without dementia.

METHODS—Daily 30 minute face-to-face communications were conducted over a 6-week trial period in the intervention group. The control group had only a weekly telephone interview. Cognitive status of normal and MCI subjects was operationally defined as Global Clinical Dementia Rating (CDR) = 0 and 0.5, respectively. Age, sex, education, Mini-Mental State Exam and CDR score were balancing factors in randomization. Subjects were recruited using mass-mailing invitations. Pre-post differences in cognitive test scores and loneliness scores were compared between control and intervention groups using linear regression models.

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Data Access and Responsibility: The principal investigator, Hiroko Dodge, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Potential conflicts of interest: None

RESULTS—Eighty-three subjects participated (intervention: n=41, control: n=42). Their mean (std) age was 80.5 (6.8) years. Adherence to the protocol was high; there was no dropout and mean % of days completed out of the targeted trial days among the intervention group was 89% (range: 77%–100%). Among the cognitively intact participants, the intervention group improved more than the control group on a semantic fluency test (p=0.003) at the post-trial assessment and a phonemic fluency test (p=0.004) at the 18th week assessments. Among those with MCI, a trend (p=0.04) of improved psychomotor speed was observed in the intervention group.

DISCUSSION—Daily conversations via user-friendly Internet communication programs demonstrated high adherence. Among cognitively intact, the intervention group showed greater improvement in tests of language-based executive functions. Increasing daily social contacts through communication technologies could offer cost-effective home-based preventions. Further studies with a longer duration of follow-up are required to examine whether the intervention slows cognitive declines and delays the onset of dementia.

Keywords

Social Engagement; Conversational Interaction; Internet; Communication Technology; Oregon Center for Aging and Technology (ORCATECH); Randomized controlled clinical trial (RCT); prevention study; Mild Cognitive Impairment (MCI)

Introduction

Almost two decades ago Rowe and Kahn [1] suggested the key elements of successful aging, which included: (1) a low probability of disease, (2) high levels of function, and (3) active engagement with life. The definition of “active engagement with life” varies across individuals and cultures. In epidemiological studies, self-reported social engagement – one component of active engagement with life - has been extensively examined in relation to cognitive well-being. However, no set of standard activities were used across studies. Various activities were included such as reading, playing games or musical instruments, going to classes, doing crosswords, playing cards, going to the cinema/theatre (often categorized as cognitive activities), visiting friends or relatives and attending organizations (as social activities), and dancing and walking (as physical activities). Furthermore, larger social networks (a structural aspect of social connectedness) were also found to be protective against dementia [2–12]. It is yet to be known which factors of social engagement or networking might reduce the risk of dementia. For example playing games is often categorized as an intellectual/cognitive stimulating activity, but playing games with someone requires social interaction. Is it the social interaction, or playing the game itself, which is protective against cognitive decline? Randomized controlled trials with clearly specified element(s) and doses of social engagement are needed to clarify the *mechanism* of the protective function of social engagement and networks on cognitive function and, ultimately to translate this knowledge into actionable programs.

One integral component of being socially active is the ability to interact with others. Linguistic ability is known to be highly correlated with late-life changes in cognition in healthy older adults as well as those with dementia [13–15]. Furthermore, psychological studies suggest that the task of conversation is highly cognitively stimulating. That is,

conversations require attention, working memory and the organization and control of thought (executive functions), as well as social cognition to understand others' intentions and feelings [16, 17], in addition to linguistic ability. To develop a prevention approach against cognitive decline, that can be easily adapted to the oldest old and those with Mild Cognitive Impairment (MCI) or with low motivation or apathy, we developed a randomized controlled clinical trial (RCT) focusing on conversation. We examined whether face-to-face conversation - a core component of social interaction - can enhance cognitive functions by stimulating social cognition. To facilitate efficiency and quantification of outcomes, we utilized contemporary technologies, including PCs, webcams and the Internet, to deliver the conversational interventions. Based on epidemiological and psychological literature discussed above, we hypothesized that our trial intervention would lead to improved attention, executive function, verbal fluency and memory, i.e., domains frequently impaired among AD patients. The objectives of this study were to assess feasibility, adherence and post-trial changes in cognitive functions and loneliness. This paper presents the protocol and the results of the above RCT.

METHODS

Subject Recruitment

Between November 2011 and August 2012, we distributed 2000 survey questionnaires targeting those living in retirement communities and senior centers located in the Portland, Oregon metropolitan area, within an approximately one hour commute from Oregon Health & Science University (OHSU), Portland, Oregon, USA. Sixteen retirement communities and senior centers that cover a wide range of socioeconomic status (including low income household retirement communities designated by the municipal government), and that had agreed to collaborate for research studies with OHSU, were included. We conducted information sessions at each community and center explaining the upcoming trial. The survey was distributed at the conclusion of the information session and also distributed by mail through the retirement communities and senior center administrative offices.

In the survey, we collected information including demographics, types and frequencies of social engagement, loneliness, and PC usage. After a brief introductory paragraph describing our trial, we asked individuals whether they would be interested in participating in the trial, and, if so, to provide their contact information. They were informed that they could decline to participate any time after hearing about the study. The main information collected in the survey is listed in Table 1 (a).

Randomization

We invited those who provided their contact information to participate in in-person screening interviews (Figure 1). The information collected at the interview is listed in Table 1 (b), and study inclusion/exclusion criteria are listed in Table 2. Trained research associates conducted the interviews. Subjects were randomly assigned to either the control or intervention group with balancing factors of age (3 groups: 65–74, 75–84 and 85 years and older), sex, Clinical Dementia Rating Scale (CDR 0 or 0.5) [18], MMSE scores (3 groups: below 24, 24–26, 27 and above) and years of education (3 categories: less than 12, 12–15,

and 16 or more). Cognitive status of normal and MCI subjects was operationally defined as Global Clinical Dementia Rating (CDR) = 0 and 0.5, respectively. A modified randomized minimization algorithm was used [19].

Duration and protocol of the conversational trial

The intervention group engaged in face-to-face conversations with trained interviewers five days a week (Monday – Friday) for 6 weeks via a dedicated video-chat-enabled PC provided to each subject. Each conversational session was designed to last between 30 and 35 minutes. The control group received weekly telephone calls to assess their social engagement activities during the previous week (i.e., no PC/internet provided). If participants in the control group were already using a PC before the trial, they were allowed to continue. After randomization, within two weeks before the start of the conversational intervention, we administered a comprehensive neuropsychological test battery. Post-trial (within two weeks after completion of the trial) and end-point (12 weeks after the post-trial assessment or 18 weeks from baseline) assessments were conducted to examine the post-trial effect and its durability.

CDR assessment

The CDR assessment was conducted by trained research nurses in a standardized manner including information from informants [18].

Development of a user-friendly web-enabled conversational system

We created our own version of a chat system where participants did not need to know how to use a computer, other than to touch the touch screen of a computer preconfigured to receive calls and automatically begin the conversational session. The study computer was enabled to record the trial sessions and store encrypted audio data automatically. Technical support personnel visited each participant's home and set up the equipment.

Development of conversational protocol

Conversation requires synthesis of multiple cognitive functions. In order to present an understandable story or "rationality", the speaker must organize his/her ideas and thoughts, while paying attention to the other's response. That is, attention, executive function and abstract reasoning are simultaneously engaged. In order to take full advantage of this synthetic aspect of conversation, we placed an emphasis on spontaneous responses rather than structured answers (i.e., the participants had to organize their thoughts). We used unstructured conversations such as talking about participants' "childhood memories", "hobbies", "siblings and parents", and "movies/books". A topic that engages one participant's attentiveness and interest may not do the same for others. Nevertheless, we attempted to create a degree of standardization by using a daily picture prompt to stimulate the conversation. For example, we presented Norman Rockwell paintings or pictures of famous events (e.g., the first moon landing) on screen as evocative pictures and asked the participant about what was going on in the picture. Then we asked whether the subject could connect their experience with the story seen in the picture. We aimed to primarily engage

executive functions, attention, semantic memory, and abstract reasoning with this type of a semi-structured session approach.

Standardization of interviewers

Interviewers practiced conversational sessions with our staff members and elderly volunteers to standardize their skills before the trial began. We also recorded each conversational session to monitor their interview quality. Permission for recording each trial session was included in the consent form. Additionally we randomly selected three recorded conversational sessions per interviewer, one session each during the baseline, 3rd and 6th week and had them transcribed by a single professional transcriber. The proportion of words spoken by interviewers was used as a tool to standardize conversational sessions; the deviation observed in the number of spoken words contributed by the participant/interviewer during recorded conversations served as a metric to improve standardization of individual interviewer's interview skills. Interviewers were blinded to the cognitive status of the participants.

Primary outcome: cognitive function

We administered the following neuropsychological tests: (1) Immediate Memory: the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Learning [20]; (2) Delayed Memory: CERAD Word List Delayed Recall [20]; (3) Language: composite of verbal fluency for letters (F, A and S) [21]; (4) Psychomotor Speed: Trail Making A [22]; (5) Executive function: Trail Making B [22] and verbal fluency for category animals [21]; (6) Selective Attention/inhibition: Stroop test [21]; and (7) Pre-morbid and general intelligence: Wide Range Achievement Test-Revised (WRAT-R) [23]. We also used the following items from computerized cognitive test batteries; two domains from the CogState [24]: (1) Psychomotor speed: Detection Test (DET) and (2) Working memory: One Back (ONB) and Two Back (TWOB), and the full battery of the Computer Assessment of Mild Cognitive Impairment (CAMCI) [25].

Secondary outcome: loneliness score

Pre-post trial changes in loneliness were assessed using a 3-item Loneliness scale developed by Hughes et al., [26]. The measurement asks three questions: "How often do you feel" (1) that you lack companionship, (2) left out and (3) isolated from others? (1 = hardly ever [or never], 2 = some of the time, and 3 = often). A higher score indicates higher levels of perceived loneliness.

Control variables—Symptoms of depression can mediate possible treatment effects especially as they can relate to socialization. Therefore we controlled for symptoms of low mood measured by the Geriatric Depression Scale, 15 items scale (GDS-15) [27] in the primary analysis. As an exploratory analysis, we also examined personality measured by the NEO-5 factor personality scales [28] and controlled for them in the multivariate analyses, hypothesizing that personality could affect changes in primary outcomes. Finally we included the interaction effect of PC usage (yes/no, questions asked are listed in Table 1a) and the study group (intervention vs. control group, the latter group as a reference) to examine whether the trial efficacy differed by PC usage/experience. This is because our

previous study found that those who provided contact information in the survey were significantly more likely to be PC users [29]. If PC users have higher or lower efficacy compared with non-PC users, this information would be useful for generalizing our study results to non-participants.

The study protocol was approved by the OHSU Institutional Review Board (IRB #5590) and all participants provided written informed consent. The project is listed in ClinicalTrials.gov (NCT01571427) and the final face-to-face interview with participants was conducted on 8/30/2013.

Statistical Analysis—Characteristics were compared between intervention and control groups using Pearson Chi-square tests for categorical variables and t-test or non-parametric Wilcoxon Ranked Sum Test for continuous variables. Adherence was calculated as the proportion of days the subjects in the intervention group completed the experiment. The pre-post differences in cognitive tests and loneliness scores were compared between control and intervention groups using t-tests (univariate analysis) and linear regression models (multivariate analysis). Statistical significance was set as $p < 0.004$, the Boneferroni multiple comparison adjusted p-value. All analyses were performed using SAS version 9.3 software (SAS Institute, Inc., Cary, NC).

Results

Participants

Out of 2000 surveys distributed, 1102 surveys were returned (55.1 % response rate). Among them, 383 subjects (19.1%) provided contact information (Figure 1). The characteristics associated with those who provided contact information in the survey as compared to those who returned the survey without providing the information (potential volunteer bias) were summarized in detail elsewhere [29]. Briefly those who provided contact information were more likely to be PC users, physically active, and to have higher social isolation scores, with the PC usage being the most significant predictor after controlling for education and other confounders. Eighty-three subjects were enrolled and randomized (Intervention group n=41; control group n=42) (Figure 1). Table 3 shows characteristics of the participants at baseline. Mean age was 80.5 years; 76% were female. Per protocol, age, sex, education, CDR and MMSE score distributions were similar between the intervention and control groups. Other characteristics not used for randomization (marital status, WRAT scores and PC usage) were also comparable between the two groups. We also compared baseline characteristics between those with CDR=0 and CDR=0.5. The MCI group was somewhat older and more likely to be female. Although CDR was assessed independently, all conventional neuropsychological test scores except letter fluency were lower among the CDR=0.5 group, with the most significant difference observed for category fluency and word-list delayed recall with $p<0.0001$, along with difference in MMSE ($p<0.0001$), supporting the validity of our CDR assessment. CAMCI overall scores were significantly lower among the MCI group, although items in CogState computerized tests showed no difference between the two groups.

Adherence

All participants completed the pre- and post-trial neuropsychological tests. Among the intervention group, session adherence was 89%, ranging from 77% to 100%. All subjects (control and intervention groups) completed the 6th and 18th week final assessment.

Outcome Measures

Table 4 shows the results of linear regression models where the outcome is differences in test scores between baseline and post-trial assessments (post trial score – baseline score) with study group as the independent variable, controlling for depressive symptoms (GDS-15). The coefficients reported in the table are "additional" changes obtained by the intervention group beyond those obtained among the control group. We found category fluency scores (semantic fluency scores) improved more among the intervention group in comparison with the control group ($p=0.02$). The stratified analysis showed that this effect came mainly from the CDR=0 group ($p=0.003$). Among the MCI group, the intervention group gained psychomotor speed indicated by CogState detection tests in comparison with the control group ($p=0.04$), though not significant using multiple comparison adjusted p-value. At 12 weeks after the end of the trial, we examined the durability of the effects (not shown in Table). Category fluency scores no longer differed between the two groups, but letter fluency scores showed a larger improvement among those with CDR=0 in the intervention group ($p=0.004$). Interestingly, although both groups had similar levels of improvement/learning effects at post-trial, the letter fluency scores improved further among the intervention group after the end of trial sessions (see Figure 2), while it declined among the control group. There was no difference between intervention and control groups in pre-post trial changes in loneliness scores, the secondary outcomes. As an exploratory analysis, we also controlled for personality scores in addition to GDS, which did not influence the obtained results. Finally we included the interaction of the study group (intervention vs. control) and PC usage. No interaction effect was found and it did not influence the obtained results.

Discussion

We conducted a pilot behavioral clinical trial to improve cognitive functions among non-demented older old subjects by enhancing their social interaction through internet-based conversation. We achieved high adherence to the protocol and the intervention groups showed improvements in language-based executive functions (semantic and phonemic fluency scores) within a short duration trial period.

Cognitive stimulation through Internet based face-to-face conversation has some ideal features as a prevention approach as: (1) Unlike video game invoked cognitive training, subjects participate in naturalistic "human" interactions which may be more engaging and require less motivation on the part of older participants, thus allowing those with low motivation and/or apathy to participate and remain in the trial; (2) One may achieve more cost-effective execution of trials by allowing a few interviewers to interact with many participants daily using the Internet, and also gain access to those who are home-bound or in remote locations; (3) Conversations with interviewers through the Internet eliminate

potential trial confounders such as indirect effects of tangible support which could affect overall and cognitive health (e.g., transportation service); (4) The trial differs in nature from the neuropsychological test itself. Therefore, observed gains in neuropsychololgical test scores at post-trial (beyond the learning effects observed among the control group) should reflect improvement in cognitive function that cannot be attributed to “test-taking” or “limited trained skills”, and (5) The methodology provides the ability to record all interactions for off-line analysis with participants’ consent; for example, for acoustic speech characteristics, word selections and sentence complexity associated with cognitive function, an area of growing research interest [13, 30–35].

We paid special attention to creating a user-friendly environment to achieve high adherence, including a large touch screen monitor which allowed eye-to-eye contact as experienced in in-person conversations in order to retain attention, and pop-up pictures on the screen to evoke conversations without any effort by the participants. Psychological literature suggests that with age, adult cognition becomes more tightly linked to socio-emotional systems, and emotional motives play an important role in driving engagement and enhancing cognitive outcomes in later adulthood [36, 37]. We believe that tailoring existing technologies to suit the current generation of the elderly, together with naturalistic human contact, is a key to achieving high adherence when using contemporary communication technologies.

We found improvements on the semantic fluency immediately after the trial sessions among the intervention group in comparison with the control group, and at the 18-week assessment from baseline on the phonemic fluency. In Alzheimer's disease (AD), semantic fluency has been found to be disproportionately impaired, whereas phonemic fluency ability is less impaired in some [38, 39], although not all studies agree [40]. It is hypothesized that the disproportionate impairment in semantic fluency, as opposed to phonemic fluency, could occur because the former relies more on temporal-lobe semantic stores, the area which is affected by AD, and the latter on frontal lobe functions. It is noteworthy that the intervention group continued to show improvement in the phonemic fluency test. Possibly the stimulation obtained from this trial might have led to sustained or an increased amount of social interaction even after the termination of the trial sessions, although we do not have data to confirm this hypothesis. Future studies which examine post-trial changes in functional and structural connectivity between medial temporal-lobe and frontal lobe using functional MRI (fMRI) and Diffusion Tensor Imaging (DTI) could be useful in identifying the underlying mechanisms of the finding.

The improvement in cognitive function described above was limited to those with intact cognition, although we saw a trend of improvement in psychomotor speed among the MCI group. The lack of improvement in cognitive functions among those with MCI is likely due to the fact that (1) this study was not powered enough to see changes among the MCI group (the sample size was predetermined for a combined analysis in this phase I study), and (2) those with MCI are a heterogeneous group and the efficacy is likely to vary depending on whether subjects have only memory or also impairment in other domains (multi-domain MCI). In fact, CDR sum of box scores in our MCI group ranged from 0.5 to 3, suggesting variability in types of MCI. Future studies which allow for stratified analyses by MCI and its sub-types are warranted. Also it will be important to identify the biomarker characteristics of

those who improved vs. those who did not improve in cognitive functions, to examine underlying mechanisms of those differences. This may aid in identifying who should be targeted for this type of behavioral trial and also in reducing confounding effects and variability in outcomes.

We did not see any improvement in loneliness scores (the secondary outcome). The scale we used asked only 3 questions (lack companionship, left out and isolated from others) with each having 3 possible answering categories. Possibly there is not much variation in the scale and therefore it is difficult to capture within-individual changes within a short period of time. Alternatively loneliness is a subjective state indicating a gap between desired levels of social interactions and the amount of available social network and support. Increasing the opportunity to converse or socialize may not be sufficient enough to modify the levels of loneliness.

Recent MRI studies found associations between the size and complexity of real-world social networks and the density of grey matter [41] and amygdala volume [42]. Modifiable effects of larger social networks on symptomatic outcomes of Alzheimer's disease pathologies have also been shown [6]. Non-human research suggests that social network size could actually contribute to changes both in brain structure and function, providing further support for causal links [43]. We previously outlined possible mechanisms of social interaction's effects on cognitive function [44]. Despite the accumulating evidence, there exist just a few RCTs examining engagement-evoked cognitive changes targeted to older adults [45, 46]. We searched the clinicaltrial.gov website where active and completed trials in the USA and 187 countries are registered, using the following search words: cognition, dementia, social engagement, prevention, intervention. Only five studies were identified besides the study reported here (as of August, 2014). This is in contrast with a relatively large number of computerized cognitive training prevention studies targeting subjects with intact cognition [47]. Increasing social engagement through user-friendly devices utilizing modern telecommunication technologies holds a high promise as a translational large scale national prevention protocol for both cognitively intact and impaired individuals.

Limitations of our study include: Selection bias. As shown in our previous study [29], those who volunteer to participate in the study differ from the general population. For example, the high adherence observed here could be partly due to the fact that the participants are self-selected volunteers. The sample size for this pilot study was determined for the normal/MCI combined analyses, not for stratified analyses by cognitive status. Our trial duration was only 6 weeks and retention effects were limited to 18 weeks from baseline. To be able to confirm whether the rates of decline in cognitive functions are actually different between the intervention and control groups, we need to follow participants for at least 6 months to a year, so that the natural history of cognitive declines can be observed and compared with declines among the intervention group. Finally, more efforts are required to control for confounding effects such as duration of daily conversation enacted outside of the trial sessions. We intended to measure the amount of daily conversations, but currently available devices were limited in their battery life and we were unable to include this confounder in the analyses.

Strengths of our study include: rigorous approaches were taken to standardize interviewers including intensive practice sessions before the trial initiation, and assessment of recorded conversations including examination of the proportion of words spoken by interviewers vs. participants during trial sessions. Second, our study participants were relatively old (mean age 80 years). This age group is the fastest growing segment of the population in most developed countries and faces the highest risk of developing cognitive impairment or dementia due to their risk factor of age alone. Developing prevention approaches with high adherence that could delay the onset of dementia even for a few years could have a large impact on the overall burden of the disease, especially among the oldest old group, and is urgently needed. To our knowledge, this study is one of the first RCTs aimed to increase social interactions among this age group.

Conclusions

Our social engagement intervention (daily conversations) using user-friendly Internet communication programs demonstrated high adherence. The intervention group showed significantly greater improvement in neuropsychological test scores that tap both semantic and phonetic fluencies, despite the short duration of the trial period. Increasing daily social contacts through communication technologies could offer cost-effective execution of home-based prevention trials. Further studies are needed which are powered to analyze efficacy among those with MCI, have longer duration of follow-up to examine the difference in rate of decline in cognitive functions between the intervention and control groups, have pre- and post-differences in biomarkers to identity the potential mechanism, and are able to assess translational effects on everyday living.

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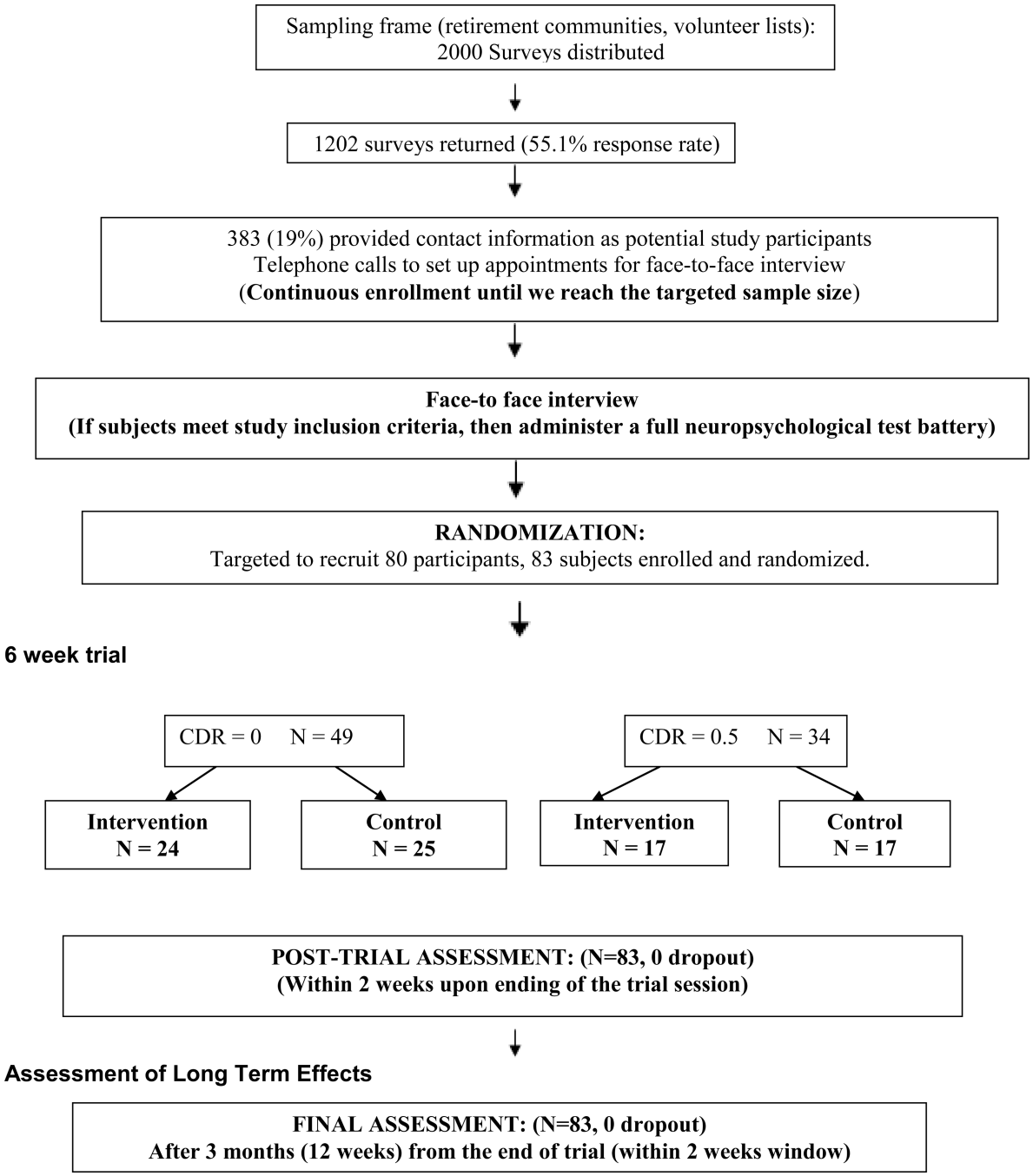

Figure 1.
Study Flow Chart

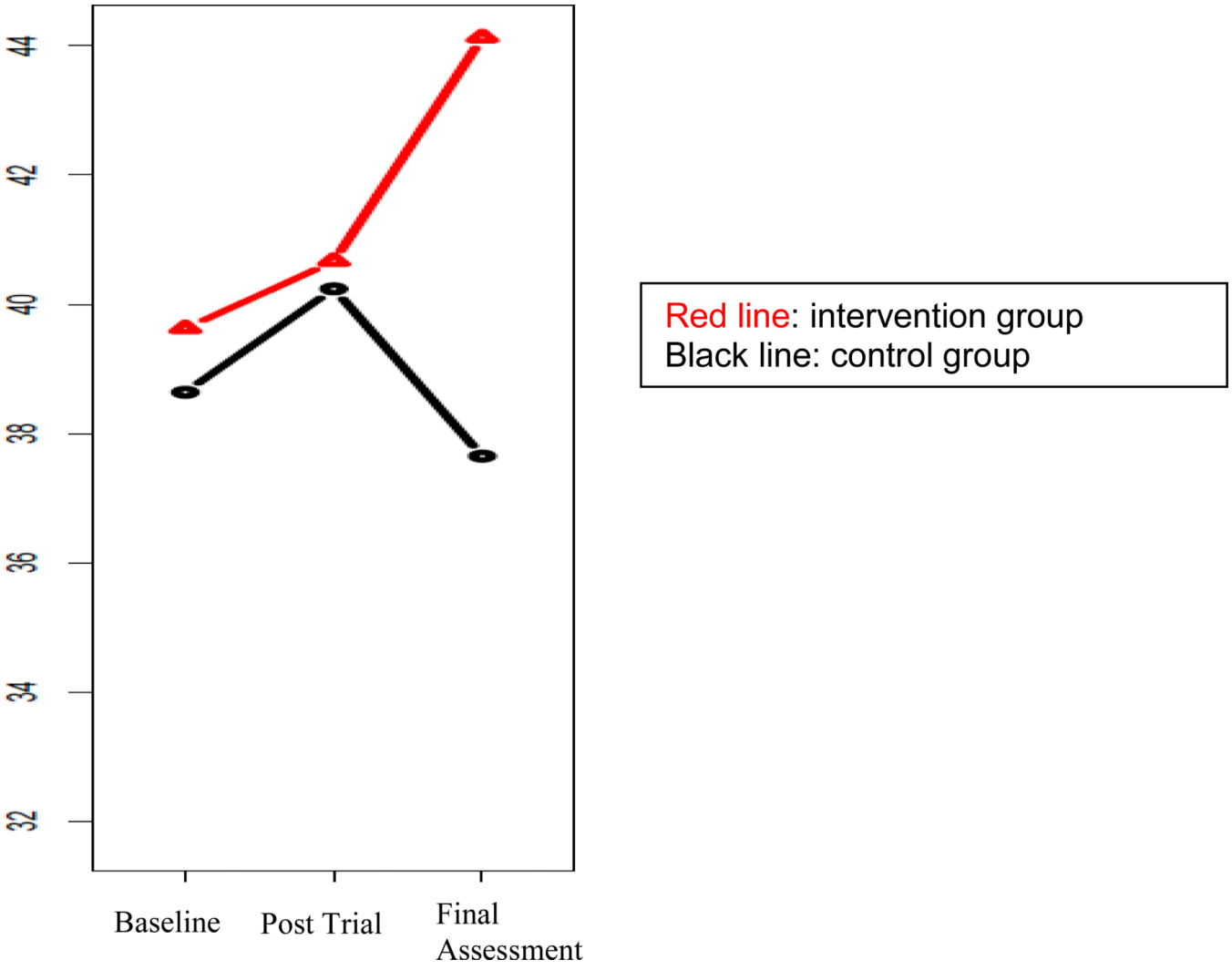

Figure 2.

Letter Fluency Test Results at Baseline, Post-Trial and Final Assessments among CDR=0 Group

Note: The figure shows that among the CDR=0 group, the intervention group kept improving the test score after the trial, but the control group experienced decline at the final assessment, leading to a significant difference between the two groups in the gain in scores from baseline to the final assessment (p=0.004)

Table 1

Information collected in survey questionnaire and baseline screening in-person interview

(0) **Survey**

- Demographic information
- Nature and frequencies of social/cognitive/physical activities
- Self-rated health
- 3-Item loneliness measurement [26]
- Older Americans Resources and Services (OARS) Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) [48]
- Brief questions on Internet and PC usage: (1) “Do you use a personal computer?” (yes/no). If yes, then asked (2a) where he/she uses it (check all that apply: 1. At home, 2. At the library, 3. At a senior center/community center, 4. Friend’s or relative’s house, 5. Other (write in), (2b) how often he/she uses it (1. Less than once a year, 2. A few times a year, 3. A few times a month, 4. A few times a week, 5. Almost every day), and (2c) what he/she does on the PC (check all that apply: 1. Send/Receive e-mail, 2. Make documents, 3. Browse websites for information, 4. Shopping, 5. Use Facebook/Other social network sites, 6. Games, 7. Video Chat (Skype, etc.), 8. Other (write in)).
- Willingness (yes, no) to participate in the future clinical trial (afterbrief explanations of prevention study protocol) and provide contact information if willing to be contacted. (detail described in [29]).

(b) Baseline interviews (subjects selected among those who provided contact information in the survey)

- Demographic information (confirming answers listed in the survey questionnaire)
- NEO Big-5 personality inventory[28]
- GDS-15 (Depression Scale) [27]
- Clinical Dementia Rating Scale (CDR)[49]
- Informant contact information to complete CDR
- List of current prescription and over the counter medications
- Neuropsychological assessment (MMSE[50], category and letter fluency tests[21], CERAD word list learning and recall[20], trail making tests A and B[22], Stroop test[21], Wide Range Achievement Test-Revised (WRAT-R) [23], Computer Assessment of Mild Cognitive Impairment (CAMCI) computerized test[25], 3 sub-items from CogState computerized test[24]).
- Feedback on computerized tests(fatigue, easiness to follow, preference of CAMCI vs. CogState, after these tests)

Table 2

Inclusion and Exclusion Criteria

Inclusion Criteria

1. Age 70 or older
2. CDR=0 or 0.5
3. Sufficient vision and hearing to engage in conversation by PC system.
4. Sufficient English language skills to complete all testing.
5. General health status that will not interfere with ability to complete longitudinal study. Conditions that will likely lead to this problem are listed below in the Study Exclusions list.

Exclusion Criteria:

1. Plan to start: taking new classes, traveling which requires more than two nights of stay away, or having significant social events such as a family wedding or a family reunion, during the scheduled prevention trial.
2. Diseases associated with dementia such as AD, ischemic vascular dementia, normal pressure hydrocephalus, or Parkinson's disease.
3. Significant disease of the central nervous system such as brain tumor, seizure disorder, subdural hematoma, cranial arteritis.
4. Current (within the last 2 years) alcohol or substance abuse
5. Current major depression, schizophrenia or other major psychiatric disorder
6. Unstable or significantly symptomatic cardiovascular disease such as coronary artery disease with frequent angina, or congestive heart failure with shortness of breath at rest.
7. Active systemic cancer within 5 years of study entry.
8. Illness that requires > 1 visit per month to a clinician.
9. Progressive vision loss (Age-related macular degeneration already beginning to significantly degrade vision).
10. Need for oxygen supplementation for adequate function.
11. Medications:
    a. Frequent use of high doses of analgesics.
    b. Sedative medications except for those used occasionally for sleep (use limited to no more than twice per week).
    c. **APPLICABLE TO CDR = 0.5 group only**: Subjects on unstable dosing of Cholinesterase inhibitors (need to be stable dosing for 2 months).

Table 3

Baseline Characteristics of Subjects

Variable	Total	Intervention Group (A)	Control Group (B)	P-value: Difference Between (A) and (B)	CDR=0 (C)	CDR=0.5 (D)	P-value: Difference Between © and (D)
	N=83	*N=41*	*N=42*		*N=49*	*N=34*	
Variables used for randomization							
Age (std)	80.5 (6.8)	80.9 (7.2)	80.2 (6.6)	0.65	78.9 (5.5)	82.8 (7.9)	0.02
Gender (% Women)	75.9%	78%	73.8%	0.65	71.4%	82.4%	0.25
Education (% High School Completed or above)	96.4%	97.6%	95.2%	0.57	100%	91.1%	0.03
CDR (% of CDR=0.5)	41%	41.5%	40.5%	0.93	-	-	-
Mini-Mental State Exam	28.3 (1.8)	28.2 (1.7)	28.3 (1.8)	0.87	28.9 (1.3)	27.3 (1.9)	<0.0001
Other variables (not used for randomization)							
Marital Status (% Married)	46.3%	45.0%	47.6%	0.81	52.1%	38.2%	0.21
Wide Range Achievement Test-Revised (WRAT-R)	72.0 (12.1)	72.0 (12.9)	72.0 (11.5)	0.75	75.1 (10.5)	67.6 (13.2)	0.007
PC Usage % (yes)	14.6	15.0	14.3	0.99	10.4	12.6	0.82
Primary outcome variables							
Category Fluency	19.9 (5.1)	19.5 (5.3)	20.4 (4.9)	0.42	21.8 (4.6)	17.3 (4.6)	<0.0001
Letter Fluency	37.4 (13)	37 (13.2)	37.7 (12.9)	0.82	39.1 (11.9)	34.9 (14.1)	0.16
Word-List Acquisition	19 (4.5)	19 (4.8)	18.9 (4.2)	0.94	20.2 (3.7)	17.2 (4.9)	0.004
Word-List Delayed Recall	4.8 (2.3)	4.8 (2.2)	4.8 (2.4)	0.96	5.6 (2.0)	3.6 (2.2)	<0.0001
Trail Making Test A	41.3 (15.8)	44.6 (17)	38.0 (14.0)	0.06	36.4 (11.3)	48.6 (18.8)	0.002
Trail Making Test B	120.1 (62.3)	123.1 (60.5)	117.4 (64.5)	0.68	102.9 (45.7)	144.5 (74.1)	0.005
Stroop Test	29.3 (8.7)	29.9 (10.5)	28.8 (6.5)	0.55	32.0 (7.9)	25.5 (8.5)	0.001
CogState computerized tests							
DET (detection test) log of speed of performance	2.6 (0.1)	2.6 (0.1)	2.6 (0.1)	0.45	2.6 (0.1)	2.6 (0.1)	0.72
ONB (one back accuracy: working memory test)	1.2 (0.2)	1.2 (0.2)	1.2 (0.1)	0.75	1.2 (0.1)	1.1 (0.2)	0.09
TWOB (two back accuracy: working memory test)	1.1 (0.2)	1.1 (0.1)	1.1 (0.2)	0.78	1.1 (0.2)	1.0 (0.2)	0.14
CAMCI computerized test							
Total score (Z score in comparison with normative scores * *provided by CAMCI)*	−0.05 (0.68)	−0.12 (0.78)	0.03 (0.56)	0.32	0.19 (0.45)	−0.38 (0.80)	0.0004
Secondary outcome variables							
Loneliness score [range 3–9]	4.0 (1.6)	4.3 (1.9)	3.6 (1.0)	0.05	3.7 (1.2)	4.3 (1.9)	0.09
Control variable							
Geriatric Depression Scale (GDS-15)	1.7 (2.2)	2.0 (2.3)	1.5 (2.1)	0.30	1.5 (1.9)	2.0 (2.5)	0.37

Variable	Total	Intervention Group (A)	Control Group (B)	P-value: Difference Between (A) and (B)	CDR=0 (C)	CDR=0.5 (D)	P-value: Difference Between © and (D)
	N=83	***N=41***	***N=42***		***N=49***	***N=34***	
Exploratory analysis							
(Neo 5-factor personality scale)							
Extraversion	3.5 (0.8)	3.4 (0.8)	3.6 (0.8)	0.16	3.5 (0.9)	3.4 (0.8)	0.47
Agreeable	4.3 (0.6)	4.2 (0.7)	4.4 (0.5)	0.05	4.3 (0.6)	4.3 (0.6)	0.97
Conscientious	3.9 (0.7)	4.0 (0.8)	3.8 (0.6)	0.46	3.9 (0.8)	3.9 (0.7)	0.68
Neuroticism	2.3 (0.8)	2.4 (0.9)	2.2 (0.7)	0.15	2.3 (0.8)	2.3 (0.8)	0.77
Openness	4.0 (0.6)	4.0 (0.6)	4.0 (0.6)	0.65	4.0 (0.6)	4.0 (0.7)	0.85

*Generated by the Computerized Assessment of Mild Cognitive Impairment (CAMCI), based on their normative distribution [8]

#"Do you use a personal computer?" (Yes/No).

Alzheimers Dement (N Y). Author manuscript; available in PMC 2015 July 20.

Table 4

Linear regression results with outcome being pre-post trial differences: overall and stratified by cognitive status (CDR=0, 0.5).

	Total (N=83)			CDR 0 (N=49)			CDR 0.5 (N=34)		
Outcome Variables:	**Coefficient for Intervention group#**	**SE**	**p-value**	**Coefficient for Intervention group#**	**SE**	**p-value**	**Coefficient for Intervention group#**	**SE**	**p-value**
Changes in Neuropsychological tests									
Mini-Mental State Exam	−0.41	0.35	0.25	−0.49	0.42	0.25	−0.11	0.62	0.85
Category Fluency	2.2	0.92	0.02	4.00	1.28	0.003**	0.52	1.14	0.65
Letter Fluency	0.03	1.33	0.98	−0.09	1.63	0.96	0.51	2.38	0.83
Word-List Acquisition	−0.27	0.64	0.68	−0.34	0.84	0.69	−0.18	1.02	0.86
Word-List Delayed Recall	−0.04	0.43	0.92	0.06	0.61	0.92	−0.05	0.62	0.94
Trail Making Test A	−2.11	2.84	0.46	−1.07	2.08	0.61	−1.66	6.42	0.80
Trail Making Test B	3.25	8.88	0.72	2.26	11.1	0.84	12.39	14.4	0.40
Stroop Test	−0.81	0.91	0.38	−1.12	1.31	0.39	−0.68	1.26	0.59
CogState computerized tests									
DET (detection test) log of speed of performance: psychomotor speed test)	−0.05	0.02	0.03	−0.03	0.03	0.24	−0.09	0.04	0.04
ONB (one back accuracy: working memory test)	−0.02	0.05	0.65	0.02	0.05	0.64	−0.08	0.10	0.42
TWOB (two back accuracy: working memory test)	−0.03	0.04	0.45	0.004	0.05	0.93	−0.07	0.08	0.40
CAMCI computerized test									
*Total score (%tile in comparison with Normative scores provided by CAMCI)**	−0.09	0.09	0.30	0.03	0.10	0.75	−0.24	0.15	0.12
Secondary outcome									
Loneliness score	−0.21	0.27	0.44	−0.06	0.27	0.82	−0.34	0.56	0.54

#The coefficients reported in the table are “additional” changes obtained by the intervention group beyond those obtained among the control group (changes among the control group as reference). For example, the table can be interpreted as follows: Among those with intact cognition, category fluency scores improved by 4 points among the intervention group beyond the changes observed among the control group.

All models are controlling for geriatric depression scores (GDS-15).

**Significant using the Bonferroni multiple comparison adjusted p-value <0.004.