Disability & Rehabilitation, 2012; Early Online: 1–5

ISSN 0963-8288 print/ISSN 1464-5165 online
DOI: 10.3109/09638288.2012.667188

informa
healthcare

RESEARCH PAPER

A pilot study of the effects of internet-based cognitive stimulation on neuropsychological function in HIV disease

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***Purpose*: Mild cognitive deficits associated with HIV disease can affect activities of daily living, so interventions that reduce them may have a long-term effect on quality of life. We evaluated the feasibility of a cognitive stimulation program (CSP) to improve neuropsychological test performance in HIV disease. *Methods*: Sixty volunteers (30 HIV-infected) participated. The primary outcome was the change in neuropsychological test performance as indexed by the Global Impairment Rating; secondary outcomes included mood (Brief Symptom Inventory subscales) and quality of life rating (Medical Outcomes Survey-HIV) scales. *Results*: Fifty-two participants completed all 24 weeks of the study, and 54% of the participants in the CSP group successfully used the system via internet access from their home or other location. There was a significant interaction between usage and study visit such that the participants who used the program most frequently showed significantly greater improvements in cognitive functioning ($F(3, 46.4 = 3.26$, $p = 0.030$); none of the secondary outcomes were affected by the dose of CSP. *Conclusions*: We found it possible to complete an internet-based CSP in HIV-infected individuals; ease of internet access was a key component for success. Participants who used the program most showed improvements in cognitive function over the 24-week period, suggesting that a larger clinical trial of CSP may be warranted.**

Keywords: Cognition, HIV, internet

Implications for Rehabilitation

- HIV disease is now a chronic condition in areas with good access to medical care.
- HIV-infected patients may have mild, but clinically critical deficits in cognitive functions.
- It may be possible to improve cognitive functions using cognitive stimulation programs over the Internet.
- Such cognitive stimulation may improve cognitive functions, and thus affect future disability, disability severity and rehabilitation potential.

Introduction

As the incidence of HIV-Associated Dementia has fallen in areas with good access to anti-retroviral treatment, the survival of HIV-infected individuals with milder forms of HIV-Associated Neurocognitive Disorder has increased [1]. These cognitive deficits can affect a range of activities of daily living, so interventions that reduce them may have a long-term effect on quality of life. Paradoxically, the success of Highly Active Anti-Retroviral Therapy (HAART) may come at the cost of inducing a mild cognitive impairment [2], the physiological basis of which is poorly understood, underscoring the need for its prevention and treatment, as HAART cannot be discontinued (see [3]). There is also evidence that the duration of HIV infection and nadir CD4+ cell counts are related to the degree of cerebral atrophy [4], suggesting that the initial insults (i.e. prior to effective therapy) play a major, and perhaps chronic role in brain structure and function. Further, there is now confirmation of earlier reports [5] of persistent metabolic disruption in the face of good virological (and immunological) control [6], and the prevalence of viral "escape" as measured in the CSF may be greater than previously thought [7].

HIV has been referred to as an "episodic disability" with periods of good health interspersed with periods of illness or disability. When these episodes may occur, how long they will

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(Accepted February 2012)

last, and how they will affect an individual is difficult to predict (http://www.hivandrehab.ca/EN/episodic_disabilities/index.php). As part of the development of a comprehensive model for persons living with HIV, the Canadian Working Group on HIV and Rehabilitation has concluded that "exploring the neurocognitive impairments of HIV and its medical treatments, the impact these might have on functional capacity, and the impact of rehabilitation cognitive treatment interventions for people living with HIV" should be a priority in research ([8], p. 13). Indeed, there have been few direct attempts at treating the cognitive symptoms associated with HIV disease, and these have met with limited success (e.g. [9,10]). Another line of potential therapeutic intervention is to involve non-pharmacological interventions (i.e. a rehabilitation approach), and one that has met with some success in Alzheimer's Disease is a "cognitive stimulation program" (CSP) [11]. Use of CSP and other non-pharmacological programs is more common in studies of aging and dementia, but is virtually unknown in the realm of HIV disease.

One CSP, called SmartBrain© (http://www.smartbrain.net/smartbrain/previo_en.html), was developed from a clinical intervention model used in adult day care settings [11]. This program has the potential to address some of the methodological weaknesses of prior studies [12], in that (a) the maximum dose of training (i.e. total time per day) can be adjusted, and (b) because the program is internet-based, the participant uses the program at home, their performance can be monitored on a task-by-task basis in order to evaluate learning, and their adherence to the training regime can be verified. The purpose of this study was to obtain pilot data from a group of HIV-infected individuals and at-risk control participants on the feasibility and efficacy of the SmartBrain© CSP to determine whether a larger, randomized trial is warranted.

Methods

This research was reviewed and approved by the Institutional Review Board of the University of Pittsburgh. All participants provided written informed consent prior to the start of any research-related activities.

Study participants and group assignment

Sixty participants – 30 with and 30 without HIV infection – were enrolled and assigned to either the CSP or Usual Care (no formal intervention) groups. Potential participants were identified from prior research activities (none of which involved CSP or other therapies) or by word-of-mouth. Assignment to groups was initially random, but changed after 30 participants were enrolled in order to meet recruitment goals and staff availability limitations. Inclusion criteria were: access to the internet; age 40 to 65 years; native language English, no active drug/alcohol abuse or dependence; no current major depression; no history of neurological disease including dementia; no history of learning disability or Attention Deficit Disorder/Attention Deficit Hyperactivity Disorder (by self-report). The first three criteria were determined during an initial screening telephone call; eligibility based on the remaining criteria was determined on the basis of assessments during the initial study visit. Sixty percent of the HIV-infected participants (18/30) had AIDS, 83.3% were using combination anti-retroviral therapy; the mean CD4+ cell count was 523.3 with a mean viral load of 2.05 $\log_{10}$.

The CSP group (n = 46, 21 of whom were HIV+) and the Usual Care group (n = 14, 9 of whom were HIV+) were similar and not statistically different (p's > 0.05) in terms of age (M(SD) = 52.1 (5.8) vs. 50.9(6.8), t(58) = 0.12), gender (92.9% vs. 82.6% male, $\chi^2(1) = 0.26$), race/ethnicity (67.4% vs. 42.9% European American, $\chi^2(1) = 2.73$), years of education (M(SD) = 15.1(1.9) vs. 14.0(2.2)), or reading level, as assessed by the Wide Range Achievement Test [13] (M(SD) = 12.0(1.9) vs. 10.9(2.7), t = 1.71). There were more European Americans in the CSP group (67.4%) than the Usual Care group (42.0%) but this difference also was not significant ($\chi^2(1) = 2.73$). They also did not differ at study entry in terms on cognitive status, based on the 9-point Global Impairment Rating described below (M(SD) = 3.58(1.6) vs. 3.14(1.7), t(58) = 0.87).

Procedure

participant received a baseline neurobehavioral evaluation and completed a series of tests with the CSP for feasibility purposes. Participants assigned to the CSP group were further instructed in the use of the internet-based program from home and on the schedule for use (control group participants did not have access to the program beyond the baseline session). All participants were re-evaluated 12 and 24 weeks after baseline.

Assessments

Neuropsychological studies

A neuropsychological test battery was administered at study entry and again after 24 weeks of follow-up [14]. It included measures from multiple cognitive domains including Memory (California Verbal Learning Test [15], Rey-Osterrieth Complex Figure [16]), Language (Boston Naming Test [17], Verbal Fluency [18]), Visual-Construction (WAIS-R Block Design [19], Rey Figure Copy), Psychomotor Speed (Trailmaking Part A [20], Digit-Symbol Substitution Task [19], Stroop Color Naming [21], Simple Reaction Time [22]), Motor (Grooved Pegboard) and Executive functions (Trailmaking Part B [20]), Stroop Interference [21], Booklet Category Test [23]).

Psychosocial evaluation

Each participant completed a semi-structured diagnostic interview, and completed questionnaires concerning psychiatric symptomatology, which were used in the adjudication of HIV-Associated Neurocognitive Disorder (HAND) outcomes. The components of the evaluation were: i) the mood and substance use disorders modules from the Structured Clinical Interview for DSM-IV [24]; ii) the Brief Symptom Inventory [25] and the Neuropsychiatric Inventory [26] to assess subclinical psychiatric symptoms, and iii) Heaton's Patient's Assessment of Own Function questionnaire [27] and the Modified Instrumental Activities of Daily Living scale [28] to provide information about the specific symptoms of cognitive decline, and their impact on activities of daily living.

Health-related quality of life

Each participant completed the Medical Outcomes Study HIV Health Survey (MOS-HIV) [29] at the baseline, 12-, and 24-week visits.

SmartBrain© intervention

The program uses very little verbal instruction (e.g. "Find the ball"), thus limiting the impact of language on task comprehension. Fourteen different activities were selected for use in the training program in the domains of memory, attention, gnosis, and executive functions (See Supplemental Table E-1). The CSP was programmed to begin each of the 14 selected stimulation exercises at the first level, and the computer adjusted each individual test level of difficulty based on the participant's performance. The difficulty of an exercise was increased automatically after three consecutive performances within a single task without error, or when an individual was 80% correct over 6 consecutive sessions. The level of difficulty was programmed to *decrease* when their performance fell below 15% correct for 3 consecutive sessions or less than 20% correct for 6 consecutive sessions. The initial session length was set for 10 min, with weekly increases to a maximum of 30 min per day; the participants could use the program up to 7 days per week. The total number of sessions of use of SmartBrain© and the total number of exercises used over the course of the study were recorded by the program.

Outcome variables

The primary measure was neuropsychological test performance as indexed by the Global Impairment Rating [30]. Each neuropsychological test score was transformed to a T-score that adjusted for age, education, gender, and race. The T-scores were then used to create a clinical rating score ranging from 1 ('Above Average') to 9 ('Severe Impairment') for each participant at each study visit for both individual cognitive domains (e.g. Memory, Speed of Information Processing) as well as a Global Impairment Rating. Inter-rater reliability was high for these ratings (r's > 0.90). The secondary outcomes were changes in scores on the eight MOS-HIV subscales, reflecting physical functional, emotional, and social well-being.

Statistical analysis

The data were analyzed using mixed effects models in SPSS (v17). To test for intervention effects, we first evaluated a model that included factors for intervention vs. control group, HIV group, and time (baseline, 12 week [when applicable] and 24 weeks), with age and education included as covariates. Then, to test whether degree of use of CSP affected the outcomes, we tested a second model that included factors for level of use, HIV group, and time.

Results

Feasibility

Seventy-nine potential participants were screened for enrollment; five were dropped due to comorbid conditions (ADD/ADHD-3, Depression-1, Stroke-1), and eight failed to arrive for their initial appointment. Only six (7.5%) were ineligible due to lack of internet access. Each of the 60 enrolled participants was able to use the CSP during baseline testing at the study office. During the study period, among participants assigned to use the CSP, 54% (25/46) were able to log in, register and repeatedly use the program without difficulty. Among remaining participants, some were willing to return to the study office to use the program, but others were unable to access the program beyond the initial instruction session due to factors such as slow speed of the internet connection and server downtime. Thus, the degree of use of the CSP varied, with the total number of activities that CSP participants completed during the 24 weeks ranging widely from 0 to 941 (mean = 235.7, SD = 250.5, median = 112.0). During the course of using SmartBrain©, none of the participants had to have the level difficulty decreased and none had a lower level of difficulty at their last session than they had when they started the program.

We categorized participants' level of use into quartiles (given this variable's skewed distribution); the quartiles ranged from little to no exposure (0 to 41 activities completed; this quartile included control group participants for purposes of analysis), low exposure (42 to 50 activities completed), moderate exposure (51 to 352 activities), and high exposure (353 to 941 activities). We found that greater use or "dose" of the CSP was associated with higher education ($r = 0.36$, $p = 0.014$), male gender (biserial $r = 0.30$, $p = 0.045$), and European American ethnicity (biserial $r = 0.42$, $p = 0.004$). Neither age ($r = -0.093$, $p = 0.540$), HIV infection (biserial $r = 0.14$, $p = 0.361$), nor reading level ($r = -0.21$, $p = 0.157$) were linked to CSP utilization.

Primary outcome

Overall, simply being assigned to use the CSP was not associated with a change in the Global Impairment Rating over time (intervention group × time interaction, $F(1,50.4) = 0.31$, $p = 0.581$); there were no other significant main or interaction effects. However, there was a significant dose effect such that participants who used the program the most showed improvements in cognitive function while the remaining participants showed little change or slight worsening (dose × time interaction, $F(3,46.4) = 3.26$, $p = 0.030$) (See Figure 1). There were no other significant main or interaction effects.

Secondary outcomes

There was no evidence that the CSP group changed at a different rate over time compared to the control group on any of the eight subscales of the MOS-HIV (intervention group × time interaction effects, all p's > 0.05). Neither was there a significant effect of dose of CSP on the MOS-HIV (all p's > 0.05).

Discussion

There are two main conclusions from this pilot investigation. First, with regard to the feasibility of using a CSP in individuals with HIV disease, we found that it is possible to complete an internet-based CSP in HIV-infected individuals, although the ease of internet access was a key component for success. While all of the participants enrolled in the study could access the program using the internet either from home or another location (e.g. a local library), if the service connection was slow, or

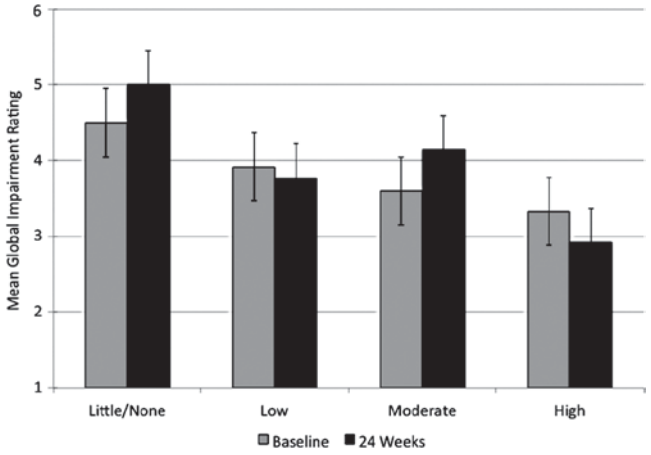

Figure 1. Bar graphs showing the effect of level of exposure to the CSP on Global Impairment in neuropsychological functioning. N.B., the lower the Global Impairment Rating, the better the performance on the neuropsychological tests. Dose, or level of exposure was defined based the total number of stimulation activities completed during the 24 weeks; participants' scores on this variable were divided into quartiles due to skewness in its distribution. The quartiles ranged from little to no exposure (mean = 31.5, SD = 7.0, activities completed; this quartile included control group participants for purposes of analyses), low exposure (43.3 (2.7) activities completed), moderate exposure (146.6 (108) activities), and high exposure (545.5 (169) activities). The CSP had its effect in the group with the highest dose, which was the equivalent of at least one session of activities each week for 24 weeks.

there were difficulties accessing the system, then many of these participants abandoned the program. Future programs of this type may benefit from more home-based systems (making it easier for individuals with less mobility or lack of access to transportation services), or perhaps they could provide internet access, inexpensive computers, "netbooks", or applications that could be run on smartphones or tablet-like devices.

Second, with regard to the efficacy of the CSP, we found that those participants who made the most use of the program did, in fact, show significant improvements in cognitive function over the 24-week period. This suggests that a larger clinical trial is warranted provided that we modify the program to maximize the use of the CSP. However, in such a trial, it will be important to attend to the participants who are "at risk" for under-utilizing the program. From Figure 1 it is clear that those who used the program the least were also the ones with more impaired Global Impairment Ratings at study entry. This would be consistent with other data from post-stroke rehabilitation that cognitive functions, especially executive processes, were critical predictors of participation in a research program [31]. Thus, any future work – either in research or clinical settings – should work to ensure that participants with poorer cognitive functions receive special attention to ensure optimal participation in the program. In addition to monitoring cognitive functions, it might also be reasonable to include the data from the International Classification of Functioning, Disability and Health as it provides a standard nomenclature and framework to describe health-related issues. This would be in addition to data from the MOS-HIV which is specific for people with AIDS, but which was not, in this study altered by the CSP (perhaps because we did not sample across a wide enough range of impairment and disability).

It should be noted, however, that our finding of "dose" effects is not exclusively due to the cognitively impaired group of respondents who used the program little to not at all: Figure 1 shows that remaining participants who were more similar in Global Impairment Ratings at baseline only showed improvements by 24 weeks if they also used the CSP more intensively. Thus, a focus on maximizing use, as noted above, will also be critical in a larger trial.

Cognitive stimulation programs are important as an adjunctive therapy in HIV disease because mental and physical activity can positively influence cognition [32]. While programs that focus on teaching specific behavioral strategies, usually do not show generalization outside of the specific area trained (e.g. [33]), those that focus on improving speed of information processing are likely the most efficacious [34,35]. Because CSP like the one used here do not target specific problems (e.g. remembering to put car keys in a specific place at home), but rather attempt to stimulate a variety of cognitive functions, at individually adjusted levels of difficulty, they may be better able to stimulate a brain plasticity response, compared to the more traditional behavioral and pharmacological interventions [36].

To our knowledge, this is the first study to attempt to use an internet-based system to stimulate cognitive functions in HIV disease. Because this was a feasibility study, our sample was small and group assignment was not random, thus limiting our power to detect statistically reliable effects and to demonstrate efficacy. We included uninfected control subjects in the trial in order to determine whether or not they were more or less affected by the intervention than the HIV-infected subjects; since HIV status did not appear relevant in this pilot study, the uninfected controls will not be necessary in future studies. In addition, the HIV-infected participants had, at worst, only mild degrees of cognitive impairment, meaning that we cannot make conclusions regarding efficacy in HAD. Nevertheless, our data provide the basis for a larger controlled trial of the relative merits of the CSP for complementing other therapies in HIV disease for the amelioration of the cognitive impairment.

In those parts of the world with access to good medical care (including HAART) HIV disease is now a chronic condition, and infected individuals are subject to many of the same risks to brain structure and function as are uninfected individuals – especially those that are age-related [37]. Further, HAART may itself exacerbate if not cause some of the observed mild cognitive dysfunction [2], and long-term survivors of the infection may have CNS damage secondary to early insults from unchecked viral replication. Thus, any therapies that have the potential to augment cognition may go a long way towards reducing disability, optimizing employment, and improving quality of life; CSP offer one promising avenue of research.

Acknowledgements

This research would not have been possible with the generous contributions of time and energy by the study volunteers. The authors are grateful to E. Skidmore, Ph.D. for serving as the Data Safety Monitor for the study. In addition, D. Galeza, D. Martineck, M. Fabrizio, and S. Straesser did yeoman work

to ensure the timely and correct completion of this study and analysis of the data. We are grateful for the assistance of *Educamigos*© who provided copies of *SmartBrain*© to the study without charge.

Declaration of Interest: This work was supported in part by funds from the National Institute of Mental Health (MH081723), the National Institute on Aging (AG05133) and the National Institute for Allergy and Infectious Diseases (AI35041). The authors have no other interests to disclose.

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