The Effects of computerized Cognitive Behavior Therapy (cCBT) on Brain Health: A feasibility study

PROTOCOL SUMMARY

Full Title	**The Effects of computerized Cognitive Behavior Therapy (cCBT) on Brain Health : A feasibility study**
Short title	HIV, depression and cCBT
Sponsor	McGill University
Funding	Canadian Institute of Health Research (CIHR)
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Objectives	Among individuals with symptoms of depression and cognitive difficulties, and whose depression is treated with computerized Cognitive Behavioral Therapy (cCBT), to what extent is reduction in depressive symptoms associated with reduced reports of cognitive difficulties. Secondarily, to what extent is the reduction self reported cognitive difficulties concordant with improvement cognitive performance.
Study Population	Inclusion Criteria • Participants in the cohort study "Understanding and Optimizing Brain Health in HIV Now" with at least one remaining visit • Able to communicate (understand and read) in English • Depression subscale of the HADS (HADS-D) ≥ 8

	• Presence of self-reported cognitive difficulties (PDQ) ≥ 30 • Score on the B-CAM > 14 • Willing to undergo 9 sessions of cCBT as per instructions and to have weekly contact with a research coordinator from the central site (by email or phone) • Access to the internet Exclusion Criteria • Current use of street drugs (excluding marijuana)
Study Design	Single cohort design with two repeated measures
Sample Size	30 participants have completed the intervention and the final evaluation
Participant involvement	Questionnaires at screening, pre- and post- intervention 9 sessions of cCBT plus regular contacts from the central site

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BACKGROUND

Among people living with HIV, challenges related to brain health are emerging. Brain health is a broad term referring to the inter-related factors of cognition, mood, anxiety, motivation, fatigue, stress and coping [1]. For example, among people with HIV, the severity of depressive symptoms has repeatedly been associated with the presence of self-reported cognitive difficulties, even in the absence of impairment on neuropsychological testing [2, 3]. There is uncertainty about the clinical importance of these self-reports, especially when neuropsychological testing is normal, as they are thought to be susceptible to patients' biases and insights into their illness.

However, there is growing evidence that these self-reports are clinically important. Among patients with major depressive disorder (MDD), evidence suggests that functional impairments is mediated by self-reported cognitive dysfunction, rather than objective cognitive dysfunction [4]. For example, Buist-Bouwman et al reported that more than one-quarter of the impact of MDD on work loss was directly attributable to self-reported cognitive difficulties and that cognition was a significant mediator of the association between MDD and work or role dysfunction [5].

When depression is treated with antidepressant medication, some degree of improvement on neuropsychological tests has been documented [6, 7] . However, many studies have evaluated cognitive outcomes before and after treatment rather than comparing them with placebo, potentially biasing the results by learning effects, which limits the strength of the conclusions that can be drawn.

Treatment of depression with Cognitive-Behaviour Therapy (CBT) has been shown to improve depressive symptoms and psychosocial functioning in patients with recurrent major depressive disorder [8], but there are few studies of the impact of psychotherapy on self-reported cognition and cognitive performance. In a group of patients with highly recurrent depression (≥4 episodes) over 2 years of follow-up, Conradi et al showed that those randomized to receive psycho-education plus CBT reported the presence of cognitive symptoms significantly less of the time compared to those receiving psycho-education only (15% of the time or 3.6 months compared to 47% or 11.3 months) [9].

In the HIV population, a single study has examined the effect of treatment of depression on self-reported cognitive difficulties and performance on neuropsychological tests, as part of a randomized controlled trial of antidepressant efficacy [10]. Following 12 weeks of antidepressant treatment, HIV+ individuals who reported a decrease in depressive symptoms also reported significantly fewer cognitive difficulties, despite an absence of improvement on neuropsychological testing.

In the context where the use of questionnaires eliciting cognitive difficulties is suggested as a first-line screening for HIV-Associated Neurocognitive Disorder [11], it is important to document the clinical factors that influence these self-reports in order to inform their clinical interpretation and develop interventions for individuals reporting cognitive difficulties.

Understanding and Optimizing Brain Health Now (BHN) cohort study: Cohort participants (N=840) are studied prospectively over a 27-month period with visits every 9 months. Patients complete questionnaires on mood (Hospital Anxiety Depression Scale-HADS), presence of cognitive symptoms (Patient Deficit Questionnaire-PDQ), and a computer-based evaluation of cognitive ability (B-CAM) [12].

Computerized Cognitive-Behavioral Therapy (cCBT): A number of computerized treatment programs have been developed to address symptoms of depression and anxiety, and several meta-analyses of randomized controlled trials (RCTs) have shown evidence for their effectiveness [13, 14]. One such program, Good Days Ahead, teaches the basic principles of CBT in nine therapy sessions, each typically taking 30 minutes to complete. Good Days Ahead has been found to be as effective as face-to-face CBT in decreasing symptoms of depression and anxiety [15]. Patients receiving treatment delivered by a computer can be provided with different levels of guidance and support: self-guidance, guidance by a technician who sends reminders, or guidance by a clinician [13]. A recent meta-analysis of cCBT for depression and anxiety has shown that the treatment delivered with no guidance or support yielded, on average, a smaller effect size (Cohen's $d = 0.17$) than cCBT delivered with at least one hour of knowledgeable assistance during the course of therapy (Cohen's $d = 0.72$) [15] . Offering some assistance thus appears to be necessary for achieving better therapy outcomes.

STUDY OBJECTIVES

Among individuals with symptoms of depression who report cognitive difficulties and whose

depression is treated with computerized Cognitive Behavioral Therapy (cCBT), to what extent is reduction in depressive symptoms associated with reduced reports of cognitive difficulties?

Secondarily, to what extent is the reduction in self-reported cognitive difficulties concordant with improvement cognitive performance?

STUDY HYPOTHESIS

The hypothesis is that people whose depressive symptoms are reduced following treatment with cCBT will also report fewer cognitive difficulties than before treatment. A second hypothesis is that changes in self-reported cognition will be concordant with changes in cognitive performance, such that people who make no improvement in self-report cognition will also show no improvement in cognitive performance and those who do improve on self-report will improve on cognitive performance.

STUDY DESIGN

This study is part of a larger project based upon a cohort multiple randomized controlled design [1]. Within a fully characterized cohort followed over time (n=840), people meeting the specific criteria for one or more interventions (here cCBT) are identified and a sample is randomly selected to receive the intervention. When the intervention is under investigation, the remaining eligible persons who do not receive the intervention serve as controls. In this study, we are not testing the effectiveness of cCBT as this has been demonstrated. Rather we are focusing on changes in cognition in relation to depressive symptoms mediated by cCBT. This study is an exploration of a hypothesis using a single cohort design with two repeated measures. For exploratory studies, an N of 30 optimizes an analysis based on means under the central limit theorem [16] .

POPULATION

Individuals who report depressive symptoms and self-reports of cognitive difficulties and who have agreed to be contacted for sub-studies will be invited to participate.

Inclusion criteria:

- Participant in the *Understanding and Optimizing Brain Health in HIV Now* (BHN) study

- Able to communicate (understand and read) in English (Good Days Ahead software is only available in English)
- Score on the Hospital Anxiety and Depression Scale- depression subscale (HADS-D) ≥ 8
- Score on the Patient Deficit Questionnaire (PDQ) [17] ≥ 30
- B-CAM score > 14 to ensure that they can navigate the computer program
- Have not had changes in medication that could potentially interfere with mood and cognition, and are not expected to undergo such changes for the duration of the study
- Have been on a stable HAART regimen for > 6 months
- Willing to participate in cCBT as per instructions and to have regular contacts with the central site
- Have access to the internet
- Have at least one remaining visit in the main cohort study

Exclusion criteria:

- Current use of street drugs (excluding marijuana)

Potentially eligible participants will be identified from the BHN cohort and will be contacted by phone or e-mail (depending on the contact information provided by the participant) by a research coordinator at the central (Montreal) site who will introduce the study. Individuals who consent verbally will be asked to provide their email address. All participants will receive an e-mail with the informed consent document and will be instructed to return the e-mail to confirm consent to participate. Those consenting will be asked to complete on-line questionnaires (HADS and HIV-specific questionnaire of cognitive difficulties, the C3Q [18]) on a secure site to confirm eligibility and collect baseline information. Those remaining eligible will enter the intervention phase. People will be contacted and screened until a maximum of 36 participants have entered the intervention phase. This number was chosen as sample sizes around 30 for analysis are often used in exploratory studies to optimize an analysis based on comparison of means under the central limit theorem [16], and we except some drop outs from the cCBT therapy.

Intervention:

Participants who are eligible will receive online access to the Good Days Ahead cCBT program. Good Days Ahead is a learning module based on scientifically proven, evidence-based techniques. The program's content follows the teachings of the basic principles of CBT. The

underlying platform generates customized learning experiences for each individual user with content including videos, text, quizzes and interactive exercises. The program comprises nine lessons of 30 minute each during which the user first learns the key concepts; then applies them to the program's main character who suffers from depression; and then applies those techniques to their own personal challenges (http://www.empower-interactive.com/solutions/good-days-ahead). Participants are expected to complete the nine sessions over 9-12 weeks.

As patients complete the cCBT program, their progress will be monitored by the research coordinator through a secure web site, using the program's dashboard feature that includes tracking of mood ratings, exercises, comprehension and completion rates. Participants will receive guidance during regular contacts by a trained research coordinator knowledgeable about the program and the basics of CBT.

MEASUREMENT

Three types of measures are under study: (i) depressive symptoms, (ii) self-reported cognitive difficulties; (ii) cognitive performance.

(i) Depressive symptoms will be measured using the Hospital Anxiety and Depression Scale (HADS) [19] before beginning and right after cCBT completion. It comprises two 7-item scales designed to rate depression and anxiety. It was developed to be brief, non-threatening and to exclude items which might reflect somatic symptoms. It has been widely used in research [20]. A score on the depression subscale (HADS-D) ≥ 8 is indicative of the presence of depression.

(ii) Self-reported cognitive difficulties will be measured using the C3Q collected before beginning and right after cCBT completion. The C3Q is a self-report measure of cognitive difficulties comprised of 18 items covering multiple cognitive domains. For each item, individuals rate the frequency of a cognitive difficulty on a three-point scale. The items fit the Rasch model, producing a legitimate total score with mathematical properties ranging from 0-36 with lower scores indicating more severe difficulties. C3Q has good content and construct validity and a good internal reliability (Person Separation Index 0.84) [18]. The mean score of C3Q among HIV+ individuals is 26.3 (SD: 8.2).

(iii) Cognitive performance will be measured by the B-CAM, a computerized test of cognition that yields a score on a continuous metric [21]. The B-CAM is administered at the regular BHN

cohort visits. Two values will be used, those closest to the beginning and end of the CBT intervention period, usually 9 months apart.

STATISTICAL ANALYSIS AND SAMPLE SIZE

Basic descriptive statistics will be used to characterize the participants including values on all the outcomes.

To meet the first aim of linking change in depressive symptoms (as a result of cCBT) to change in self-reported cognitive difficulties, an analysis based on a comparison of two means will be carried out. The cCBT cohort will be classified as having changed on depressive symptoms if the score on the HADS-D has either fallen to below 8 or decreased by ½ SD (2 points). The mean value of change on the C3Q will be compared between these two groups (depression improved vs no change), using an adjusted t-test based on linear regression, adjusted for covariates that differ between the two groups. This t-test is an estimate of between group effect size. The parameter of interest, however, is the within group effect size for cognitive change using the standardized response mean (SRM), which is the average within group change divided by the standard deviation of change. The two SRMs will be compared using relative effectiveness: SRM (depression improved group) / SRM (depression no change group)[16]. If this ratio exceeds 1.0, there is supportive evidence for a greater response in the depression improved group. This information on the between and within-effect sizes will be used to develop a fully powered study of this association.

The extent to which changes in self-reports are concordant with changes in cognitive performance will be assessed using percent agreement and 95% confidence intervals (CI). Each person will be classified as a responder or not based on change on the C3Q and on the B-CAM, with responder status defined as improvement of ½ SD. This represents a change of 4 points on the C3Q and 2.3 points for the B-CAM. The table below shows the potential outcome patterns. If the value of c=0, all persons with decreased reports of cognitive difficulties also had improved cognitive performance with cCBT.

		Cognitive difficulties C3Q	
		Decreased	no change
Cognitive performance B-CAM	improved	**a**	**b**
	no change	**c**	**d**

To illustrate, if 12 people among the 30 were concordant on response to the two types of cognitive measures, the estimate of concordance would be 0.40 with a 95% CI ranging from 0.25 to 0.58. This exploratory analysis will allow for comparison of characteristics between people who were concordant to those who were not.

POTENTIAL RISKS AND BENEFITS

There are no foreseeable risks associated with participating in the study. The intervention offered through this trial (Good Days Ahead) has already been shown to have positive effects on mood. Therefore similar clinical benefits will be expected in the population of the current study. Participants will receive compensation for their time, $20 for completing the screening questionnaires and $80 at the completion of the study.

ETHICS/ PROTECTION OF HUMAN SUBJECTS

Informed consent

All subjects will be given written information about the study and will confirm their consent to participate by e-mail prior to starting the study. Each subject will have sufficient opportunity to discuss the study and consider the information in the consent process prior to agreeing to participate. Subjects may withdraw consent at any time during the course of the trial. A copy of the consent e-mail will be retained in the subject's study files.

Participant Confidentiality

All records will be kept in a secure, locked location and only research staff will have access to the records. Each participant will be assigned an identification code for anonymously linking

data. The identification information will only be accessible to the research coordinator in a password-protected document.

Upon request, clinical information may be reviewed by or released to auditors, CIHR or regulatory agencies. For participants who are invited to participate but refuse, the positive screen for the presence of depressive symptoms is communicated to the site PI as a "red flag" of potential significance for clinical care, according to a procedure already established in the *Brain Health Now* cohort study.

The Good Days Ahead program is in compliance with Health Insurance Portability and Accountability Act (HIPAA) regulations, which ensure that personal health information remains private and secure. Good Days Ahead does not collect personal information such as email address unless the participant requests that it does so. Good Days Ahead does log the IP address to give an idea of which parts of the website is visited and how long the participant spends there, but it does not link the IP address to anything personally identifiable (http://www.mindstreet.com/privacy-statement).

Record Retention

Data and study documents will be stored securely for 7 years, after which they will be destroyed in keeping with the privacy and confidentiality regulations and guidelines.

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