STUDY PROTOCOL: COMPUTERIZED PRACTICE VS. STRATEGY MONITORING IN COGNITIVE TRAINING FOR PSYCHOSIS

Version 1 – May 12, 2020

Principal Investigator:
Michael W. Best, Ph.D.
Assistant Professor
Departments of Psychology and Psychological Clinical Science
University of Toronto Scarborough

Table of Contents

STUDY INTRODUCTION

Background

Schizophrenia-spectrum disorders are the most persistent, debilitating, and economically burdensome mental illnesses worldwide, and are associated with the greatest per-patient expense of all mental health conditions.[1] Schizophrenia is associated with a 15-20 year decrease in life expectancy, 5-fold increase in likelihood of death by suicide,[2] and a significant decrease in quality of life.[3] Antipsychotic medications are the first line treatment for individuals with schizophrenia-spectrum disorders and are prescribed to nearly every service-user. However, in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial (one of the largest antipsychotic trials in 1493 individuals with schizophrenia), medication effects on psychosocial functioning were small (d = 0.25).[4] Thus, the primary treatment available to all individuals with schizophrenia does little to improve community functioning. This may partially be a result of the limited efficacy of antipsychotic medication to improve neurocognitive abilities, widely recognized as a core feature of schizophrenia, and one recommendation stemming from the CATIE trial was that "more intensive psychosocial rehabilitative services, **including cognitive rehabilitation**, may be needed to affect more substantial gains in functioning."[4]

Cognitive remediation (CR) is a psychological intervention based on principles of learning and neuroplasticity to improve neurocognitive abilities with the ultimate goal of improving community functioning. The neuroplastic effects of CR are well established with evidence for increased gray matter volume in the hippocampus and amygdala,[5] increased activation of the medial prefrontal cortex,[6] and increased amplitude of the mismatch negativity event-related potential[7] following CR. In two recent randomized controlled trials (RCTs), I also demonstrated that CR improves synchronization of neural networks in the alpha and theta frequency bands.[7,8] Meta-analyses support moderate transfer of these neurophysiological improvements to neurocognitive abilities (d = 0.45) and community functioning (d = 0.37).[9] In a recent systematic review, I reported that CR approaches vary widely, but approaches that incorporate training of executive functions are generally the most effective.[10] Based on these findings **I developed a novel CR intervention specifically targeting executive functions** and conducted two double-blind RCTs, in which targeted executive function training (ET) produced greater improvements in neurophysiology, neurocognition, functional skills and real-world community functioning compared to other leading forms of CR.[7,8] This intervention is approximately half the duration of other CR programs, yet produces larger effect size improvements in community functioning.

Justification for Research

In order to further increase the efficiency and effectiveness of ET it is necessary to determine the active component of treatment. There are two primary components of ET and neither have ever been examined in isolation: 1) computerized cognitive training, and 2) strategy development. It is unclear whether both components are necessary to stimulate neurophysiological changes and improve functioning or whether one component drives the observed treatment effects. Dismantling ET will provide critical information regarding whether a single component is necessary or whether it is the interaction of these components that results in effective CR.

This will be the first study to dismantle CR and examine components necessary to effectively improve neurocognition and functioning for individuals with schizophrenia. These findings will directly inform methods of improving CR efficacy.

Purpose and Hypotheses

The primary goal of this study is to:

(1) Examine the efficacy of computerized training alone, compared to strategy monitoring alone, compared to full ET on neurocognition, and functioning.

STUDY DESIGN

Sample Size/Subject Selection

90 participants with schizophrenia-spectrum disorders will be recruited.

Inclusion Criteria

The target population for this study are those who meet the criteria for schizophrenia based on the DSM-V diagnosis. The inclusion criteria is anyone who meets the criteria of schizophrenia, schizoaffective disorder or any other psychotic disorder, are also 18-65 years of age, know how to use a computer, are not abusing drugs or alcohol and can read and speak English.

Exclusion Criteria

Exclusion criteria include anyone enrolled in a cognitive training program in the last 6 months, anyone with a neurological disease or neurological damage, medical illnesses that can change neurocognitive function, medical history of head injury with loss of consciousness and those with physical handicaps.

Method of Recruitment

The participants will be recruited from various sources including mental health agencies and referrals from mental health providers.

Limitation of the study

The primary limitation of the study will be attrition if participants do not complete the study or the follow-up assessment.

Informed Consent

A consent form will be given to all participants to sign. The language of the consent form will be written at an elementary school level. A research assistant will read out the consent form to participants and will clarify anything and answer any participant questions. They will also ask the participant questions during the consenting process to ensure that the participant understands. Participants will also be reminded that it is their right to refuse to participate or withdraw from the study and that doing so will not affect their existing treatments or services.

STUDY PROCEDURE

Randomization

Participants will be randomized to receive Computerized Cognitive Training only, Strategy Development only, or both (ET).

Study Intervention/Standard of Care

All interventions will involve 4 weeks of group treatment consisting of two 1-hour group sessions per week and additional practice at home between sessions. The **Executive Training** condition will consist of the ET intervention that I previously developed and evaluated.[7] ET sessions consist of 50% of the session practicing computerized cognitive training exercises, and 50% of the session developing cognitive strategies to use in the computerized exercises. Participants are encouraged to complete 40 minutes of computerized training per day, and complete strategy worksheets, at home between sessions. In **Computerized Cognitive Training only** participants will spend the entire one-hour session practicing computerized training exercises. Between sessions participants will be encouraged to practice the computerized exercises at home for 40 minutes per day. There will be no strategy development in this condition. In **Strategy Development only** participants will engage in cognitive strategy discussions to develop new executive function strategies that can be used in daily life. Between sessions, participants will be encouraged to practice their cognitive strategies in their daily life and track their strategies using the strategy worksheet. There will be no computerized cognitive training in this condition. All interventions will be delivered virtually in the participant's home and group sessions will be conducted using the online platform Zoom.

Outcome Measures

The primary outcome measure is community functioning measured using the Specific Levels of Functioning scale which will be rated by a participant's case manager who is familiar with their everyday activities and independent from the trial. I have successfully used this method of objectively measuring functioning in several previous studies.[7,8]

The secondary outcome measures include the Cambridge Neuropsychological Test Automated Battery (CANTAB), the Virtual Reality Functional Capacity Assessment Tool (VRFCAT), the Wide Range Achievement Test (WRAT), the Questionnaire About the Process of Recovery (QPR), the Brief Psychiatric Rating Scale (BPRS), the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), the Dysfunctional Attitudes Scale (DAS), the Brief Core Schema Scale (BCSS), the Generalized Self-Efficacy Scale (GSES), the Cognitive Failures Questionnaire (CFQ), the Need for Cognition Scale (NCS), the Davos Assessment of Cognitive Biases (DACOBS), and the Motivation and Pleasure Scale - Self-Report (MAP-SR).[11-23]

The CANTAB is a battery consisting of highly sensitive, precise and objective measures of cognitive function. It includes tests of working memory, learning and executive function; visual, verbal and episodic memory; attention, information processing and reaction time; social and emotion recognition, decision making and response control. The VRFCAT is a measure of functional capacity that simulates activities of daily living in a virtual environment and improves clinical trials by detecting functionally meaningful improvements in patients' everyday lives. The WRAT is an academic skills assessment which measures reading skills, math skills, spelling, and comprehension. The QPR was developed from service users' accounts of recovery from psychosis in collaboration with local service users. It asks people living with psychosis about aspects of recovery that are meaningful to them, and is strongly associated with general psychological wellbeing, quality of life and empowerment. The BPRS measures psychopathology and symptom severity and is sensitive to changes in symptom levels. The Q-LES-Q is a sensitive measure of the degree of enjoyment and satisfaction experienced by subjects in various areas of daily functioning. The DAS measures self-

defeating attitudes theorized to underlie clinical depression and anxiety. The BCSS assesses four dimensions of self and other evaluation: negative-self, positive-self, negative-other, and positive-other. The GSES assesses optimistic self-beliefs to cope with a variety of difficult demands in life. The CFQ was designed to measure perception, memory, and motor lapses in daily life. The NCS measures "the tendency for an individual to engage in and enjoy thinking." The DAVOS measures cognitive biases and discriminates between schizophrenia spectrum patients and normal control subjects. The MAP-SR assesses the motivation and pleasure domains of negative symptoms.

Visits and Rationale

Visits: All interventions will involve 4 weeks of group treatment consisting of two 1-hour group sessions per week and additional practice at home between sessions.

Rationale: In order to further increase the efficiency and effectiveness of ET it is necessary to determine the active component of treatment. It is unclear whether both components are necessary to stimulate neurophysiological changes and improve functioning or whether one component drives the observed treatment effects. Dismantling ET will provide critical information regarding whether a single component is necessary or whether it is the interaction of these components that results in effective CR. Therefore, the proposed number and length of sessions are justifiable because the proposed number and length of sessions are congruent with ET and will allow the present research questions to be addressed.

Data Collection, Storage, Privacy, Destruction

Privacy: Information provided will not have any identifying features on it. A random code will be assigned to each participant and those numbers will be used to refer to a participant's data. The document linking names to codes will be kept in Dr. Best's locked laboratory on a password protected computer.

Limits to Confidentiality: Limitations that will require confidentiality to be broken include: if a research member is aware of child abuse where the child might still be a risk, if a participant expresses that they are risk of harming themselves or others, and if a participant expresses that another health professional has engaged in sexual abuse.

Data Storage: All de-identified forms will be kept in a locked cabinet where only members of the research team have access to it. Information kept on a computer will be password protected. All filing cabinets and computers will be located in Dr. Best's locked laboratory that only research staff have access to. All research staff receive data protection and confidentiality training and sign a confidentiality form.

Data Retention/Destruction: De-identified data will be kept for seven years before being destroyed. Only members of Dr. Best's lab will have access to the data.

STUDY ANALYSIS

Sample size Statistics

90 participants with schizophrenia-spectrum disorders will be recruited. Power analyses, conducted with GPower, indicate that 90 participants (30 per treatment condition), accounting for an upper limit of 25% attrition observed in my previous trials of ET,[7,8] provides 80% power to detect a medium effect size (cohen's f = 0.2) difference between conditions.

Statistical Plan

Primary and secondary outcomes will be examined using Linear Mixed Models on the Intent-to-Treat sample with missing data interpolated using maximum likelihood estimation. The primary endpoint is the 3-month follow-up assessment, and secondary endpoint of post-treatment will also be examined.

STUDY ETHICS

Potential Benefits

The direct benefit to the participant includes improvements in attention, memory and problem solving, caused by the treatment. Also, if the results are released to the participant's clinical treatment team, they can use it to help with the ongoing care. There is also a potential benefit to the scientific community because the results may help in understanding individual differences.

Potential Risks

Psychological/emotional risks may arise during assessment procedures due to frustration or embarrassment during the neurocognitive assessment trials. Participants may feel uncomfortable discussing personal topics related to their symptoms or they may become tired. These risks are equal to those that occur within the clinical contest. Participants will be reminded that they are able to stop the interview at any time to take a break or to postpone the procedure to a different day. Participants will also be given the phone number of a mental health professional if discomfort does occur.

Safety Provisions

All therapists and lab staff will be trained in suicide risk assessment procedures. Therapists will follow established protocols to conduct a risk assessment if there is any indication of suicide risk. Therapists will create a safety plan with the participant if risk is low or moderate. If risk is high, then therapists will collaboratively discuss the risk with the participant and escort participants to the emergency department at the respective hospital site (CAMH, Ontario Shores, or Scarborough Health Network). If a risk assessment is required during an assessment, one of the assessors will conduct an initial assessment with the participant. If risk is above minimal, assessor will immediately consult with Dr. Best on the best course of action before continuing the assessment. If risk is determined to be high then the participant will be collaboratively escorted to the emergency department.

During the consenting process participants will be asked comprehension questions about the consent form to ensure participants are aware of what they are consenting to.

Ethics Approval

This protocol is currently under review at the University of Toronto Research Ethics Board. Approval from the University of Toronto REB will be forwarded to Ontario Shores Centre for Mental Health Sciences upon approval.

Dissemination

Results from this research will be presented at academic conferences and submitted for publication at peer-reviewed journals.

Statement of Right to withdraw from the study

Participants can withdraw from the study at any time. If participants decide that they would like to withdraw their data from the study, then their data will be destroyed.

REFERENCES

[1] Wu, E. Q. et al. The Economic Burden of Schizophrenia in the United States in 2002. J. Clin. Psychiatry 66, 1122–1129 (2005).

[2] Palmer, B. A., Pankratz, V. S. & Bostwick, J. M. The Lifetime Risk of Suicide in Schizophrenia: A Reexamination. Arch Gen Psychiatry 62, 247–253 (2005).

[3] Eack, S. M. & Newhill, C. E. Psychiatric Symptoms and Quality of Life in Schizophrenia: A Meta-Analysis. Schizophr. Bull. 33, 1225–1237 (2007).

[4] Swartz, M. et al. Effects of Antipsychotic Medications on Psychosocial Functioning in Patients with Chronic Schizophrenia: Findings from the NIMH CATIE Study. Am J Psychiatry 164, 428–436 (2007).

[5] Eack, S. M. et al. Neuroprotective Effects of Cognitive Enhancement Therapy Against Gray Matter Loss in Early Schizophrenia. Arch Gen Psychiatry 67, 674–682 (2010).

[6] Subramaniam, K. et al. Computerized cognitive training restores neural activity within the reality monitoring network in schizophrenia. Neuron 73, 842–853 (2012).

[7] Best, M. W., Milanovic, M., Iftene, F. & Bowie, C. R. A randomized controlled trial of executive functioning training compared with perceptual training for schizophrenia spectrum disorders: Effects on neurophysiology, neurocognition, and functioning. Am. J. Psychiatry 176, 297–306 (2019).

[8] Best, M. W., Gale, D., Tran, T., Haque, M. K. & Bowie, C. R. Brief executive function training for individuals with severe mental illness : Effects on EEG synchronization and executive functioning. Schizophr. Res. 203, 32–40 (2019).

[9] Wykes, T. & Spaulding, W. D. Thinking about the future cognitive remediation therapy - what works and could we do better? Schizophr. Bull. 37, s80–s90 (2011).

[10] Best, M. W. & Bowie, C. R. A review of cognitive remediation approaches for schizophrenia: from top-down to bottom-up, brain training to psychotherapy. Expert Rev. Neurother. 17, 713–723 (2017).

[11] CANTAB® [Cognitive assessment software]. Cambridge Cognition (2019). All rights reserved. www.cantab.com

[12] Ruse, S. A., Harvey, P. D., Davis, V. G., Atkins, A. S., Fox, K. H., & Keefe, R. S. (2014). Virtual reality functional capacity assessment in schizophrenia: Preliminary data regarding feasibility and correlations with cognitive and functional capacity performance. Schizophrenia Research: Cognition, 1(1), e21–e26.

[13] Wilkinson, G. S., & Robertson, G. J. (2017). WRAT-5: Wide Range Achievement Test Professional Manual. Psychological Assessment Resources. https://books.google.ca/books?id=amQXtAEACAAJ

[14] Neil, S. T., Kilbride, M., Pitt, L., Nothard, S., Welford, M., Sellwood, W., & Morrison, A. P. (2009). The questionnaire about the process of recovery (QPR): A measurement tool developed in collaboration with service users. Psychosis, 1(2), 145–155. https://doi.org/10.1080/17522430902913450

[15] Faustman, W. O., & Overall, J. E. (1999). Brief Psychiatric Rating Scale. In M. E. Maruish (Ed.), The use of psychological testing for treatment planning and outcomes assessment (p. 791–830). Lawrence Erlbaum Associates Publishers.

[16] Endicott, J., Nee, J., Harrison, W., & Blumenthal, R. (1993). Quality of life enjoyment and satisfaction questionnaire: A new measure. Psychopharmacology Bulletin, 29(2), 321–326.

[17] Weissman AN, Beck AT. Development and validation of the dysfunctional Attitude Scale: A preliminary investigation. Paper presented at the Association for the Advancement of Behavior Therapy; Chicago. 1978.

[18] Fowler, D., Freeman, D., Smith, B. E. N., Kuipers, E., Bebbington, P., Bashforth, H., ... & Garety, P. (2006). The Brief Core Schema Scales (BCSS): psychometric properties and associations with paranoia and grandiosity in non-clinical and psychosis samples. Psychol Med, 36(6), 749-759.

[19] Schwarzer, R., & Jerusalem, M. (1995). Generalized Self-Efficacy scale. In J. Weinman, S. Wright, & M. Johnston, Measures in health psychology: A user's portfolio. Causal and control beliefs (pp. 35-37). Windsor, UK: NFER-NELSON.

[20] Broadbent, D.E., Cooper, P.F., FitzGerald, P., & Parkes, K.R. (1982). The Cognitive Failures Questionnaire (CFQ) and its correlates. British Journal of Clinical Psychology, 21, 1-16.

[21] Cacioppo, J. T., & Petty, R. E. (1982). The need for cognition. Journal of Personality and Social Psychology, 42, 116–131.

[22] van der Gaag, M., Schütz, C., ten Napel, A., Landa, Y., Delespaul, P., Bak, M., ... & De Hert, M. (2013). Development of the Davos assessment of cognitive biases scale (DACOBS). Schizophrenia Research, 144(1-3), 63-71.

[23] Llerena, K., Park, S. G., McCarthy, J. M., Couture, S. M., Bennett, M. E., & Blanchard, J. J. (2013). The Motivation and Pleasure Scale–Self-Report (MAP-SR): Reliability and validity of a self-report measure of negative symptoms. Comprehensive psychiatry, 54(5), 568-574.