Personalized and Scalable Cognitive Remediation Approaches

NCT01945333

Last Update: 01/13/2023

Personalized and Scalable Cognitive Remediation Approaches

This protocol has been approved by the New York State Psychiatric Institute Institutional Review Board (IRB).

Summary of Research Protocol:

Cognitive Remediation (CR) is an empirically based behavioral intervention utilized to target the cognitive impairments prevalent in people with schizophrenia. CR is often implemented in clinical research settings but there is hope for broader implementation in community clinics in order to serve a larger population. The research literature on CR indicates that there are substantial individual differences in response to CR interventions and that there are specific neurocognitive and psychological factors that predict a positive response. Yet large-scale CR programs are not typically designed to be so personal so as to address the specific needs of every individual. There is therefore a need to refine intervention strategies to better meet the specific needs of treatment participants when CR is delivered in a community clinic setting. The ultimate aim of this research is to develop an approach that matches patients to appropriate CR treatment based on their baseline neurocognitive profile, and to make these CR treatments useable for community clinics. The current study will gather preliminary data on the feasibility of delivering personalized CR to people with schizophrenia and schizoaffective disorder in a community outpatient clinic setting.

There are three phases of this study.

(1) **Development and Adaptation**: First, we assembled two packages of computer-based cognitive exercises which, based on what we know from prior research about neurocognitive predictors of a positive response to CR, addressed the learning needs of people with different neurocognitive profiles. These types of computer-based exercises have been used in prior CR research.

(2) **Open Trial and Refinement**: Second, we pilot tested the two cognitive interventions in a sample of adults with schizophrenia and schizoaffective disorder attending a community psychosocial rehabilitation clinic. Participants completed a 10-session open trial which allowed for the collection of qualitative feedback from the subjects and quantitative cognitive assessment data. These data were used to further refine assessment procedures and treatment parameters. The goal of this phase was to the increase acceptability and feasibility of the assessments and CR interventions.

(3) **Pilot Feasibility Trial:** The third phase is a randomized controlled trial evaluating if baseline cognitive profile predicts response to the different treatment approaches. In addition to examining efficacy, we are assessing the feasibility of recruiting, enrolling, randomizing, stratifying, retaining, and assessing outcomes in the participants. These data will enable us to design a larger trial which will provide a more rigorous test of the impact of personalized intervention methodologies on cognitive and functional outcomes in schizophrenia and schizoaffective disorder.

Research Participants

Subjects include adults recruited from Columbia University Medical Center (CUMC) and New York metro area mental health residences and facilities. Participants are between the ages of 18 and 65 and have a primary DSM-IV Axis I diagnosis of schizophrenia or schizoaffective disorder. Subjects may be self-referred by responding to advertisements, or

may be referred by a clinician where their primary mental health services are received. All subjects will be psychiatrically stable and will be maintained on their current psychotropic medication.

Recruitment

Potential participants might respond to a posted advertisement at CUMC or at a participating mental health facility. Potential participants may be referred by their treating clinician. Information regarding study procedures including inclusion criteria, will be provided during a preliminary informational discussion. If the potential participant volunteers information that renders them ineligible, (e.g. participant has a hearing impairment) the potential participant will be notified. Eligibility for study participation will be formally assessed following informed consent to participate in the study.

Consent to Participate

Following a preliminary discussion of study purpose and procedures, those who express continued interest in the study will meet with a member of the research team. The consent form will be provided to the participant to review while the researcher describes study purpose, procedures, risks, benefits, participant rights, and measures to protect confidentiality. During this process, the researcher will assess whether the participant has an evident visual impairment or auditory disorder that would make them ineligible, or if the participant cannot understand the study procedures as written and presented verbally in English. If the potential participant voluntarily agrees, written consent will be obtained. The researcher will ascertain and document that the participant understands (a) the study procedures, (b) the voluntary nature of study participation, and (c) the risks and benefits. The participant will have the opportunity to ask any questions about the study prior to and following signing the consent form. The participant will be provided with a copy of the consent form, which provides the PI's contact information and the information for the IRB.

In addition to signing informed consent, participants will be asked to sign a HIPAA Authorization Form, which will be approved by the NYSPI IRB. The HIPAA Authorization Form indicates with whom research data, such as cognitive assessment results, will be shared. This includes the research team, comprised of investigators from Columbia University Medical Center and the New York State Psychiatric Institute, and the clinic where mental health services are received. Enrollment and attendance data may also be shared with the mental health service team so as to coordinate clinical and research services. Finally, de-identified research data may be shared with the Database of Cognitive Training and Remediation Studies (DoCTRS), a computer system run by the National Institutes of Health that allows researchers studying cognitive remediation to collect and share information with each other. Participants who sign informed consent to participate in the study will have the option to withdraw their data from DoCTRS at any time. This will be fully explained during informed consent.

Study Procedures: Pilot Feasibility Trial

(1) Participants will be assessed by a trained research assistant for sociodemographic data (e.g. age, education), medication and psychosocial treatment status, estimated IQ (Wechsler Test of Adult Reading), Axis I diagnosis (SCID), neuropsychological ability (MATRICS Consensus Cognitive Battery), Tone Matching ability, symptoms severity (PANSS), functioning (UCSD Performance-Based Skills Assessment-Brief), self-report of cognitive problems (Measure of Insight into Cognition – Self Report) and motivation for treatment (Intrinsic Motivation Inventory, Perceived Competency Scale). Those with IQ estimate below 70 or meeting substance dependence criteria at the time of evaluation will be exited from the remainder of the study. Assessment sessions may be divided into 2 meetings in order to reduce

burden. The total amount of time for assessment is approximately 2.5 hours.

(2) Following completion of all baseline assessments, participants will be stratified (i.e. classified) by auditory processing ability using performance on the Tone Matching Test (cut-off of 70% correct) and then randomized to receive one of two treatment conditions: “Brain Basics” or “Brain Training”. Each condition consists of 30 treatment sessions delivered at 3 times a week over a 10-week period, structured in a group format of up to 5 participants with rolling admission. Each condition is described here.

"Brain Basics" will use commercially available computer-based training software to exercise basic auditory processing in addition to processing speed, attention, working memory, verbal learning and memory. In each training session, a participant will work with four exercises for 10-12 minutes per exercise. Examples of the types of exercises that may be used are 1) making distinctions between auditory stimuli that increase or decrease in frequency while auditory sweeps become progressively faster and are separated by shorter inter-stimulus intervals, 2) distinguishing between two difficult-to-distinguish phonemes or open syllables using synthesized speech, 3) accurately identifying increasingly long arrays of open and closed syllables in spatial and sequential contexts, 4) listening to and carrying out a sequence of verbal instructions, 5) remembering details of a conversation.

"Brain Training" will consist of similar computerized exercises which are designed to directly target neuropsychological skills including attention, processing speed, verbal working memory, verbal learning and memory, abstract reasoning, and problem solving, without training on basic auditory processing. In each training session, a participant will work with four exercises for 10-12 minutes per exercise. Examples of the types of exercises that will be used are 1) tracking two objects on a screen, 2) simultaneously executing simple auditory and visual tasks, 3) remembering a word list, 4) remembering the sequence of a conversation, 5) remembering and following verbal instructions 6) sorting words by semantic category.

Both conditions will entail 45-50 minutes on the computer and 10-15 minutes group discussion (60 minutes total). In the discussion, participants will review the cognitive activities they are working on and how they will help them achieve their recovery goals.

(3) Participants will be re-tested on outcome measures approximately 1 week following end of treatment, and again 3 months later. All assessments will be conducted by an evaluator, who is blind to treatment conditions, and separate from the person administering treatment.

Measures

Early Auditory Processing: assessed with the Tone Matching Test (TMT), consisting of 5 sets of 26 pairs of 100-ms tones in series, with 500-ms inter-tone interval. Within each set, tones (50% each) are either identical or differ in frequency by a specified amount in each block (2.5%, 5%, 10%, 20%, or 50%). Subjects indicate whether the pitch is the same or different. Three base frequencies (500, 1000, and 2000 Hz) are used within each block to avoid learning effects. The TMT has demonstrated good test-retest reliability in both schizophrenia (ICC = 0.83) and healthy control (ICC = 0.821) samples (Petkova et al., 2014). The mean (SD) total percent correct in 10 studies ranges from 65.5% (9.9) to 73.3% (2.2) for 371 schizophrenia patients and 73.8 (2.3) to 92.3 (9.9) for 342 healthy controls, with a large effect size (1.17) difference (Donde et al., 2017). Within schizophrenia samples two clusters are consistently identified, with about half of the individuals having total correct scores that are significantly lower than those of healthy controls (Donde et al., submitted manuscript; Donde et al., 2017; Lee et al., 2018; Petkova et al., 2014). A cut-off score of 70% correct, based on the distribution of performance

deficits, was used to classify participants in this study as EAP impaired or EAP intact.

The NIMH MATRICS Consensus Cognitive Battery (MCCB; Nuechterlein et al., 2008) assessed neurocognitive functioning with measures of: a) working memory; b) attention/ vigilance; c) verbal learning; d) visual learning; e) processing speed; and f) reasoning and problem solving. The MCCB neurocognitive composite T-score was the primary outcome measure.

The functional outcome measure was the Brief UCSD Performance-Based Skills Assessment (UPSA-B; Mausbach et al., 2007), an assessment of functional capacity that requires participants to complete a series of role-play tasks that assess everyday life skills. The UPSA-B total score was the outcome variable.

The Structured Clinical Interview for the Positive and Negative Syndrome Scale (SCI-PANSS; Kay et al., 1992) was used to assess symptoms of psychotic disorders including positive, negative and general psychopathology.

Criteria for Early Discontinuation

1. The participant reports active use of substances (e.g. alcohol, street drugs) and meets criteria for substance dependence.

2. The participant reports active use of substances and this use consistently interferes with the subject's ability to regularly attend and participate in study sessions (e.g. 3 or more sessions). PI Medalia will be responsible for determining whether early discontinuation is necessary.

3. The participant demonstrates significant clinical worsening as given by increased risk to self or others or psychiatric hospitalization.

4. The participant is unable to attend sessions or complete study tasks (e.g. 3 or more sessions) due to psychiatric symptoms such as hallucinations (e.g. hearing voices) or disorganization. PI Medalia will make the determination that early discontinuation is warranted based on evidence gathered in-session by the group leader that the subject is unable to complete study tasks due to clinical symptoms.

Any of the above circumstances will be discussed with the clinical team prior to discontinuation.

Compensation Procedures

To offset the burden of completing the assessments, participants will be compensated $40, $40, and $70 for their participation in baseline, post-treatment, and 3-month follow up assessments respectively. The additional compensation for the 3-month follow-up is to offset any undue burden associated with maintaining participation through the follow-up time. These amounts are in accordance with a standard rate of research subject payment. If the participant travelled to the study site for assessments, we will reimburse participants for travel ($5.00).

Benefits

Cognitive rehabilitation and computerized learning software have been administered to many patient populations in various settings and are well-recognized procedures without serious risk.

There is potential for direct benefit to the participant and potential benefits for the treatment of other people with neuropsychiatric disorder. The potential for direct benefit is improvement in cognitive abilities such as attention, memory, logical reasoning, and problem solving. Participants will not be subjected to any expenses associated with their participation.

Risks

This study involves obtaining sensitive medical information (e.g. psychiatric history). One risk is a loss of confidentiality. To minimize this risk, identifying information will be protected by coding participant data and storing all information in locked offices and/or on password protected computers. The second risk is that participants may become mildly uncomfortable or tired while working on the cognitive training programs. There are no additional anticipated risks as a function of the intervention. Given that this research study will involve people with psychotic disorders, it is conceivable that participants may feel burdened by assessments or intervention participation, or may experience risks unrelated to the study, such as clinical worsening. Clinical worsening may be defined as suicidal/homicidal ideation, increase in severity of positive symptoms (e.g. hallucinations, delusions) that impact functioning and/or cause significant distress.

Procedures for minimizing risks

Assessment: There are no physical risks involved in any of the assessments, although there is a potential risk of discomfort or fatigue in answering questions about oneself, as well as working on the cognitive tests. In order to protect the rights of participants, subjects may terminate any interview and any cognitive test at any time. Breaks and refreshments may be provided to minimize burden. If feasible, assessment sessions may be divided to minimize burden and fatigue.

Intervention: There are no physical risks involved in any intervention procedures, although there is a potential risk of fatigue during computer-based intervention sessions. Subjects may take breaks during sessions as needed. Of note, PI Medalia and Co-Investigator Saperstein use similar software as part of cognitive remediation programs at many large city and community centers for psychiatric patients. There have been no adverse reactions reported and a majority of patient report a high level of satisfaction. We have also chosen a variety of engaging computerized programs that may protect against mild fatigue.

Unanticipated Adverse Events: In the case that there is evidence of clinical worsening in session (defined as suicidal/homicidal ideation, increase in severity of positive symptoms that impact functioning and/or cause significant distress) the researcher conducting the treatment session will notify the participant's treating clinician if available, or a designated clinician on-site. Such incidences will be reported to PI Medalia. All human subjects protection issues will be reviewed quarterly by PI Medalia and Co-investigator Saperstein, who will be directly involved in the assessment and treatment phases of the study.

Methods to protect confidentiality

Confidentiality of all subjects will be preserved by coding all data sheets and other data sources with an ID code, and maintaining hard copy data forms in locked files. Participating subjects are never identified by name, only by ID number. The ID will have no reference to personal identifying information. Principal investigator Medalia will be responsible for the coded list of participants. Public dissemination of the results of this research will contain no identifying information about individual subjects. Consent forms will contain identifying information and will thus be kept in a locked file cabinet in a locked office at CUMC. Consent

forms with names will be stored separately from hard copy data files. Electronic data will be stored in password protected databases on protected computers in a locked office. Electronic databases will include the participant ID number and will not use participant names.

Data Analysis Plan

Analyses addressed the following hypotheses:

1) **EAP impaired patients, as measured by performance on the Tone Matching Test, would benefit more from CR that included EAP training, while EAP intact patients would not experience greater cognitive and functional advantage with EAP training**
2) **EAP impaired patients who improved most during EAP training would show the largest gains in cognition**
3) **Cognitive gains would mediate the relationship between gains in EAP and functional outcome.**

Analyses first checked the balance of participant baseline characteristics between treatment conditions using 2 sample t-tests for continuous variables, and Chi-squared tests for categorical variables. The same approach was used to identify baseline characteristics that affect EAP status. To characterize overall response, improvements on the MCCB neurocognitive composite and UPSA-B were assessed using Cohen's d effect size, and tested using paired-sample t-tests, which for the MCCB compared change to practice effect, i.e., >2 T score points (Keefe et al., 2011).

Wilcoxon's rank-sum test, a non-parametric test which is more robust to potential outliers and error variance assumptions as compared to t-test in relatively small samples, examined the main effect of treatment condition, and the main effect of EAP status on improvement in MCCB and UPSA-B from baseline to post-treatment and from baseline to follow-up. Cohen's d effect size was also computed. The same approach was used to quantify the treatment effect within each EAP subgroup. In addition, the treatment by EAP subgroup interaction was tested using ANOVA F-test. Post-hoc, we examined the treatment effect on verbal learning using the same approach.

To test hypothesis 2, Pearson's correlation examined the association between APS and MCCB improvement. In addition, we classified Brain Basics participants as auditory learners or non-learners using a median split of APS improvement. Auditory learners and non-learners were compared on average MCCB improvement using Wilcoxon's rank-sum test, and percentage of participants with MCCB gain of 9 or more (Harvey and Keefe, 2016) using Fisher's exact test. To further address hypothesis 2, these analyses were conducted separately for EAP– and EAP+ subgroups. The interaction effect between learner status and baseline EAP status on MCCB was tested using two-way ANOVA.

To address hypothesis 3, Sobel's method of mediation analysis was used to examine neurocognition (MCCB) as a mechanism through which EAP (TMT) impacted functioning (UPSA-B) at baseline, as well as improvement at follow-up