Thursday June 3rd, 2021

TITLE: Enhancing Cognition in Older Persons: A Randomized Controlled Trial of Mindfulness-Based Stress Reduction (MBSR) and Transcranial Direct Current Stimulation (tDCS).

NCT03653351

METHODS

Study design and participants

We conducted a randomized, double blind, sham-controlled trial of tDCS combined with MBSR in adults aged 60 years or older with symptoms of depression or anxiety plus subjective cognitive complaints in two academic centers (Centre for Addiction and Mental Health, Toronto, ON, Canada; and Washington University in St. Louis, MO, USA). The study was approved by both institutional review boards and all participants provided written informed consent.

Participants were recruited between June 27, 2018 and March 6, 2019. They completed an initial phone screen followed by an in-person screening assessment, which included a review of medical history and medications to determine eligibility. Participants reported cognitive complaints but had intact cognitive function as ascertained by a Short Blessed Test [27] score ≤ 10 and a Montreal Cognitive Assessment (MoCA; [28]) score ≥ 25. The Patient Reported Outcomes Measurement Information System (PROMIS) measures were used to assess depression and anxiety over the past seven days [29] including self-reported negative mood, views of self, social cognition, decreased positive affect, engagement self-reported fear, anxious misery, hyperarousal, and somatic symptoms related to arousal [30]. Participants were included if their baseline PROMIS 8-item depression score was ≥ 16 or their baseline PROMIS 7-item anxiety score was ≥ 14, indicating moderate to severe symptoms.

Exclusion criteria included unstable medical illness, metal implants, significant neurological conditions, use of cognitive enhancers (e.g., donepezil) within the past 6 weeks, use of anticonvulsants or antipsychotics (other than low-dose aripiprazole (≤ 2mg) or low dose gabapentin (≤ 100mg) if prescribed for pain), current cognitive training with brain training software, regular participation in mindfulness practice or yoga, IQ < 70 as estimated by the Wechsler Test of Adult Reading (WTAR; [31]), lifetime diagnosis of bipolar disorder, schizophrenia, schizoaffective disorder, or untreated post-traumatic stress disorder, or substance abuse within six months, as diagnosed by the Mini-International Neuropsychiatric Interview (MINI; [32]). Participants meeting all eligibility criteria completed the baseline assessments, which included self-report and neuropsychological assessments of outcomes, listed below.

Interventions

All participants received MBSR; they were randomly assigned (1:1) to active or sham tDCS, using a permuted block approach to ensure treatment balance within each study site. Participants, MBSR instructors, and outcome raters were blinded to the tDCS condition (i.e., active vs. sham). Following the protocol of a large trial assessing the efficacy of combing tDCS with cognitive remediation in preventing dementia among older adults with mild cognitive impairment or remitted depression [33], active tDCS administration involved applying excitatory bilateral stimulation to the left and right DLPFC. To achieve this bilateral stimulation, the anode was placed at Fz and the cathode at Iz as per the 10-20 international electrode placement system. The tDCS was applied using a direct current of 2 mA (current density of 0.57 A/m^2) for 30 minutes per day [33]

during meditative practices of MBSR. The same parameters were used for sham stimulation, except the device shut off after 30 seconds of active stimulation. This brief period of active stimulation is not known to produce active neurological effects, but does ensure blinding because it is associated with common side effects of active tDCS, such as tingling and itching under the electrodes [34-36].

Prior to the initiation of the intervention, all participants completed tDCS training provided at the local academic hospital using a group format. During five one-hour group sessions provided over five consecutive days, participants were given an overview of the tDCS device and detailed instructions for administration, programming, resetting, electrode placement, and safety procedures (such as aborting sessions safely). They were also trained on how to troubleshoot tDCS problems, such as managing side effects e.g. tingling and itching, and self-record necessary data. At the end of training, participants were required to demonstrate their competency self-administering tDCS by passing an assessment administered by the study coordinators. Throughout the tDCS training sessions and the intervention trial, participants had access to a training video detailing the procedures to guide them through tDCS administration as needed. A manual and coordinator contact information was also provided to each participant, and the study coordinator was available to troubleshoot over the phone during at-home tDCS sessions.

The MBSR training was based on the program developed by Jon Kabat-Zinn at the Center for Mindfulness University of Massachusetts Medical School [14, 15]. The in-class MBSR training was conducted at the academic hospital using a group format over

approximately ten weeks; group sessions included an orientation session, 8 weekly 2.5-hour classes, and a half-day retreat. All participants were required to attend the MBSR in-person classes and instructed to refrain from discussing tDCS treatment amongst themselves to protect blinding. Content included instruction in mindfulness meditation, mindful movements, and discussion of home practices to enhance mindfulness in everyday life. At the end of each in-class session, the MBSR instructor gave the group a structured MBSR activity and associated audio files to complete at home for the week. The study used "A Mindfulness-Based Stress Reduction Workbook" as a companion guide [37]. In summary, participants attended weekly in-class group MBSR plus tDCS sessions at the hospital, and then asked to complete at least 30 minutes of guided MBSR and tDCS at home the other six days of the week.

Outcomes

Trained research staff blinded to participants' tDCS assignment performed pre- and post-intervention assessments. Follow-up assessments were performed within two weeks of completing the intervention. Feasibility was assessed by examining participants' in-class attendance (i.e., number of in-person MBSR group sessions attended) and adherence to at-home mindfulness practice while using tDCS. Participants completed hand-written logs daily, detailing their at-home use of tDCS and the frequency and duration of MBSR practice; these self-report logs were used to determine the at-home adherence rates. To determine the at-home adherence rate, we first determined how many at-home sessions each participant completed by looking through the at-home logs. We then calculated the

total expected number of sessions that should have been completed at home over the period of the intervention. Lastly, we divided the total number of sessions each participant completed by the total number of expected sessions to get a percentage of at-home adherence. Participants also documented any failures of the tDCS device during stimulation and any adverse events (AEs). AEs that required the discontinuation of tDCS or MBSR were identified, as were serious adverse events (SAEs) defined as AEs that resulted in life-threatening health issues, hospitalization, or death.

The main cognitive measure was the Fluid Cognition Composite from the National Institutes of Health (NIH) Toolbox Cognition Battery [38], a computer-based instrument measuring both crystalized and fluid cognition. In addition, immediate memory and delayed recall were measured using a standard 16-word list validated at the Washington University Alzheimer's Disease Research Center that is sensitive to change and does not have ceiling effects in preliminary studies.

The Cognitive Affective Mindfulness Scale – Revised (CAMS-R; [39]) was used to measure the four domains of mindfulness – attention, present-focus, awareness, and acceptance. CAMS-R is a self-report measure of everyday mindfulness that is not specific to any one type of meditation. CAMS-R asks questions about translating and integrating the domains of mindfulness into everyday life, for example, being able to focus on the present moment, and keeping track of one's thoughts and feelings. CAMS-R

was administered pre- and post-intervention to determine how well participants integrated the teachings from MBSR into their everyday lives.

In addition to the PROMIS measures of depression and anxiety, the two following PROMIS measures were used to assess satisfaction with, and ability to perform usual social roles and activities: the 8-item short form v2.9 PROMIS Scale for Satisfaction with Social Roles and Activities [40] and the 8-item short form v2.0 PROMIS Ability to Participate in Social Roles and Activities [40].

Statistical Analyses

All data were analyzed using the Statistical Program for Social Sciences (SPSS) version 25.0 [41]. Extreme outliers (±3 standard deviations) were removed for each time point. Data were visually inspected for normal distribution and were checked statistically with the Shapiro-Wilk test. Chi-square and independent samples *t*-tests were used to evaluate differences between the active and sham tDCS groups on baseline demographic, clinical, and cognitive measures.

Measures of feasibility, tolerability, and safety were analyzed descriptively. While the primary goal of this pilot study was to assess feasibility, tolerability, and safety, preliminary evaluations of changes in efficacy measures were performed using repeated measures analyses of variance (RM-ANOVAs), with randomization as the between-subjects variable, and time-point (pre- or post-intervention) as the within-subjects

variable. For cognition, the three dependent variables were: NIH Toolbox Cognition Battery Fluid Cognition Composite, total recall score of the word list, and the delayed recall score of the word list. The effects of the intervention on subjective changes were explored with the following five dependent variables: CAMS-R, PROMIS depression scores, PROMIS anxiety scores, PROMIS satisfaction with social roles and activities, and PROMIS ability to participate in social roles and activities. For this pilot trial, a $p < 0.05$ was considered significant and no corrections were made for multiple comparisons.