Title: An assessment of combined cognitive remediation and trans-cranial direct current stimulation for the improvement of verbal learning and memory in people with schizophrenia.

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A. Study Purpose and Rationale

Neurocognitive impairment is present in almost all patients with schizophrenia (Keefe et al., 2005). Currently no medication can fully address this deficit with the newest generation of antipsychotics providing only minimal improvement (Hagan and Jones, 2005). Cognitive remediation seeks to improve cognitive impairment through drills, practice exercises, compensatory strategies and group discussions (McGurk et al., 2007). The brain fitness program developed by Posit Science is a form of cognitive remediation that utilizes a bottom up strategy. The program initially seeks to improve auditory discrimination mechanisms in primary auditory cortex using simple sounds similar to speech in frequency content. As the user becomes more proficient at these simple exercises, more advanced exercises are introduced using phoneme, whole word and narratives as stimuli. It is likely that these more advanced exercises utilize both primary sensory, limbic and associative regions of cortex.

Both psychophysical and neurophysiological studies support the notion of deficits in early sensory processing in schizophrenia (Stelt and Belger, 2007; Javitt et al., 2008; Javitt 2009). One possibility is that these deficits are amenable to change by the use of cognitive remediation programs utilizing a bottom up approach (Fischer et al., 2009). This theory posits that improving frequency discrimination, for instance, will lead to improved performance in more complex tasks such as remembering a list of items.

Evidence supporting the efficacy of the brain fitness program in improving cognition in patients with schizophrenia emerged in a single study that reported that 50 hours of training increased verbal working memory, verbal learning and verbal memory that persisted for at least six months (Fischer et al., 2009; Adcock et., 2009). However, a recent study supported by GlaxoSmithKline Inc. using the brain fitness program found no changes in these measures (Murthy et al., 2010). This unpublished study is consistent with a number of studies that failed to identify changes in diverse neuropsychological measures following extended periods of cognitive remediation (Dickinson et al., 1010; Owen et al., 2010). In light of these negative findings, it has been suggested that cognitive remediation could be enhanced by concurrently administering cognitive enhancing medications in a manner analogous to administering steroids with exercise. (Keefe et al., 2010).

From a mechanistic perspective, this possibility of treatment synergy is sensible. Cognitive remediation is thought to result in improved brain function due to the induction of plastic changes in relevant brain circuits (Buonomano and Merzenich, 1998; Simos et al., 2002; Tallal, 2004; van Wassenhove and Nagarajan, 2007) and some cognitive enhancing medications are in development that may help to promote plasticity or activate critical dysfunctioning pathways (Hagan and Jones, 2005; Apud and Weinberger et al., 2007; Lewis et al., 2008; Kantrowitz et al., 2010). Herein I propose non-invasive brain stimulation using electric fields as an alternative method of promoting brain plasticity synergistic with cognitive remediation.

Fundamentally, electric fields influence brain activity by locally polarizing regions of membrane with active properties (Weiss and Faber., 2010). The magnitude and sign of the field effect depend on a multitude of factors including the orientation of the field and the geometry of the neurons affected. Yet, it is becoming increasingly clear that electric fields by affecting populations of single neurons elicit network effects mediated by chemical synapses which magnify the changes felt by any one single neuron (Purpura and McMurtry, 1965; Francis et al., 2003; Frohlich et al., 2010; Ozen et al., 2010). Therefore even minute fields applied through the skull using a variety of electrode configurations can significantly influence neuronal populations (Matsunaga et al., 2004; Polonia et al., 2010).

Physiological effects that outlast the stimulation, i.e. tDCs plasticity, have been identified and may be mediated by modulation of NMDA receptors (Liebetanz et al., 2002; Nitsche et al., 2003; Siebner et al., 2004). tDCs induced plasticity has been attributed to the involvement of catecholamines (Nitsche et al., 2004), acetylcholine (Kuo et al., 2007), and alterations of excitatory-inhibitory balance (Stagg et al., 2009). Most recently, in rats it was found that long term potentiation (LTP) of synapses in primary motor cortex could be elicited by pairing anodal tDC with low frequency synaptic activation. The successful induction of LTP depended on both the expression of BDNF and Trk-B. Furthermore, applying anodal tDCs in behaving animals increased motor learning in wild type animals but not in BDNF knock out littermates (Fritsch et al., 2010). On the basis of these findings it is likely that anodal tDCs may directly or indirectly promote brain plasticity by influencing population activity in cortical networks that ultimately promotes the release of BDNF and increases in fast excitatory neurotransmission.

In human studies, the application of anodal tDCs has been shown to produce lasting improvements in both motor (Reis et al., 2010) and language (Baker et al., 2010) domains, for instance. When tDCs was applied for several days during practice of a motor and word naming exercise, respectively, performance in these tasks was improved, compared to subjects given sham stimulation, both initially, and at a 1 week (Baker et al., 2010), or 3 month (Reis et al., 2010) follow up. It is believed that these stable gains in performance occur because of heightened off-line consolidation of practiced material (Reis, 2010). Notably, in the case of language, performance gains were observed in both practiced and non-practiced material supporting the notion that learning modulated by tDCs can be generalized to other contexts (Baker et al., 2010).

In the present study, I hope to test whether applying anodal tDCs to language related cortical regions while subjects engage in the brain fitness program leads to significant persistent benefits in language processing and performance. Developing a successful cognitive remediation approach for patients with schizophrenia would benefit patients, caregivers, and society.

B. Study design

This study seeks to enroll 52 patients with schizophrenia randomly assigned to an active and a sham arm. These patients will engage in the brain fitness program for one-hour daily, five days a week, for four weeks. During the session the patients will have anodal or sham tDCs while performing the brain fitness program. In total each subject will complete 20 hours of the brain fitness program, and the subjects in the active arm will receive 20 hours of tDCs.

I plan to stimulate left auditory cortex, Wernicke's area (Floel et al., 2008; Ferrucci et al., 2008), angular gyrus and Broca's area (DeVries et al., 2009; Baker et al., 2010) with HD-tDCs electrodes (Datta et al., 2009; Minhas et al., 2010). I would most likely use a stimulation intensity of 2 mAmps or equivalent. Electrode placement would be based on MRI derived modeling approach (Datta et al., 2009; Minhas et al., 2010) using EEG electrode conventions. It would thus be essential for each subject to obtain a head MRI before participating in the experiment. Sham tDCs will be provided by exposing the subject to 30 sec transients of stimulation at the beginning and end of the session (Baker et al., 2010).

Assessments of performance will be multifaceted. The brain fitness program uses an internal system of points and progress bars to score accuracy and reaction time on the tasks. On the basis of these measurements I can assess whether tDCs is beneficial. To assess if the combined tDCs and brain fitness program protocol improves verbal memory and learning I will use MATRICS based measures such as The Hopkins Verbal Learning Test (immediate and delayed), and the Letter Number Span Test (Fisher et al., 2009)(Nuechterlein et al., 2008; Kern et al., 2008).

At the beginning and at the conclusion of the study subjects will have a MEG performed. I will record activity at rest, during the auditory oddball task, as well as during a task similar to the Brain Fitness Program (Weiss et al., in preparation).

C. Statistical Analysis

The sample size of the study was calculated on the basis of the documented effect size from prior investigations of cognitive remediation (Fisher et al., 2009), and tDCs (Baker et al., 2010). These studies as well as my own shall compare metrics between the two arms using the unpaired t-test.

In the process of investigating whether the combined use of tDCs and the brain fitness program influences verbal processing and performance, this study seeks to better characterize the lasting effects of tDCs on brain physiology (Polonia et al., 2010). In our previous magnetoencephalography study of the brain fitness program we identified mesoscale correlates of performance (Bassett et al., 2009) and practice (van Wassenhove and Nagarajan, 2007; Penolazzi et al., 2010; Liu and Ioannides, 2004) using both a signal power and coherence based analysis. Thus, we are prepared to apply a similar analysis to tDCs induced changes in resting and active brain states with the hopes of interpreting changes in MEG activity elicited by tDCs and cognitive remediation in a functional context. Furthermore, I plan to use an auditory oddball paradigm and to record event related fields, such as the M300, to determine if tDCs and training influence this biomarker of schizophrenia (Javitt et al., 2008)

D. Study Procedure

In a designated testing facility subjects will be assigned individually to computers running the Brain Fitness Program. All subjects will wear a tDCs stimulation device. A trained expert will initiate and monitor the cathodal or sham tDCs stimulation over the course of the experiment. MEG experiments will be conducted at a core facility and subjects will be monitored throughout the duration. Subjects will practice together as a group.

E. Study Drugs and Devices

Optimizing the delivery of tDCs for maximal efficacy is still an active area of research. Currently most experiments are conducted using electrodes consisting of saline soaked sponges. While, most of the encouraging results using tDCs have emerged from studies using this methodology, modeling suggests it is spatially non-specific (Datta et al., 2009). Dr. Marom Bikson's group at CUNY has developed an alternative ring electrode configuration that has increased focality (Datta et al., 2009; Minhas et al., 2010). Clinical trials using this electrode configuration are currently underway at NIH (Bikson, personal communication). Furthermore, Dr. Bikson's group has developed models that based on electrode placement and a brain MRI can accurately predict the regions stimulated and the strength and orientation of the field.

F. Study Subjects

Patients, male or female, must be 18-50 years old and diagnosed with schizophrenia. They must be competent to consent and currently being treated with antipsychotic medication. Patients will be excluded if they have a history of substance use or dependence in the last 6 months, concomitant major medical or neurological illness, are currently taking carbamazepine, or are pregnant. Patients will be withdrawn if they withdraw consent, experience significant clinical deterioration, fail to tolerate the procedure, or develop a serious adverse event.

G. Recruitment

Patients undergoing treatment for schizophrenia will be recruited by informed healthcare professionals. The clinical trial will also be listed on the internet at clinicaltrials.org.

H. Confidentiality of Data

All data will be kept confidential. Each subject will be given an encrypted study number. Under no circumstances will personal information be released or associated with the results.

I. Potential Risks

The safety of tDCs is well documented (Iyer et al 2005; Vandermeeren et al., 2010; Liebetanz et al., 2009; Poreisz et al., 2007; Nitsche et al., 2003). However, the safety of tDCs in the context of this specific protocol is unknown. EEG can be used to monitor for seizures.

J. Potential Benefits

Subjects in both arms of the study can potentially benefit from participation. On the basis of Fisher et al., 2009 findings, subjects may demonstrate improved global cognition, particularly with verbal learning, and memory.

K. Compensation

Subjects will be compensated for participating in this study. Compensation will be paid at an hourly rate. Additional compensation will be provided for the MEG scan.

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