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Neuroscience-informed auditory training in schizophrenia: A final report of the effects on cognition and serum brain-derived neurotrophic factor☆

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ABSTRACT

Objective: We previously reported the interim effects in a per protocol analysis of a randomized controlled trial of an innovative neuroscience-informed computerized cognitive training approach in schizophrenia. Here we report the effects of training on behavioral outcome measures in our final sample using an intent-to-treat analysis. We also report the effects on serum brain-derived neurotrophic factor (BDNF).
Method: Eighty-seven clinically stable participants with schizophrenia were randomly assigned to either targeted auditory training (AT, N=46) or a computer games control condition (CG, N=41). Participants were assessed on neurocognition, symptoms and functional outcome at baseline and after 50 hours of intervention delivered over 10 weeks. Serum BDNF was assessed at baseline, at 2 weeks, and at 10 weeks.
Results: After the intervention, AT participants showed significant gains in global cognition, speed of processing, verbal learning, and verbal memory, relative to CG participants, with no changes in symptoms or functioning. At baseline, schizophrenia participants had significantly lower-than-normal serum BDNF. AT participants showed a significant increase in serum BDNF compared to CG participants, and "normalized" levels by post training.
Conclusions: Participants with chronic schizophrenia made significant cognitive gains after 50 hours of intensive computerized training delivered as a stand-alone treatment, but no improvement in symptoms or functioning. Serum BDNF levels were significantly increased, and may serve as a peripheral biomarker for the effects of training. Future research must focus on: 1) Methods of integrating cognitive training with psychosocial treatments; 2) A deeper understanding of underlying neurophysiology in order to enhance critical mechanisms of action.

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1. Introduction

We previously reported our interim findings from a randomized clinical trial of targeted cognitive training of auditory processing and auditory/verbal working memory in schizophrenia. Using a per protocol analysis on data from 55 participants, we found significant cognitive gains after 50 hours of auditory cognitive training as a stand-alone treatment relative to an active control condition of computer games (Fisher et al., 2009), and a significant increase in serum brain-derived neurotrophic factor (BDNF) relative to the control condition (Vinogradov et al., 2009). Here, in our final sample of 87 participants, we report the behavioral effects of the training using an intent-to-treat analysis, as well as the effects on serum BDNF.

The study of cognitive remediation in schizophrenia has grown substantially over the past 20 years. Meta-analytic studies indicate that a vast array of cognitive training approaches have a small to medium effect on cognition, on functioning, and on durability of effects at follow-up, and a small but non-durable effect on symptoms (McGurk et al., 2007; Wykes et al., 2011). Wykes et al. (2011) found a mean global cognition effect size of 0.45, with heterogeneity of effect sizes in global cognition, speed of processing, and reasoning and problem solving; however, the meta-analysis did not find that type of training, participant characteristics, or trial quality could account for this heterogeneity in cognitive outcomes. It does appear that a wide range of approaches providing various forms of cognitive stimulation for variable amounts of time and treatment intensity *all* have a modest beneficial effect in schizophrenia. However, it is difficult to draw too many definitive conclusions from the currently available data from previous cognitive remediation studies, given the wide disparity in assessment measures, study designs, patient samples, cognitive remediation methodologies, and control groups used. Further,

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differences in methodology and design – including trials that combine cognitive remediation with other treatments – make it difficult to discern which components of improved cognition or functioning are the result of the cognitive training per se and which may be due to other study features, such as increased staff contact, computer exposure, or the provision of strategy coaching or other forms of skills training.

In the present study, we performed a double-blind randomized controlled trial of an innovative, neuroscience-informed approach to cognitive training in schizophrenia, delivered as a stand-alone treatment relative to a computer games control condition. The primary goal of the computerized exercises is to train the individual to become more efficient in the early processing of auditory and verbal information, and to increase auditory working memory capacity. This approach is based on the large body of research that demonstrates impairments in early sensory processing as well as associated frontally-mediated cognitions in schizophrenia (e.g., Adcock et al., 2009; Kasai et al., 2002; Ragland et al., 2004, 2007). We posed two questions: 1) Using an intent-to-treat analysis in our final sample of 87 participants, do we replicate our earlier interim findings on the significant cognitive effects of 50 hours of training? 2) What is the effect of training on serum BDNF in our final sample?

Brain-derived neurotrophic factor (BDNF) plays a critical role in neurodevelopment, neuronal function, and neural plasticity. Schizophrenia may be related in part to decreases in normal BDNF functioning (Buckley et al., 2007; Carlino et al., 2012). Meta-analyses indicate that blood BDNF levels are significantly lower in schizophrenia relative to healthy controls (Green et al., 2011), and that peripheral BDNF and cognition are positively associated in schizophrenia (Ahmed et al., 2015; Carlino et al., 2012), however there is considerable heterogeneity across studies.

While the relationship between peripheral and central BDNF remains speculative, peripheral BDNF is hypothesized to reflect central BDNF based on evidence that BDNF crosses the blood-brain barrier (Pan et al., 1998), and based on findings of significant associations between peripheral and central BDNF levels. For example, Karege et al., 2002) found a strong correlation between serum and cortical BDNF levels in rats. In healthy individuals, BDNF serum concentration showed an association with in vivo level of cerebral N-asetylaspartate – a marker of neuronal integrity (Lang et al., 2007). In a study of drug-naïve patients with first-episode psychosis, plasma BDNF level and BDNF level in cerebrospinal fluid were significantly associated (Pillai et al., 2010).

We previously found a significant increase in serum BDNF at two weeks and 10 weeks of training relative to the computer games control condition (Vinogradov et al., 2009). In the active condition, participants' BDNF level increased to that of a healthy comparison sample by post-training, whereas the control group showed no change. A deeper understanding of the role of BDNF in cognitive enhancement in schizophrenia will likely provide important insights for the design of future treatments.

2. Methods

2.1. Participants

We describe below our final sample of 87 participants who participated in the trial (ClinicalTrials.gov Identifier: NCT00312962). Clinically stable, chronically ill, volunteer schizophrenia participants were recruited from mental health treatment settings in the community. All participants gave written informed consent and underwent a series of baseline clinical and cognitive assessments. Participants were stratified by age, education, gender, and symptom severity, and randomly assigned to either the neuroplasticity-based auditory cognitive training (AT) condition or a control condition of engaging commercial computer games (CG). Participants were receiving case management in the community but were not enrolled in any psychiatric rehabilitation program, and reported no prior cognitive remediation treatment. Participants remained on stable doses of medications during the study, defined as no change in dosage greater than 10%. All participants received nominal payment for each successful day and week of participation, which was contingent on attendance only.

A CONSORT diagram of enrollment and allocation is shown in Fig. 1. Demographic characteristics and medication regimens of the participant groups are presented in Tables 1 and 2.

2.2. Auditory cognitive training exercises

Auditory training (AT) was provided by software developed by PositScience, Inc. Participants were driven to make progressively more accurate distinctions about the spectro-temporal fine-structure of auditory stimuli and speech under conditions of increasing working memory load (i.e. increasing number of stimuli, and decreasing inter-stimulus intervals and duration of stimulus presentation). Stimuli across the exercises spanned the acoustic and organizational structure of speech, from very simple acoustic stimuli and tasks (e.g., time order judgments of rapidly successive frequency modulated sweeps) to the complex manipulations of continuous speech (e.g., narrative memory). The exercises were continuously adaptive in that they first established the precise parameters within each stimulus set required for an individual participant to maintain 80% correct performance; once that threshold was determined, task difficulty increased or decreased systematically and parametrically as performance improved or declined. In all exercises, correct performance was heavily rewarded in a game-like fashion: each correct response was followed by novel and amusing visual and auditory embellishments as well as the accumulation of points. After several correct responses, a longer and more elaborate animation was provided.

2.3. Computer games control condition

The computer games (CG) condition was designed to control for the effects of computer exposure, contact with research personnel, and monetary payments. Participants in the CG condition came to the lab five days a week, one hour per day, and were monitored by staff in the same manner as AT participants. CG participants rotated through a series of 16 different enjoyable commercially available computer games (e.g., visuospatial puzzle games, clue-gathering mystery games) playing 4–5 games on any given day.

2.4. Assessments

The Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987), an abbreviated version of the Quality of Life Scale (QLS, Bilker et al., 2003; Heinrichs et al., 1984), and MATRICS recommended cognitive measures (Nuechterlein and Green, 2006) were administered at baseline and after training. For problem solving, the BACS Tower of London (Keefe et al., 2004) was used in place of the NAB Mazes. At the time this study was initiated, the MCCB battery was not yet available but the list of recommended measures for the MCCB Beta Version were available on the MATRICS website (http://www.matrics.ucla.edu). We obtained the MATRICS recommended measures from test publishers, and converted raw scores to z-scores using normative data, stratified by age, published by the test authors. All measures were distinct and independent from tasks practiced during training. Alternate forms of tests were administered and counterbalanced for tests sensitive to practice effects.

At study entry, each participant received a standardized diagnostic and clinical evaluation performed by research personnel trained in research diagnostic techniques. Evaluations included the Structured

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