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D-Cycloserine augmentation of cognitive remediation in schizophrenia

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ABSTRACT

D-Cycloserine (DCS) has been shown to enhance memory and, in a previous trial, once-weekly DCS improved negative symptoms in schizophrenia subjects. We hypothesized that DCS combined with a cognitive remediation (CR) program would improve memory of a practiced auditory discrimination task and that gains would generalize to performance on unpracticed cognitive tasks. Stable, medicated adult schizophrenia outpatients participated in the Brain Fitness CR program 3–5 times per week for 8 weeks. Subjects were randomly assigned to once-weekly adjunctive treatment with DCS (50 mg) or placebo administered before the first session each week. Primary outcomes were performance on an auditory discrimination task, the MATRICS cognitive battery composite score and the Scale for the Assessment of Negative Symptoms (SANS) total score. 36 subjects received study drug and 32 completed the trial (average number of CR sessions = 26.1). Performance on the practiced auditory discrimination task significantly improved in the DCS group compared to the placebo group. DCS was also associated with significantly greater negative symptom improvement for subjects symptomatic at baseline (SANS score ≥20). However, improvement on the MATRICS battery was observed only in the placebo group. Considered with previous results, these findings suggest that DCS augments CR and alleviates negative symptoms in schizophrenia patients. However, further work is needed to evaluate whether CR gains achieved with DCS can generalize to other unpracticed cognitive tasks.

1. Introduction

Efforts to develop pharmacologic treatments for cognitive deficits and negative symptoms of schizophrenia over the past decade have proven mostly disappointing (Goff et al., 2011). This lack of success may reflect several problems, including heterogeneity of the illness and the inadequacy of current disease models for drug development. If cognitive deficits and negative symptoms result from aberrant neurodevelopment involving structural defects in synaptic function and connectivity, traditional pharmacologic models are unlikely to ameliorate symptoms. An alternative approach aims to enhance neuroplasticity by exploiting the brain's inherent capacity to modify function in response to environmental demand, a process that appears to be impaired in schizophrenia (Daskalakis et al., 2008). Cognitive remediation (CR) is an example of this strategy, employing cognitive exercises to optimize efficiency of compromised brain circuits. In a carefully controlled trial, a CR program emphasizing auditory discrimination exercises was found to improve a broad range of cognitive functions in schizophrenia subjects (Fisher et al., 2009); similar findings have been reported with other CR approaches, although effect sizes have been small to moderate (Wykes et al., 2011). It remains unclear, however, whether the benefits of CR extend to cognitive domains that are not practiced and whether the cognitive gains translate into improved functioning if not combined with psychosocial interventions (Dickinson et al., 2010; Hooker et al., 2012; Murthy et al., 2012).

Neuroplasticity involves a series of biochemical steps often beginning with activation of glutamatergic N-methyl D-aspartate receptors (NMDARs). Stimulating NMDARs induces calcium entry, protein kinase activation, gene expression and protein synthesis (Kandel, 2001). Protein synthesis is required for long-lasting forms of synaptic plasticity (e.g. long-term potentiation or LTP) and long-term memory (LTM). Many forms of learning and memory depend on NMDARs including auditory discrimination conditioning (Tan et al., 1989; Dunn and Killcross, 2006; Dix et al., 2010).

As a strategy to enhance neuroplasticity and thereby optimize functioning of compromised brain circuits in schizophrenia, we have studied intermittent treatment with the NMDAR agonist, D-cycloserine (DCS).

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Although DCS may affect multiple NMDA receptor subtypes, it has greater efficacy at receptors containing the NR2C subunit compared to endogenous agonists D-serine and glycine (Dravid et al., 2010). NR2C-containing NMDARs are important for memory (e.g. Hillman et al., 2011) and show reduced expression in prefrontal cortex (PFC) of schizophrenia patients (Beneyto and Meador-Woodruff, 2008; Weickert et al., 2013). DCS has been shown to enhance LTP and improve LTM in rodents after a single dose (Watanabe et al., 1992; Walker et al., 2002), however, tolerance develops with repeated dosing (Quartermain et al., 1994; Parnas et al., 2005). DCS also improves auditory discrimination performance in rodents (Thompson and Disterhoft, 1997). Consistent with D-cycloserine's memory effects being mediated by activity at NR2C-containing NMDARs, CIQ, a more selective potentiator of NR2C/2D-containing NMDARs, enhances retention of fear conditioning and extinction learning in rats and reverses MK801-induced deficits in prepulse inhibition and working memory (Ogden et al., 2014; Suryavanshi et al., 2013).

Schizophrenia patients exhibit memory impairments in tasks known to be sensitive to DCS facilitation. For instance, cortical neuroplasticity associated with motor training is impaired in schizophrenia (Daskalakis et al., 2008), and similar neuroplasticity is enhanced by DCS in healthy subjects (Nitsche et al., 2004). We have found deficits in fear extinction in subjects with schizophrenia (Holt et al., 2009; Holt et al., 2012), and numerous studies have demonstrated facilitation of fear extinction with DCS (Davis, 2011). We also found that a single dose of DCS selectively improved LTM in schizophrenia patients as measured by 7-day thematic recall on the Logical Memory Test (Goff et al., 2008).

We hypothesized that once-weekly DCS in schizophrenia patients would augment neuroplasticity induced by an 8-week "Brain Fitness" CR program, which emphasized auditory discrimination exercises. We further hypothesized that gains observed with the practiced task would generalize to other cognitive domains measured by the MATRICS battery. In addition, our design allowed us to attempt a replication of our prior finding that once-weekly DCS improves negative symptoms as measured by the Scale for the Assessment of Negative Symptoms (SANS) (Goff et al., 2008).

2. Materials and methods

The study was registered as clinical trial NCT00963924 and received approval from the Partners Healthcare institutional review board. Subjects were adult outpatients, ages 18–65, recruited by advertisement and clinician referral at an urban community mental health center, with a diagnosis of schizophrenia or schizoaffective disorder, depressed type, and treated with a stable dose of any antipsychotic other than clozapine for at least 4 weeks. Patients were excluded from participation for significant medical illness, renal insufficiency, seizure disorder, substance abuse, pregnancy or nursing, or inability to perform the cognitive remediation program or cognitive battery. After the study was explained to them, subjects provided written consent to participate and were assessed by a research psychiatrist to confirm the diagnosis based on interview, review of records and consultation with treating clinicians. The research psychiatrist also completed a medical history and review of medical records to identify unstable medical illness.

Subjects were randomly assigned in a 1:1 ratio to DCS (50 mg) or placebo prepared in identical capsules administered once weekly for 8 weeks, 60 min prior to training. The DCS dose was based on a single-blind dose finding trial conducted in schizophrenia subjects in which 50 mg produced improvement in working memory and negative symptoms whereas neither 15 mg or 250 mg was effective (Goff et al., 1995). A DCS dose of 50 mg has subsequently been demonstrated to improve negative symptoms and memory consolidation in schizophrenia subjects (Goff et al., 1999, 2008) and doses ranging from 50 to 500 mg improved response to CBT in individuals with anxiety disorders (Ressler et al., 2004; Norberg et al., 2008). In contrast, a DCS dose of 250 mg has been associated with worsening of psychosis in schizophrenia subjects (Cascella et al., 1994). The study biostatistician provided a computer-generated randomization sequence using the permuted block method stratified according to whether subjects enrolled in CR 3 or 5 times weekly. All study personnel were kept blind to treatment assignment except for the research pharmacist. The study, which was initiated in August, 2009, was designed to include 64 evaluable subjects in order to achieve 80% power to detect an effect size of 0.72, but was terminated in November, 2011, for administrative reasons (departure of the principal investigator) after 54 subjects were enrolled. Subjects were allowed to choose a frequency of 3 or 5 sessions per week for their participation in CR sessions during the 8 week trial. Subjects performed the Brain Fitness Program (Posit Science, San Francisco, CA) exercises in a specialized laboratory free of environmental distraction and were monitored by a technician. At the first session, subjects viewed a 20 minute overview developed by the manufacturer which outlined the program and provided instructions. They then completed a baseline measure of auditory discrimination (also provided by the manufacturer) which sets the level of difficulty for the first CR session. Study drug was administered 1 h prior to the first CR session each week. Subjects could complete a maximum of 40 one-hour sessions during which they were presented with three (of five possible) different cognitive exercises in addition to the auditory discrimination training. Each exercise lasted 15 min.

The following assessments were completed at baseline: Positive and Negative Symptoms Scale (PANSS), Calgary Depression Scale for Schizophrenia (CDSS), Global Assessment Scale (GAS), Heinrich Carpenter Quality of Life Scale (QoL), the Systematic Assessment for Treatment-Emergent Side Effects (SAFTEE), the MATRICS cognitive battery, and the Scale for Assessment of Negative Symptoms (SANS, modified by removing the attention subscale). Subjects were queried for side effects at every visit. The clinical rating scales were repeated at weeks 4 and 8, the auditory discrimination measure was repeated at weeks 1, 2, 4, and 8, and the MATRICS battery was repeated at week 8 — all prior to drug administration.

The auditory discrimination task, described in detail elsewhere (Fisher et al., 2009; Keefe et al., 2012), involved trials in which the subject differentiated between rapidly-presented frequency-modulated sweeps separated by a short interstimulus interval (ISI). In this task, sustained successful performance is more difficult with shorter stimulus presentations and ISIs (which were equal within a trial). Thus, our dependent measure was the shortest stimulus duration/ISI for trials in which subjects were able to perform the task at 85% accuracy, referred to as ISI for simplicity.

Baseline differences between the two groups were compared using t-tests and Fisher's exact test. The principal analyses were performed under a Repeated Measures Mixed Model (MMRM) with time represented by discrete visits. The model included fixed effect terms for treatment group, visit and their interaction. The covariance model for the repeated measures was assumed to follow a compound symmetry covariance matrix, which is equivalent to assuming a random participant-specific intercept. Estimated contrasts include differences between treatment groups at each visit, changes over time for each group and group by time interactions, which are changes over time in difference between treatment groups. In cases where the response was measured at more than two time points, such as ISI and SANS, the model contains multiple parameters that represent group by time interaction effects. In these cases a claim of significance is made only when a test of the null hypothesis that all the relevant parameters are equal to zero yields a p-value less than 0.05. These mixed model results were produced by using SAS PROC MIXED (version 9.2, SAS Institute, Cary, NC).

3. Results

Fifty-four schizophrenia patients were enrolled; 40 were randomized, 36 received at least one dose of DCS or placebo, and 32 completed the 8 week trial (Fig. 1). Subjects assigned to DCS did not differ from the