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Short communication

Neuroimaging predictors of response to cognitive remediation and social skills training: A pilot study in veterans with schizophrenia

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ABSTRACT

Neuroimaging may predict response to cognitive remediation therapy and social skills training (CRT + SST) in schizophrenia. Identifying biological predictors of response is crucial for treatment decision making given not all patients respond to such interventions. Nineteen veterans with schizophrenia enrolled in an 8-week trial of CRT + SST. Ten participants completed diffusion tensor imaging (DTI) at baseline. Baseline fractional anisotropy (FA) in the superior longitudinal fasciculus (SLF) and overall average FA predicted improvements in visual-spatial working memory, and social cognition, respectively. Neuroimaging may be useful in identifying therapeutic targets in schizophrenia.

1. Introduction

Cognitive impairment in schizophrenia is pervasive (Green, 2006), and is associated with low adaptive and social skills (Bowie and Harvey, 2005). Pharmacological interventions to treat these deficits have demonstrated little effect (Harvey and McClure, 2006), likely reflecting the symptoms' complex neurobiological underpinnings; however, behavioral interventions, such as cognitive remediation therapy (CRT), are beneficial (Harvey and Sand, 2017). CRT focuses on acquisition of skills in areas most impaired in schizophrenia: attention and concentration, psychomotor speed, learning and memory, and executive functioning (McGurk et al., 2005). They are frequently and to good effect paired with a social skills training (SST), emphasizing skill transferability (Wykes et al., 2011) and increasing efficacy (Harvey and Sand, 2017).

There is robust evidence demonstrating structural and functional changes in the brain following CRT (Eack et al., 2010; Isaac and Januel, 2016; Wykes et al., 2002). Additionally, baseline differences in brain volume and connectivity may predict better treatment response in schizophrenia to psychological interventions like CRT. Larger dorsolateral prefrontal cortex volume predicts better response to cognitive behavior therapy (Kumari et al., 2009). Higher gray matter volume and cortical surface area predicts more rapid social-cognitive improvement during CRT (Keshavan et al., 2011). Further, CRT response correlates with baseline measures of cortical thickness in the frontal and temporal lobes (Penades et al., 2016).

Changes in the brain white matter may in particular play a role in successful cognitive remediation. For example, preservation of fibers connecting prefrontal-thalamic-sensorimotor regions were linked to the success of training-induced neurocognitive plasticity (Subramaniam et al., 2017). Changes in putative white matter integrity within the corpus callosum were also reported following cognitive remediation in schizophrenia (Penades et al., 2016). Given connectivity in regions such as the superior longitudinal fasciculus (SLF), which is present in both hemispheres and connects all four lobes, is associated with deficits in cognition and social functioning (Szeszko et al., 2018), baseline connectivity in this region may predict better treatment response.

The current project was a pilot study of the feasibility of a brief CRT + SST intervention in a sample of Veterans with schizophrenia. A subset of participants underwent baseline diffusion tensor imaging (DTI) to identify predictors of treatment efficacy following CRT + SST.

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2. Methods

2.1. Participants

Nineteen individuals (16 males, 3 female), 14 with schizophrenia and five with schizoaffective disorder, ranging in age from 29–57 (M = 48.1, SD = 9.3), participated in an 8-week trial of twice-weekly CRT + SST. Ten (9 males, 1 female, age range = 31–55, mean age = 50.6, SD = 7.4) also underwent DTI at baseline. All were outpatients receiving psychiatric care at the James J. Peters VA Medical Center, stable on their current antipsychotic regimen (no changes of dosing greater or less than 25%, within the last 4 weeks), and medically healthy with no history of significant head trauma or current substance use or depressive disorder comorbidities. All participants signed written informed consent and study procedures were approved by the IRBs.

2.2. Procedure

The Structured Clinical Interview for DSM-IV (SCID) (First et al., 1995) was administered by a master's level or doctoral level interviewer. Participants then underwent DTI and completed the baseline neurocognitive battery before beginning CRT + SST. Prior to imaging, participants completed a urine toxicology screen and, for females, a pregnancy test.

CRT + SST consisted of a combination of computer-based cognitive enhancement exercises (Psychological Software Services) and manualized-social skills training modified from the Cognitive Enhance Therapy program (Hogarty and Greenwald, 2006). Participants met for 60 min of CRT plus 60 min of SST twice weekly (4 h total per week), for a total of 30 sessions (15 CRT + 15 SST). CRT consisted of group members selecting any of the eight memory exercises or six problem solving exercises at a given session. Each exercise provides several permutations of graduated difficulty levels and other modifiable parameters. Participants were encouraged to challenge themselves and a group facilitator monitored their performances, adjusting the difficulty for each exercise to approach approximately 70% correct responses. In each session of every cohort, participants were divided into small groups no greater than two to three members and engaged in the exercises; participants worked independently on an individual laptop but were encouraged to interact with one another. Each group was led by a Bachelors or Master's level research assistant who had received training to operate audio visual equipment and was familiar with each of the exercises. Although, not present during computer sessions, a trained doctoral level psychologist knowledgeable of CRT was available for consultation as needed.

The twice-weekly SST followed the manualized curriculum outline and materials provided from CET program. This manualized program was specifically designed to augment training with Psychological Services Inc., software. Substantial modifications were made from the full CET program to the current study; however, the basic design, structure and execution of the program was maintained. Similar to the full program, the current study incorporated the core material from each of the three modules. Module one provided participants with an orientation to CET and an overview of basic concepts. The second module consists of social cognitive skills training. The final module focuses on the real-world applications of cognitive and social-cognitive skills acquired during the treatment. All groups were led by a doctoral-level clinical psychologist. Participants received a small monetary compensation for attendance at each session.

The current study included four cohorts (mean size = 4 participants, range: 3–6) with excellent attendance (mean attendance: 79.11%), and no drop-outs, although two participants did not complete the MASC and three did not complete the UPSA at follow-up.

The neurocognitive battery was repeated at the conclusion of CRT + SST.

2.3. Measures & materials

We administered five subtests of the MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein and Green, 2006): speed of processing, working memory, verbal learning, visual learning, and organization and planning. This battery, which is the gold standard outcome assessment for trials targeting cognitive performance in schizophrenia, has multiple forms to limit practice effects; age- and gender-corrected T-scores for each subtest were dependent variables (DVs).

In addition, we administered the DOT Test (Silver et al., 2003) (visual-spatial working memory), and the PASAT (Gronwall, 1977; Stuss et al., 1998) (auditory working memory), which were chosen as primary outcome measures for this study as both have shown sensitivity in our population. The *DOT Test* (Silver et al., 2003) is a test of visuospatial working memory in wide research use. Subjects are presented a dot at a specific position on a standard size paper and then asked to reproduce it at the same location on a separate sheet after different periods of delay (no delay, 10, 20, or 30 s delay). Performance is measured as the distance in cm between the drawn dot and the actual dot (distance error). The distance error at the 30 s delay (longest memory load of all three delays) minus the distance error at the immediate condition is the dependent variable. DOT Test difference score between copy and 30-second delay and PASAT total score served as DVs. The *Paced Auditory Serial Addition Test (PASAT)* is a test of auditory verbal working memory that has been well described and validated in this population (Gronwall, 1977; Stuss et al., 1998). Briefly, subjects listen to a tape-recorded voice presenting a series of numbers (50 numbers at a rate of one digit per two seconds) and are asked to add each adjacent pair of numbers and respond by verbalizing the sum. The total number of correct responses is the dependent variable. We also administered two secondary measures: the UCSD Performance Based Skills Assessment (UPSA) (Patterson et al., 2001), to assess functional skills, and the Movie for the Assessment of Social Cognition (MASC) (Dziobek et al., 2006), to assess social cognition. UPSA total score and MASC total correct and hypomentalizing errors served as DVs.

A 3-Tesla Siemens Skyra scanner was used to acquire 75 diffusion tensor images using a pulsed gradient spin-echo sequence with an echo planar imaging pulse sequence (EPI) acquisition (voxel dimensions = 1.79 × 1.79 × 3.64; b value = 1500, TR = 3.64; TE = 0.0868 s; 70 directions). We employed the tract-based spatial statistics (TBSS) pipeline that was adapted by the Enhanced Neuroimaging Genetics by Meta-Analysis (ENIGMA) DTI Working Group at the USC to compute white matter regions-of-interest (Jahanshad et al., 2013).

For this exploratory analysis, we used t-tests for paired samples to compare baseline and post-treatment. We computed difference scores (post-test minus pre-test) for MCCB subtests and supplemental measures, and used Spearman's correlations to examine associations between difference scores and imaging variables. Given the multitude of brain regions available with this technology, we employed a region of interest (ROI) approach based on prior work, which focused our analyses on overall FA and the SLF.

3. Results

Following CRT + SST, participants demonstrated statistically significant improvement for MCCB reasoning and problem solving, $t(16) = 2.7$, $p = .01$, MCCB verbal learning, $t(16) = 2.5$, $p = .02$, and MASC total correct score, $t(14) = 2.6$, $p = .02$. Improvements on UPSA total score approached significance $t(13) = 2.0$, $p = .07$.

Baseline average FA correlated significantly with improvement on the MASC for total score ($r = 0.78$, df = 8, $p = .01$) and hypomentalizing errors ($r = -0.70$, df = 8, $p = .04$). That is, more improvement following CRT + SST was associated with higher FA at pre-treatment baseline. Moreover, investigation of pre-treatment FA in the SLF correlated significantly with DOT Test difference score improvement

($r = -0.72$, df = 8, $p = .02$) following CRT + SST. To help account for threats to internal validity (i.e. repeated testing) due to the lack of a control group, we re-ran our analyses of the SLF with both baseline FA and baseline cognitive performance entered into our models as covariates and the significant differences remained.

4. Discussion

Veterans with schizophrenia demonstrated an improvement in cognitive functioning in this CRT + SST trial. Participants were highly engaged with excellent attendance across cohorts and demonstrated significant improvement in reasoning and problem solving, verbal learning, and social cognition following CRT + SST. Baseline FA in the SLF predicted improvements in visual-spatial working memory while overall baseline FA predicted improvements in social cognition.

A wealth of evidence for the efficacy of CRT exists (Harvey and Sand, 2017); however, not all participants exhibit gains following treatment. Although several treatment variables may account for this variability (Harvey and Sand, 2017), these results suggest that individual differences in neurobiology are also important in predicting treatment response. In fact, these findings are consistent with prior work (Penades et al., 2016), suggesting that frontal and temporal thickness and connectivity may predict better response to CRT + SST. The results highlight potential neuroimaging biomarkers associated with improvements in visual spatial working memory in response to CRT among individuals with schizophrenia that may be useful in identifying therapeutic targets for improving functional outcome.

Limitations to this study include the small sample size and the lack of a control group. In addition, the lack of a control condition makes it difficult to determine if improvements are due to nonspecific variables. Despite these limitations, the results are promising in terms of supporting the concept that determining the neurobiology underlying individual differences in treatment response is important for precision medicine in psychiatry.

Declaration of Competing Interest

At this time, we would like the make the following disclosure: Dr. Perez is site-PI of a study funded by Neurocrine Biosciences. Drs. McClure, Graff, Triebwasser, Rosell, Szeszko, Chu, Hazlett, Siever, & New report no financial relationships with commercial interests.

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