Title: Evaluating the impact of Targeted Cognitive Therapy on clinical symptoms in schizophrenia

1. Introduction:

Schizophrenia (SZ), schizoaffective, and bipolar disorders are severe, disabling, and common psychotic illnesses that affect approximately 2% of the world's population[1,2]. Neurocognitive impairments affect the vast majority of psychosis patients and are correlated with severity of psychosocial disability[3,4]. Evidence increasingly suggests that various cognitive therapies (CTs) significantly improve outcomes in psychosis patients, with effect sizes of d≈0.40 vs. antipsychotic medications (APs) alone[5-11]. Many studies document the safety, acceptability and efficacy of CTs in SZ with benefits often lasting years[6,9,12-14]. In addition to the efficacy of "top-down" CTs, growing evidence suggests that improved neurocognition can also be achieved through "bottom-up" cognitive and sensory training delivered via cost effective computerized cognitive remediation programs[15-17]. These therapies are being studied across many levels of basic and clinical neuroscience[18,19].

One distinct form of "bottom-up" CT – termed Targeted Cognitive Training (TCT;[15]) — is a "neuroplasticity-based" computerized approach to cognitive remediation. In TCT, the user performs progressively difficult learning trials to improve pitch and temporal acuity of processing in auditory sensory, attention-related, and working memory systems. Conceptually, the goal of TCT is to foster the recovery of key neurocognitive functions by harnessing mechanisms of brain plasticity under constrained and carefully controlled conditions rather than to promote the development of compensatory cognitive or behavioral operations. TCT relies on repetitive practice and procedural learning - mechanisms that appear to be relatively intact in psychotic patients - by providing auditory training exercises that are: 1) *intensive*, with thousands of trials per exercise; 2) *attentionally engaging*, with self-paced initiation of each trial; 3) *adaptive*, with the difficulty of each training task adjusted trial-by-trial based on user performance; and 4) *rewarding*, with entertaining animations that reinforce correct responses[20]. As studies have shown across a series of published reports[17] after 30-50 hours (h) of TCT, psychosis patients show large effect size gains (d=0.86-0.89;[15]) in auditory-dependent cognitive domains (verbal learning and memory), global cognition and quality of life that persist for at least 6 months post-TCT[16]. However, the effect of TCT on the severity of clinical symptoms has not been previously characterized. The aim of this paper is to evaluate the effects of TCT on clinical symptoms in patients with schizophrenia.

2. Methods

2.1 Participants

Participants were recruited at the Alpine Special Treatment Center (ASTC), a 113-bed residential step-down program that specializes in the treatment of patients with severe and persistent mental illnesses following an acute hospitalization. Eligibility was determined by ASTC clinical treatment team. Interviews and baseline assessments were be performed by UCSD study team members blind to subsequent group assignment. Study exclusion criteria included an

estimated premorbid IQ below 70, substance abuse within the past month, a history of significant medical or neurological illness or head injury resulting in >30 minute loss of consciousness, or an inability to comprehend the informed consent form for any reason (e.g., severe thought disorder, lack of English proficiency).

2.2 Study design and randomization

A parallel, randomized controlled trial design with stratified random sampling according to sex, age, and race was utilized and participants were assigned to one of two treatment arms — Treatment as Usual (TAU) or TAU augmented with TCT. Treatments lasted 10 weeks. Participants randomized to TAU alone engaged in their usual course of treatment that included medication management and participation in psychosocial and targeted skills training therapies. Participants randomized to TCT were scheduled 3-5 days per week to complete 1h of training per day (~40h total) in addition to their usual course of treatment. TCT was implemented by UCSD staff members. Patients from both groups underwent all assessments at baseline and post-treatment. Research staff conducting baseline and post-intervention assessments were blind to randomization status. Participants were asked not to disclose their intervention randomization to study personnel. Clinicians who delivered TCT were not present for, and had no knowledge of, participants' baseline or post-intervention assessment results.

2.3 Standard Clinical Assessment Rating Scales

All symptom and behavioral measures were assessed at baseline and after 40 hours of TCT for patient characterization and mediator/moderator analyses of treatment response or at 16 weeks after baseline assessment for those in TAU group. Clinical symptoms were evaluated with the 1) Scale for the Assessment of Negative Symptoms (SANS), 2) Scale for the Assessment of Positive Symptoms (SAPS), 3) Psychotic Symptom Rating Scales (PSYRATS), 4) and Patient Health Questionnaire-9 (PHQ-9)

2.4 Statistical analysis

Linear-mixed effects regression models were utilized to analyze outcome measures providing a regression coefficient "beta" which was also converted to a Cohen's d measure of effect size. Statistical significance was based on a one-tail test with alpha set to .05.

3. Results

Participants included 44 unrelated patients diagnosed with either schizophrenia or schizoaffective disorder. Mean age (SD) of participants in TAU vs TCT was 35.57 (13.3) and 34.96 (12.23) years, respectively. 12 (57.1%) participants in TAU were female vs 10 (43.5%) female in TCT. In TAU group, 3 (14.3%) identified as African American, 2 as Asian (9.5%), 11 as Caucasian (52.4%), 5 as having >1 race (23.8%) and 0 as Native American. In TCT group, 5 (21.7%) identified as African American, 1 (4.3%) as Asian, 12 (52.2%) as Caucasian, 3 (13.0%) as having >1 race, 2 (8.7%) as Native American. In TAU, 6 (28.6%) self-identified as Hispanic vs 4 (17.4%) in TCT group. Mean (SD) number of hospitalizations was 14.1 (11.2) and 14.8 (11), in TAU vs TCT, respectively. Baseline clinical symptom ratings, along with demographics

can be found in Table 1. There was no significant difference between TAU and TCT groups in any demographic or baseline clinical symptom score.

Table 1

Demographics of study participants in TAU vs TCT group

	TAU (N=21)	TCT (N=23)	P-value
Age (years), mean (SD)	35.57 (13.30)	34.96 (12.23)	0.8748
Gender			0.3652
Female	12	10	
Male	9	13	
Education (years), mean (SD)	11.95 (2.22)	11.78 (1.99)	0.7901
Race			0.5101
African American	3	5	
Asian	2	1	
Caucasian	11	12	
>1 race	5	3	
Native American	0	2	
Ethnicity			0.3767
Hispanic	6	4	
Non-Hispanic	15	19	
Hospitalizations	14.048 (11.165)	14.818 (10.99)	0.7516
Baseline Clinical Symptoms mean (SD)			
Global positive	1.095 (1.315)	1.337 (.985)	0.4910
Global negative	1.20 (0.795)	1.521 (.910)	0.2216
PSYRATS mean	0.697 (1.023)	0.834 (1.068)	0.6668
PHQ 9 total	4.905 (5.319)	5.870 (5.362)	0.5527

The model coefficient for global positive symptom rating (beta) was -0.201, corresponding to a Cohen d of 0.409, which was not significant. The model coefficient for global negative symptom rating was -0.048, corresponding to a Cohen d of 0.097, which was not significant. The model coefficient for PSYRATS mean score was -0.384, corresponding to a Cohen d of 0.831, which was mareginally significant. The model coefficient for PHQ-9 total score was 0.79, corresponding to a Cohen d of 0.159, which was not significant. Results are summarized in Table 2.

Table 2

Effects of TCT on clinical symptom measures vs TAU

Clinical symptom measure	Beta	d	P-value
Global positive	-0.201	-0.409	0.193
Global negative	-0.048	-0.097	0.447
PSYRATS	-0.384	-0.831	0.094
PHQ 9	-0.79	-0.159	0.4

4. Discussion

The mechanisms behind clinical symptoms in schizophrenia are not well understood, but many have been proposed. Positive symptoms, including auditory hallucinations are often much more effectively targeted by traditional pharmacologic treatments, despite the fact that their origins are unclear. Auditory hallucinations are often a hallmark characteristic of patients with schizophrenia, and may be related to processing dysfunctions in the primary auditory cortex [25,26]. As TCT is designed as a bottom-up approach to improving auditory processing, it is possible to this may decrease aberrant activity in the primary auditory cortex.

Although the findings in this paper were not significant, a trend towards reduction in symptoms, specifically positive symptoms was seen in the TCT group compared to the TAU group. A moderate effect size (d=0.41) was seen in global positive symptoms and a large effect size (d=0.83) was seen in PSYRATS mean score, which is a more specific characterization of auditory hallucinations, and was marginally significant. It is possible that if these trends were to continue and become significant, that the effect on auditory hallucinations may be accounting in large part to the decreased overall in global positive symptoms rating. At this point in time, the study is still being carried out and only 44 patients were included in the model. Thus, as more participants complete the study, greater power may lead to measures achieving statistical significance.

Another potential limitation in determining effects on clinical symptoms is that subjects in both groups reported relatively low baseline scores in symptom ratings. If significant symptoms are not present at baseline, the likelihood of reducing them further may be lower than if more symptoms were present initially.

5. Conclusion

Schizophrenia is a progressive, disabling, psychiatric disorder affecting nearly 1-2% of the world's population. Some symptoms can be managed with traditional pharmacologic interventions, but many patients still have significant difficulties with social functioning due to untreated or undertreated symptoms. Further research to determine to mechanisms and potential alternative, or adjunctive treatments, including TCT, is desperately needed in order to improve the lives of these patients.

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