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Divergence of Subjective and Performance-Based Cognitive Gains Following Cognitive Training in Schizophrenia

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Abstract

Background: Cognitive training is effective for improving cognitive performance among people with schizophrenia. An individual's perception of their own cognition is dissociable from performance on objective cognitive tests. Since subjective cognitive benefit may impact engagement, motivation, and satisfaction with time-intensive cognitive interventions, this study aimed to determine whether subjective cognitive difficulties improve in conjunction with cognitive gains following 30h of cognitive training.

Methods: Patients with schizophrenia or schizoaffective disorder (N=46) were randomized to treatment as usual (TAU) or TAU augmented with auditory-targeted cognitive training (TCT). All participants completed assessment batteries at baseline and follow-up. As previously reported, the TCT group showed significant improvements in verbal learning and memory and reductions in auditory hallucinations relative to the TAU group.

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Contributors

Drs. Treichler, Thomas and Light obtained extramural funding for research. Dr. Treichler completed all statistical analyses, and wrote the first drafts of this manuscript. Dr. Thomas provided statistical consultation. All other authors participated in aspects of study design, including recruitment and data collection. All authors were responsible for reviewing and approving the final manuscript.

Conflict of Interest

Dr. Light reports having been a consultant to Astellas, Boehringer-Ingelheim, Dart Neuroscience, Heptares, Lundbeck, Merck, NeuroSig, Neuroverse, and Takeda.

Results: Subjective cognitive difficulties did not significantly improve following TCT, even among TCT participants who showed improvements in cognitive performance (all *p*s>0.05). Subjective cognitive difficulties were significantly associated with severity of depressive symptoms and hallucinations (r=0.48 and r=0.28, p<0.001), but not global or specific domains of cognition (all *r*s<0.1) at baseline. There were no significant relationships between change in subjective cognitive difficulties and change in cognitive or clinical variables (all *p*s>0.05).

Discussion: Patients with schizophrenia do not detect change in their cognition following cognitive training, even among patients who showed robust gains in cognitive performance. Failure to detect improvement may undermine treatment engagement, motivation, and satisfaction. Translating score improvements *on the cognitive exercises* into tangible metrics, and providing ongoing, clinician-delivered feedback on performance may facilitate patient ability to detect improvements and improve motivation to engage *with cognitive training interventions*.

Keywords

Schizophrenia; Cognitive Training; Subjective Cognitive Difficulties; Patient-Reported Outcomes; Symptoms

1. Introduction

Previous studies have shown that self-ratings of cognitive difficulties are only weakly and non-significantly correlated with performance on objective measures of cognitive ability (Balzan et al., 2014; Burton et al., 2016; Carrigan & Barkus, 2016). This discrepancy is not just observed in neuropsychiatric disorders such as schizophrenia, but also in healthy populations (Marino et al., 2009). *Self-ratings of symptoms, functioning, and other clinically relevant variables are often markedly different from clinician or researcher ratings, although associated with constructs like quality of life* (Bell et al., 2007; Bowie et al., 2007). This divergence of subjective cognitive difficulties from performance on cognitive tasks appears to be driven, in part, by severity of depressive symptoms and insight into illness (Burton et al., 2016; Medalia et al, 2008; Medalia et al., 2010; Saperstein et al., 2012).

Subjective cognitive difficulty is an important, but often overlooked, construct to consider in the context of cognitive remediation interventions (Balzan et al., 2014; Gooding et al., 2012). Patient perception of treatment benefit is an important contributor to treatment engagement, motivation, and satisfaction (McCabe et al., 2007; McKee et al., 2005; Reininghaus et al., 2012). Outcome measures in cognitive remediation studies include objective measures of task-based performance (e.g., Fisher et al., 2009; Fisher et al., 2015; Loewy et al., 2016; Tarasenko et al., 2016), brain-based biomarkers (Bhakta et al., 2017; Biagianti et al., 2017; Dale et al., 2016; Hochberger et al., in press), and/or ratings of outcomes in other domains including symptom severity and functioning (e.g., Fisher et al., 2009; Fisher et al., 2015; Loewy et al., 2016). Commonly used assessment batteries do not assess patient reports of cognitive complaints in their daily lives (Kitchen et al., 2012). While cognitive training is generally effective at improving performance across multiple domains, no studies have yet examined whether subjective cognitive difficulties decrease after cognitive training. *In aging populations, changes in day-to-day functioning and memory complaints are positively correlated with changes in cognitive impairments (Smith* *et al., 1996; Tucker-Drob, 2011), indicating the potential for self-rated cognitive difficulties to change due to changes in cognitive performance*.

Understanding the impact of cognitive training on subjective cognitive difficulties may illuminate a source of variability in treatment response due to differences in engagement during cognitive training and in behavior following cognitive training. Participants who believe cognitive remediation is valuable attend more sessions (Bryce et al., 2018). Without perception of benefit, likelihood of maintaining continuous effort and engagement over the full course of treatment (typically 30–40 hours) is diminished (Bryce et al., 2018; McKee et al., 2005). Perception of cognitive gain may also have secondary impacts on generalization of treatment gains to functioning. Self-perceived improvements may promote behavioral changes resulting in increased participation in other psychosocial activities (Thomas et al., 2018), while the absence of perceived improvement may make engagement in other potentially beneficial psychosocial activities less likely, resulting in a 'wasted gain.'

The present study assessed patient perception of cognition in the context of targeted cognitive training (TCT). Findings of a randomized effectiveness trial of TCT in this cohort indicated that TCT resulted in significant improvements in the targeted domains of verbal learning and auditory hallucinations in schizophrenia patients (Thomas et al., *2018*). The present study aimed to: 1) determine whether subjective cognitive difficulties decrease following cognitive training; 2) identify whether changes in cognitive performance and symptom severity are associated with change in subjective cognitive difficulties following cognitive training; and 3) replicate existing work regarding associations between subjective cognition, cognitive performance, and symptoms. We hypothesized that subjective cognitive difficulties would improve following cognitive training, and that change in symptom severity would be associated with change in subjective cognitive difficulties.

2. Methods

2.1. Participants

The Institutional Review Board of the University of California, San Diego, approved all experimental procedures (IRB #130874). Details of the trial design, participants, measures, and cognitive training intervention are described in Thomas et al. (*2018*). Briefly, the participants included patients with schizophrenia or schizoaffective disorder ($n = 46$) based on a clinical interview using the Structured Clinical Interview for DSM-IV-TR (First, Spitzer, Gibbon, & Williams, 2002). Exclusion criteria included an inability to understand the consent process; inability to provide consent or assent; not being a fluent English speaker; previous significant head injury with loss of consciousness >30 minutes; neurological illness; severe systemic illness; or current mania. Participants completed baseline assessments and were then randomized to either TCT ($n = 24$) or treatment as usual (TCT, $n = 22$) using stratified random assignment by age, ethnicity and gender.

TCT uses six computer-based exercises supplied by Brain HQ by Posit Science Corporation intended to improve cognitive functioning by targeting auditory perception, auditory processing speed, and auditory memory. Exercises apply an n-up/m-down algorithm to participant responses to estimate capability threshold. This design ensures that nearly all participants, regardless of initial impairment, can successfully complete exercises. By that strategy, regardless of individual learning rate, participants are continuously challenged at an appropriate level (approximately 80% criterion accuracy) throughout their training. The complete TCT program is 40 hours long, typically completed in hourly segments over ten weeks. The average TCT participant in this study completed 27.94 hours of TCT.

2.2. Measures

Subjective Cognitive Difficulties: The Measure of Insight into Cognition-Self Report (MIC-SR, Saperstein et al., 2012). The MIC-SR is a 12-item self-report measure of cognitive complaints (e.g., "I am easily distracted from tasks by background noises or activities") including three subdomains of cognition: attention, executive functioning, and memory. Each item is rated in terms of frequency, from "never" to "almost daily." Total scores and subdomain scores were used as the outcome measures. Range for the total score is 0–36, and each subdomain has a range of 0–12. Higher scores indicate worse cognitive complaints. Previous research indicates that people with schizophrenia report a total score of 13.32 on average (Saperstein et al., 2012). *Saperstein's psychometric study of the MIC-SR also found strong internal consistency (Chronbach's alpha = .93), test-retest reliability (r = .92), and concurrent validity with a clinician-rated version of the measure (rs = −.70–75).*

Objective Cognitive Performance: MATRICS Consensus Cognitive Battery (MCCB; Nuechterlein et al., 2008) was used to assess cognition. The MCCB was designed for schizophrenia populations (e.g., Kern et al., 2008; Nuechterlein et al., 2008). The MCCB neurocognitive composite and MCCB Verbal Learning and Memory subscale t-scores (corrected for age and gender) were primary measures of cognition in this study. MCCB Verbal Learning and Memory was chosen because TCT participants *in this study* displayed significant improvements in this subdomain (*Thomas et al, 2018*).

Depressive Symptoms: Patient Health Questionnaire, 9 item depression subscale (PHQ-9; Kroenke, Spitzer & Williams, 2001). The PHQ-9 is a measure of depressive symptoms that can detect presence of a depressive disorder as well as subclinical depressive symptoms (Martin et al., 2006). The 9 items were summed and used as a measure of self-reported depressive symptom severity. Total scores range from 0–27; scoring 10 or above is indicative of a positive depression screen (Kroenke et al., 2001; Martin et al., 2006). Depressive symptom severity was chosen for this study because of its association with MIC-SR in past research (Burton et al., 2016).

Positive and Negative Symptoms: Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984a) and Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1984b). The SAPS global hallucination severity score was included in these analyses. Range of the global hallucination severity score is 0–5. The hallucinations score was chosen for this study because TCT participants *in this study* displayed significant improvements in this subdomain (*Thomas et al, in press*).

2.3. Procedure

All measures were assessed at baseline and at the end of the study, approximately ten weeks apart. To identify associations between MIC-SR and the other target variables, bivariate correlations among MIC-SR total scores and subscale scores, MCCB composite scores and Verbal Learning and Memory subscale scores, PHQ-9 scores, and SAPS-Hallucination r scores were examined. To examine change in MIC-SR during the study, *a set of linear mixed-effects models were fitted to the data as they have a less restrictive missing data assumption compared to analysis of covariance models*. Linear mixed-effects models included fixed effects of time (baseline vs. post-treatment [coded −1 vs. 1 in analyses]) and group assignment (TAU vs. TCT, [coded −1 vs. 1 in analyses]), as well as random intercepts. Outcome variables were MIC-SR total scores and subscale scores, examined in separate models. Finally, in order to identify potential moderators of MIC-SR change in patients who underwent TCT, individual change scores (post minus baseline) in all outcome measures were calculated and analyzed using bivariate correlations.

All analyses were conducted using R (2018). We used the lme4 package (Bates et al., 2015) for linear mixed-effects model analyses. In correlation analyses, missing values were handled using pairwise deletion. Linear mixed-effects model analyses included all data regardless of dropout or study compliance, consistent with the intent-to-treat model. For bivariate correlation analyses, an r^2 of 0.1 was interpreted as a small effect, an r^2 of 0.3 was interpreted as a medium effect, and an r^2 of 0.5 was interpreted as a large effect. For linear mixed-effects models, a β of 0.02 was interpreted as a small effect, a β of 0.25 was interpreted as a medium effect, and a β of 0.40 was interpreted as a large effect.

3. Results

Demographic, clinical, and cognitive characteristics of the sample by group are described in Table 1. *There were no significant differences at baseline between groups in these characteristics, all ps>.05*. Means and standard deviations of the outcome variables over time are shown in Table 2. There was no significant time by group interaction effect on MIC-SR total scores, *Estimate* = 0.06, *SE* = 1.97, β = 0.01, t[36.67] = 0.03, p = 0.98. There was also no significant main effect of time, *Estimate* = −0.33, *SE* = 1.33, β = −0.04, t[37.21] = −0.25, p = 0.81. That is, MIC-SR did not significantly change over time, and there was no significant change associated with TCT participation. Analyses of the MIC-SR subscales also indicated no significant time or group by time effects (all ps > 0.60).

Calculation of individual-level changes in MIC-SR ratings revealed that 10 of the 16 TCT completers reported a lower MIC-SR score at follow-up compared to baseline, indicating fewer cognitive complaints. Bivariate correlation analyses of individual-level change scores indicated that change in MIC-SR total and subscale scores was not significantly associated with change in cognition or symptoms for TCT participants. However, the magnitudes of some correlations (e.g., between MIC-SR Memory and MCCB Verbal Learning and Memory) were small to medium sized. These associations varied in direction; higher MIC-SR Memory scores were associated with higher MCCB Verbal Learning and Memory scores, while higher MIC-SR Executive Functioning scores were associated with lower MCCB Verbal Learning and Memory scores.

A second set of bivariate correlation analyses revealed a large sized, significant relationship between PHQ-9 scores and MIC-SR total scores and a medium sized, significant relationship between SAPS-Hallucinations scores and MIC-SR total scores. In both cases, higher MIC-SR scores were associated with higher symptom severity scores. No significant relationships between MCCB scores and MIC-SR scores, including composite scores and subdomain scores, were detected. The magnitudes of these relationships were beneath r^2 = 0.1, the threshold for a small effect size.

Figures depicting both sets of bivariate correlations are available in Supplement 2.

4. Discussion

This study examined subjective cognitive difficulties among patients with schizophrenia in the context of a randomized effectiveness trial of TCT. Despite our previously reported finding of significant improvements in verbal learning and severity of hallucinations among TCT participants (Thomas et al., *2018*), subjective cognitive difficulties did not decrease over time. On average, patients reported mild-to-moderate cognitive difficulties at both baseline and after 30h of treatment, approximately ten weeks later. *Computation of individual level change scores suggest that perceived cognition improved following treatment among 62.5% of TCT completers, although this effect failed to reach statistical significance at the group level*. Analyses examining potential moderators of change in subjective cognitive difficulties failed to identify significant relationships between changes in subjective cognitive difficulties and changes in cognition or symptom severity. *This indicates that cognitive training did not impact participants' experience of day-to-day cognitive difficulties, suggesting that performance improvements due to cognitive training either do not generalize into daily functioning, performance improvements are not large enough to impact subjective experience of cognition, or both*.

Consistent with past studies (Balzan et al., 2014; Burton et al., 2016), no significant relationships among measures of subjective cognitive difficulties and objective cognitive performance were detected, with less than 6% of shared variance. In contrast, depressive symptoms accounted for 23% of the variance in subjective cognitive difficulties. The latter association could be due to a number of reasons, including overlap between PHQ-9 items and MIC-SR items (i.e., subjective attention/concentration impairment), the impact of depression on cognitive functioning, and the impact of depression on self-perception (Potvin et al., 2016; Rock et al., 2014).

Previous work in this area has debated the utility of attributing the disconnect *between subjective cognitive difficulties and objective cognitive performance* to impaired insight. Balzan and colleagues (2014) argued that attributing incongruous patient report solely to poor insight might result in minimizing or dismissing patient report. Bowie and colleagues (2007) *note that inaccuracy in self-assessment of functioning could be due to other factors including comparing personal functioning to misunderstood or nonrepresentative standards (e.g., comparison to other people with schizophrenia versus healthy populations; comparison to one's own best or average functioning). Self-reported cognitive difficulties nevertheless provide a report of difficulties the patient notices in their daily life, which may serve as an* *important focus of treatment*. Patient-reported outcomes considered broadly are often divergent from their objective or clinician-rated counterparts (Bell et al., 2007), *but still provide essential context that drives patient outcomes (McCabe et al., 2007). Therefore, we argue that self-reported cognitive difficulties should be considered a separate and meaningful construct. Decreasing perception of cognitive difficulties may facilitate improved quality of life and decreased emotional distress regardless of improvements in cognitive performance*. In the age of person-centered, recovery-oriented care, patient-reported outcomes are a foundational component of evidence-based practice.

Subjective cognition likely contributes to both treatment engagement and the generalization of treatment gains (cf., Balzan et al., 2014). Patients who perceive that mental health treatment is beneficial have higher motivation to engage in treatment (Bryce et al., 2018; McKee et al., 2005), a key component for ultimate treatment success (Dixon et al., 2016). *Conversely, patients who do not perceive impairment are more likely to disengage from care* (Dixon et al., 2016). Therefore, although cognitive performance is a more accurate and sensitive measure of changes in cognitive function, subjective cognition may nonetheless serve as a helpful indicator of likely treatment engagement, motivation, and satisfaction. Similarly, patients who do not perceive improvement are unlikely to attempt new behaviors outside of treatment, constraining the ability of effective interventions to improve daily life.

Two primary approaches may facilitate effective targeting and harnessing of subjective cognition during cognitive training. First, increasing feedback about progress made on TCT *exercises* may help patients identify immediate and long-term gains from TCT. Related research has supported the concept that patient feedback regarding cognitive test scores significantly improves patient outcomes (Rosado et al., 2018). Although adaptive feedback is integral to TCT, the feedback itself is limited to the individual exercises using metrics that may not have functional significance (e.g., millisecond changes in performance). *Moreover, the adaptive exercises automatically adjust difficulty according to performance so that patients maintain a score of approximately 80%, which may limit an individual's ability to detect improvement via increased success on tasks*. Thus, translating score improvements into more tangible and meaningful metrics, and providing ongoing, clinician-delivered feedback on performance may improve patient ability to perceive improvements and facilitate improved motivation to engage in tasks.

Second, *integrating cognitive training with other rehabilitation strategies is needed to maximize perception of benefit and generalization into real-world functioning*. Contemporaneous real-world skills training approach may facilitate the generalization of gains on cognitive performance tasks into improvements that are more easily recognizable by patients. Findings from integrative interventions indicate that cognitive training outcomes benefit from being coupled with skills training (Bowie et al., 2012; Eack et al., 2009; Kurtz et al., 2015). Future studies should therefore consider combining cognitive training with real-world skill training practice to maximize generalizability of gains. *Likewise, since severity of depressive symptoms was significantly associated with subjective cognition, consistent with previous findings* (Burton et al., 2016), *systematic integration of depression treatment within the context of cognitive rehabilitation may improve patient awareness of improvements in their cognition along with associated symptoms of distress, amotivation,* *and inattention which may impact cognition* (Silver et al., 2009). *Lastly, as previous work connects perception of treatment needs and benefits with treatment behaviors including motivation and engagement, integration of interventions such as motivational interviewing (Fiszdon et al., 2016) or treatment-relevant skills training (Treichler et al., 2018) may enhance treatment engagement and outcome*.

Limitations

Results of the present study should be considered in the context of several caveats. The modest sample size limits the exploration of more complex analyses that could disentangle factors that may influence the dissociation of gains in cognitive performance from patient reports of cognitive problems. In addition, the patients in the present study were older, had well-established diagnoses of schizophrenia, moderate to high levels of symptoms, and marked functional impairments. *However, average complaints of cognitive difficulties in daily life in this study were similar to those from previous reports (e.g.*, Saperstein et al., 2012). *Future studies should consider using a direct measure of participant perception of cognitive training benefits, to allow for the possibility that cognitive training improves aspects of subjective cognitive function not captured via the MIC-SR. Future work should also study how variance on baseline MIC-SR scores impacts treatment motivation and engagement, potentially by examining subgroups defined via high vs. low MIC-SR scores. Medication can impact daily cognitive function; future studies are needed to identify the potential impact of medication of subjective cognitive difficulties*.

Conclusion

This study examined subjective cognitive difficulties in the context of an effectiveness study of TCT among patients with schizophrenia. Despite previously reported robust improvements in verbal learning in the TCT group (Thomas et al., *2018*), subjective cognitive difficulties did not decrease over time, and no moderators of change in subjective cognitive difficulties were identified. Consistent with previous reports, subjective cognitive difficulties correlated with depressive symptom severity but not neuropsychological measures of cognition (Balzan et al., 2014; Burton et al., 2016). This dissociation suggests that subjective cognition is an independent construct and important target for future remediation strategies. Augmenting cognitive interventions by providing user-friendly performance metrics, regular clinician-delivered feedback, concurrent skills training, and concurrent depression treatment as needed may be a pathway towards improving patient-relevant outcomes. *This study adds to the mounting literature supporting that cognitive rehabilitation is most effective when integrated into a comprehensive, individualized, and person-centered rehabilitation program*.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Demographic and clinical characteristics at baseline by group.

	TCT		TAU	
	N (%)	**M (*SD*)**	**N (%)**	**M (*SD*)**
Sample Size	24		22	
Age		34.54 *(12.13)*		35.73 (*13.00*)
Gender: Male	13 (54%)		9 (41%)	
Ethnicity: Hispanic	4 (17%)		6 (27%)	
Race				
European American	13 (54%)		12 (55%)	
African American	5 (21%)		3 (14%)	
More than one race	3 (12%)		5 (23%)	
Asian	1 (4%)		2 (9%)	
Native American	2 (8%)		0 (0%)	
Education (years)		11.71 (*1.99*)		11.95 *(2.17)*

Table 2.

MIC-SR and symptom rating scale descriptive statistics.

	TCT		TAU	
	T1* M *(SD)	***T2* M *(SD)***	***T1* M *(SD)***	***T2* M *(SD)***
MIC-SR Total	11.42 *(7.53)*	11.81 *(8.92)*	10.50 *(7.73)*	9.90 *(6.99)*
MIC-SR Attention	4.79 *(3.08)*	4.75 *(4.07)*	3.77 *(2.96)*	3.80 *(2.97)*
MIC-SR Executive Functioning	3.13 *(2.83)*	2.83 *(2.62)*	3.17 *(2.93)*	2.85 *(2.43)*
MIC-SR Memory	3.42 *(2.86)*	4.06 *(3.45)*	3.18 *(2.84)*	3.20 *(2.31)*
MCCB-NC Composite (*t*-score)	23.13 *(6.19)*	28.56 *(6.18)*	23.95 *(13.71)*	26.80 *(14.77)*
PHQ-9	1.17 *(1.61)*	1.20 *(1.47)*	1.14 *(1.28)*	1.58 *(1.35)*
SANS Global Summary	7.75 *(4.50)*	7.31 *(3.91)*	6.18 *(3.97)*	7.26 *(4.81)*
SAPS Global Summary	5.12 *(4.00)*	3.25 *(4.37)*	4.45 *(5.14)*	3.79 *(4.08)*
SAPS-Hallucinations	1.75 *(1.75)*	0.94 *(1.48)*	1.32 *(1.91)*	1.58 *(1.92)*