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Letter to the Editors

A pilot study of cognitive training in clinical high risk for psychosis: Initial evidence of cognitive benefit

Dear Editors

Individuals at clinical high risk (CHR) for psychosis have cognitive deficits that are associated with functional impairment and psychosis conversion (Giuliano et al., 2012). Targeted cognitive training (TCT) (i.e., intense, progressively difficult practice of a cognitive skill) improves cognition and daily functioning in schizophrenia (Wykes et al., 2011). TCT has been proposed as a preventive intervention for CHR, but research is minimal and optimal training parameters, including dose, intensity, and setting, are unknown. Because prolonged duration of untreated CHR symptoms can compromise outcome, rapid treatment response is essential (Fusar-Poli et al., 2009). However, ambiguous risk status, psychosis-related stigma, and practical scheduling problems can reduce treatment motivation and compliance. Without pilot data to guide intervention development, the randomized-controlled trials necessary to show efficacy of cognitive training in CHR may be unsuccessful.

This study investigated the feasibility and potential behavioral benefits of 40 h/8 weeks of computer-based TCT in a single group of CHR participants. Cognitive and functional outcome were assessed with measures recommended for clinical trials, including the MATRICS Consensus Cognitive Battery (MCCB) and Global Functioning (GF): Role and Social scales (Cornblatt et al., 2007). Training performance was analyzed to: verify the relationship between training engagement and treatment outcome; identify an early predictor of treatment response; and evaluate intervention dose.

Methods

The intervention was designed to enhance compliance. Training was completed online from home (or elsewhere) on a structured but flexible schedule. Exercises were engaging computer-games from two programs: Lumosity (<http://www.lumosity.com>) which targeted cognition (processing speed, memory, attention, flexibility/cognitive-control, and problem-solving); and SocialVille (<http://www.positscience.com>) (Nahum et al., 2013) which targeted social cognition (social perception, emotion recognition, and theory-of-mind). 28 Lumosity and 11 SocialVille exercises rotated in a predetermined sequence delivered in one-hour increments. Each hour included four 15 minute sessions completed together or separately that day (3 × 15 min cognition; 1 × 15 min social cognition). Training 1 h/day, 5 days/week was recommended. Participants could not train more than 3 h/day or miss more than 5 consecutive days.

Eligible CHR participants were 15–35 years old with attenuated positive symptoms (3–5 score on 1 or more positive symptoms) on the Structured Interview for Prodromal Syndromes (SIPS) (Miller et al., 2003). Healthy controls (HC) were recruited to group-match CHR on IQ and demographics. Exclusions (for all participants): major

medical/neurological illness, non-fluent English, MR contraindications, and IQ < 70. HC exclusions: IQ > 130, past/current Axis I/II disorder, family history of psychosis.

The MCCB was assessed immediately pre/post TCT. Symptoms and functioning were assessed pre-TCT and one-month post-TCT, so assessments covering the previous month were not confounded with training. To minimize experimenter bias, assessment staff and participants believed that subjects were randomly assigned to TCT or a computer-game control condition, and that 'blindness' to group assignment must be maintained. Participants were paid for participation.

Eighteen CHR participants enrolled. Staff monitored training daily online. N = 3 were excluded for missing >5 days of training (non-compliance); N = 1 finished TCT but not post-testing. N = 1 missed testing one-month post-TCT.

Results

Mean (SD) are reported for fourteen CHR with post-TCT assessments. Fourteen HC were tested at baseline to identify CHR deficits. Groups were similar in age [HC: 24.1 (3.2); CHR: 21.9 (4.2)], gender [HC: 8F/6M; CHR: 7F/7M], and IQ [HC: 113.3 (8.5); CHR: 110.9 (12.7)].

Cognition: Fig. 1A. Global Functioning: (rated 1-to-10; 10 = highest) *Role:* HC: 8.7(0.8); CHR Pre: 7.4 (1.8), Post: 6.9 (2.1); *Social:* HC: 9.0 (0.4); CHR Pre: 6.1 (1.1), Post: 6.0 (1.9). *SIPS Total (CHR): Positive:* Pre: 14.3 (4.8), Post: 9.5 (5.5); *Negative:* Pre: 8.9 (5.6), Post: 7.4 (6.6); *Disorganized:* Pre: 3.4 (2.0), Post: 2.8 (2.2); and *General:* Pre: 5.4 (4.1), Post: 4.5 (3.8).

Compared to HC, CHR had worse visual learning and memory ($t(25) = 2.36, p = .03, d = .91$), processing speed ($t(25) = 1.92, p = .07$ (trend), $d = .74$), and social and role functioning (GF Social: $t(25) = 9.24, p < .0001, d = 3.62$; GF Role: $t(25) = 2.50, p = .02, d = .97$).

From pre-to-post TCT, CHR participants had significant improvement in processing speed [Pre: 48.9 (11.7); Post: 56.3 (12.1); $t(13) = 3.15, p = .01, d = .63$] and trend-level improvements in visual learning and memory [$t(13) = 2.11, p = .06, d = .54$] and global cognition [$t(13) = 2.10, p = .06, d = .45$]. From pre-TCT to one-month post-TCT, SIPS positive symptoms declined ($t(13) = 2.18, p = .05, d = .93$), but possible regression-to-the-mean precludes conclusions about TCT benefits. Other symptoms did not change nor did social and role functioning. However, greater pre-to-post TCT improvement in processing speed predicted greater improvement in role functioning ($r(12) = 0.55$).

Training performance was measured with the 'Brain Performance Index' (BPI): a standardized measure of Lumosity game performance that allows different performance metrics (reaction time, accuracy, etc.) to be aggregated. Training performance improvement after 10 h (i.e. BPI 10th hour–1st hour) was tested as an early predictor of treatment response. Training performance over time was examined by fitting an exponential curve: $y = A - B * \exp(-C * n)$, where y is the BPI, n is the training hours, A is the extrapolated maximum

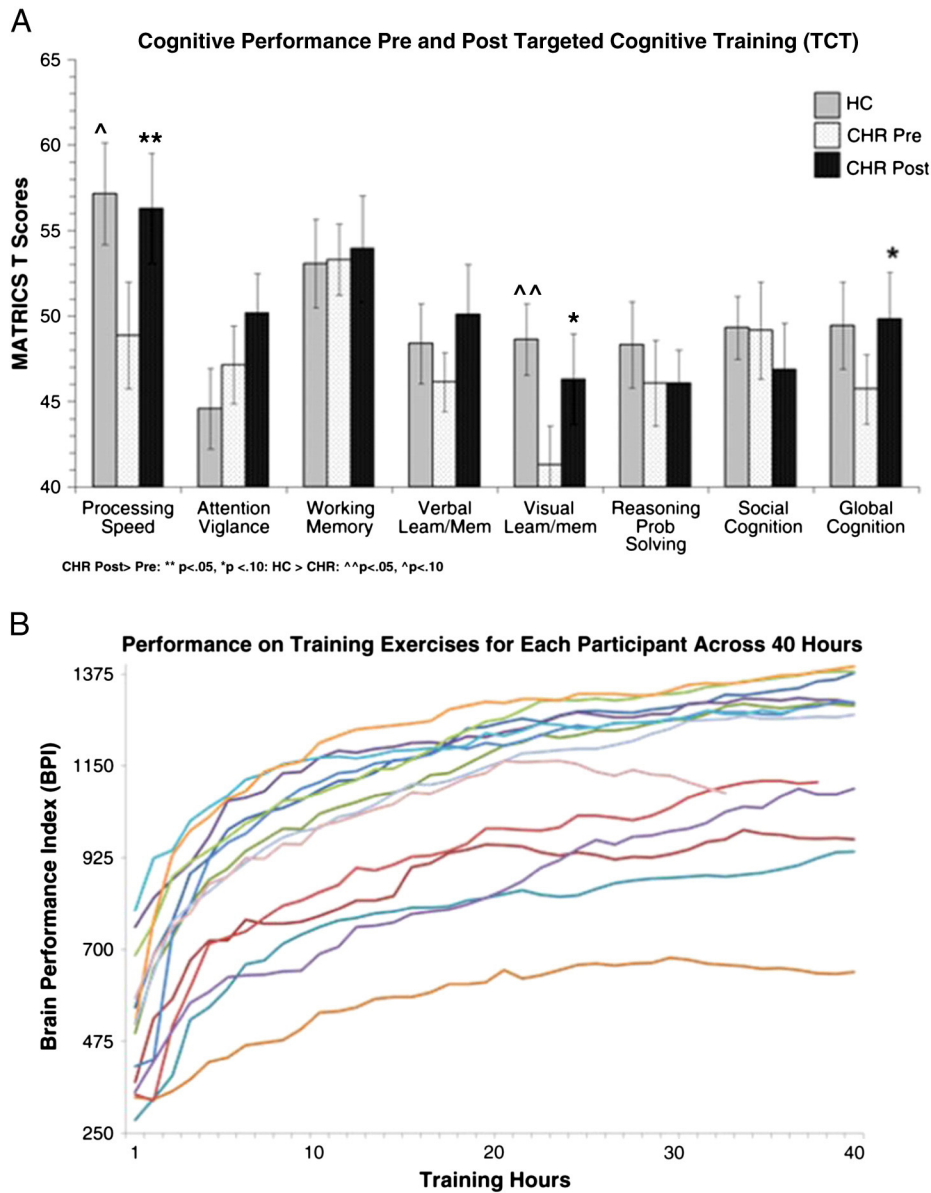


Fig. 1. A. Cognitive performance (T Scores) for each domain in the MATRICS Consensus Cognitive Battery. Error bars represent standard error of the mean. 1B. Training performance on Lumosity exercises is charted for each participant over the entire TCT intervention. Performance on Lumosity games is measured with the 'Brain Performance Index' (BPI) which is a standardized measure (normalized on Lumosity users system-wide) and has values ranging from 0 to 1700.

$BPI_{(n \rightarrow \infty)}$, (A-B) is the extrapolated pre-training $BPI_{(n=0)}$, and C is the BPI change rate constant (higher values indicate a steeper learning curve).

Results showed that greater improvement on training exercises after 10 h significantly predicted greater gains in processing speed ($r(12) = .54$) after TCT and role functioning one-month later ($r(12) = .70$). The CHR group achieved 50%, 75%, and 90% of the total improvement on training exercises (i.e. maximum BPI) after 5.98, 11.95 and 19.85 h of training, respectively. Individuals with a faster rate of improvement on training exercises had larger improvements in processing speed ($r(12) = 0.56$) and role functioning ($r(12) = 0.53$). Fig. 1B shows individual learning curves.

These findings provide initial evidence that an intensive, internet-based TCT intervention is feasible and has potential cognitive benefits for CHR. However, as an uncontrolled study, no conclusions can be drawn about specific benefits of TCT over other interventions or the natural fluctuation in cognition and function. Nonetheless, results inform intervention design and support pursuit of larger clinical trials. Processing speed, which was marginally below normal before TCT, significantly improved after TCT, and larger improvement was associated with

greater gains in role functioning. Moreover, performance on training exercises was directly related to improvement in both processing speed and role functioning. This suggests that cognitive improvements from training may facilitate better day-to-day functioning. In addition, initial training performance might be an early indicator of treatment response; if so, non-responders could switch to more effective treatment quicker, and, thus, improve outcome. Learning curves illustrate that trained skills improved substantially the first 20 h but only minimally thereafter. This suggests that ~25-30 h of TCT may be sufficient for cognitive benefit.

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The funding agencies provided funding for the study, but played no other role.

Contributors

Christine I. Hooker designed the study, supervised the data collection, conducted the data analysis and wrote the first draft of the manuscript. Matcheri S. Keshavan, and Larry J. Seidman helped design the study and write the manuscript. Emily E. Carol, T.J. Eisenstein, Hong Yin, Sarah Hope Lincoln, Laura M. Tully, and David Dodell-Feder assisted with the data collection and analysis. Mor Nahum developed the SocialVille program and supervised and analyzed SocialVille training data.

Conflict of interest

Mor Nahum is an employee of PositScience, the company that developed the SocialVille program. Christine I. Hooker is a consultant for PositScience. Emily E. Carol, T.J. Eisenstein, Hong Yin, Sarah Hope Lincoln, Laura M. Tully, David Dodell-Feder, Matcheri S. Keshavan, Larry J. Seidman have no conflicts of interest related to this study.

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