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Letter to the Editor

Improvement on visual cognitive training exercises in schizophrenia is present but less robust than in healthy individuals

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Though cognitive remediation is arguably the only treatment for cognitive deficits in schizophrenia (Prikken et al., 2018; Wykes et al., 2011), little is known about how patients interact with cognitive training software. To be effective, cognitive training must target disorder-specific impairments, engage intact learning mechanisms, and generalize to non-trained tasks. To address the first two requirements, we compared patients' and control users' performance on computerized exercises targeting visual processing and memory. Comparing patients' and healthy controls' progress on cognitive remediation interventions can help determine whether training targets impairments, and whether training progress differs in schizophrenia.

32 outpatients with schizophrenia participated in two cognitive remediation studies (NCT00339170, Bell et al., 2014, and NCT00312962, Fisher et al., 2009) using InSight, a suite of computerized visual processing exercises developed by Posit Science. Paid consumers of InSight provided control data shared by Posit Science. Controls ($n = 31$) were chosen from 313 InSight consumers, without regard to their performance, to be age-matched to patients. Available information about consumers was age, gender, and years of education (demographics in Table S1).

Insight had 4 four exercises: Sweep Seeker (foveal orientation discrimination exercise), Bird Safari (peripheral vision exercise), Road Tour (peripheral vision and divided attention exercise), and Jewel Diver (multiple object tracking exercise, Delahunt et al., 2008). During training, each exercise varied one parameter to titrate difficulty to maintain 85% correct responses (Fig. S1 explains exercises). During training, participants took standardized assessments for each exercise to measure training progression. We analyzed these assessments. Training procedures differed across the 3 participant sites (Table S2), but training times on InSight did not differ between groups (Table S3). Pre- and post-training, patients had neurocognitive testing and Positive and Negative Syndrome Scale ratings (PANSS, Kay et al., 1989).

Patients performed significantly worse than controls on initial assessments for two visual processing exercises: Sweep Seeker (Mann Whitney $U = 592$, $p < 0.0001$) and Bird Safari ($U = 475$, $p = 0.045$). Patients and controls did not perform differently on Road Tour, the divided attention task, or on the working memory task Jewel Diver (Fig. 1, Table S3).

Both groups had significant improvement on all four exercises with training (Fig. 1, Table S4). Though improvement effect sizes were large in patients for Road Tour (Cohen's $d = 0.6$, $t(22) = 8.3$, $p < 0.001$) and Jewel Diver (Cohen's $d = 2.0$, $t(22) = -4.32$, $p < 0.001$), they were consistently smaller for patients than for controls. The largest improvement difference between groups was for Sweep Seeker, with Cohen's $d = 1.01$ ($t(25) = 5.88$, $p < 0.001$) for controls compared to $d = 0.3$ for patients ($t(26) = 2.53$, $p = 0.02$).

Patients had improved post-training (>baseline) scores on fewer exercises (Fig. S2). The proportion of people improving on all exercises was significantly different between groups: 87.5% of controls versus 47% of patients ($X^2(1, 43) = 8.1$, $p = 0.004$).

Neither global neurocognition nor visual working memory showed improvement with training (Table S5).

Responder analysis comparing patients who improved on all exercises to those who did not revealed two variables associated with better training: PANSS positive scores were lower ($t(17) = -2.5$, $p = 0.02$, Cohen's $d = 1.2$) and Digit Symbol Coding (SC) scores were higher ($t(17) = 1.9$, $p = 0.05$, Cohen's $d = 1.0$) prior to training in patients who improved on all 4 exercises. Age, education, gender, antipsychotic doses, InSight training time, negative symptoms, and baseline neurocognitive and InSight assessments did not differ between patients who improved on all exercises versus those who did not. The two groups did not differ in neurocognitive change scores either.

Patients' deficits were most pronounced in Sweep Seeker, designed to train spatial frequency and orientation tuning in primary visual cortex (V1). Orientation tuning is broadened in schizophrenia and related to decreased gamma-aminobutyric acid (GABA) concentration and decreased inhibitory surround of receptive fields in V1 in schizophrenia (Anderson et al., 2017; Rokem et al., 2011). Sweep Seeker thus has the potential to treat abnormalities early in visual processing, with the added possibilities of normalizing upstream processing, GABA concentrations, and inhibitory surround in V1.

Two exercises with more complex stimuli — the exercise of divided attention between central and peripheral stimuli Road Tour, and the multiple-object tracking exercise Jewel Diver — did not differentiate patients from controls. Counter intuitively, the increased stimulus complexity of those exercises could mask deficits by increasing reliance on the parvocellular visual pathway, which processes fine detail and color and may be spared in schizophrenia compared to the magnocellular pathway (Kim et al., 2006), which rapidly processes information about movement and location.

These findings suggest that future cognitive remediation should initiate training using simple stimuli, where patients' deficits are clear, so target deficits can be engaged rather than bypassed. As simple stimuli are mastered, cognitive training programs can progress to gradually increase stimulus complexity and promote generalization of benefits.

Less severe positive symptoms and better SC scores were associated with training improvements, suggesting two factors that could predict the patients more likely to improve during cognitive training. Predicting

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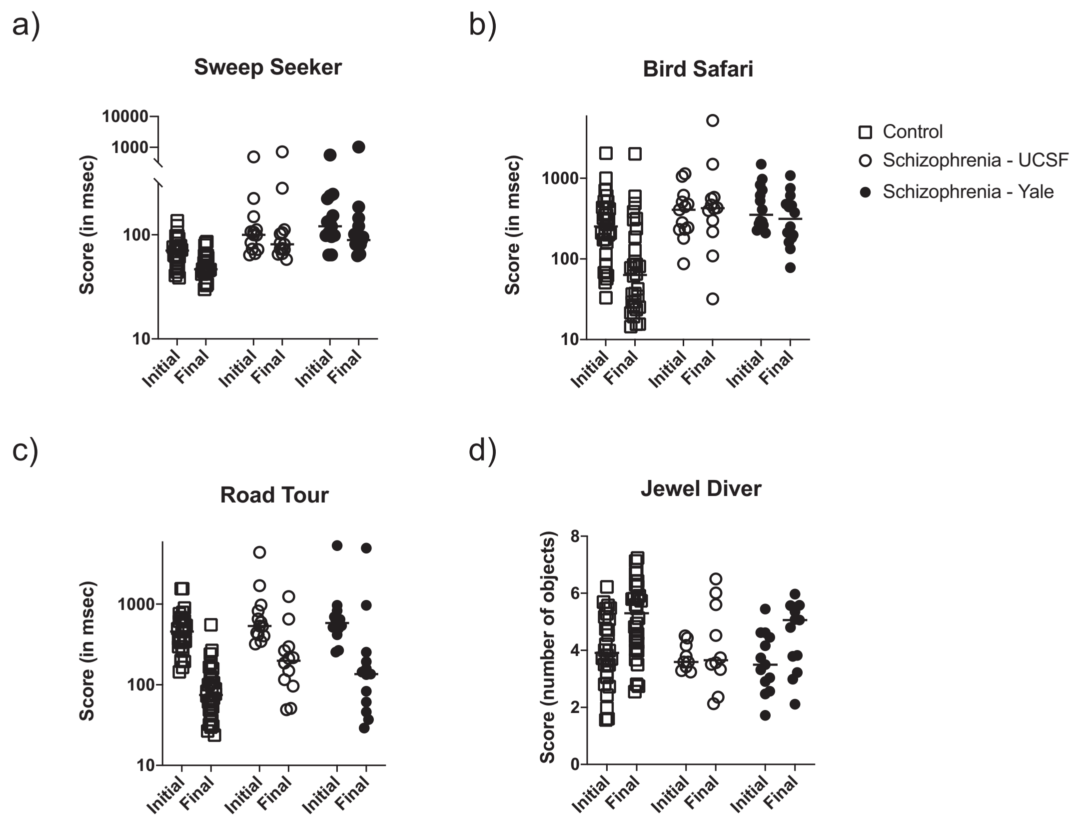

Fig. 1. Initial and final assessments on the 4 trained exercises. Scatter plots of initial and final performance on Sweep Seeker (a), Bird Safari (b), Road Tour (c), and Jewel Diver (d) for participants from each of the three studies: control participants from Posit Science (open squares); patients from study NCT00312962 at University of California, San Francisco (UCSF, open circles); and patients from study NCT00339170 at Yale School of Medicine (filled circles). Horizontal lines represent the median value.

generalization with training improvements, however, may not be straightforward. Improvements in visual processing exercises have been associated with improvements in visual working memory (Surti et al., 2011; Surti and Wexler, 2012), but we did not find this relationship here. Larger, controlled studies can test whether visual training results in improved visual working memory.

Patients did not have as much improvement in training as control participants. Further work to identify more efficient learning mechanisms in schizophrenia should guide developments of cognitive treatment.

We recognize the limitations of our analyses. Patients and matched controls used the same software in different settings, potentially adding confounders. Because the analyses were exploratory, corrections for multiple comparisons were not made, and the sample is small, so, though some effects are large, findings may not be robust. Finally, the psychometric properties of InSight assessment tasks are unknown, potentially complicating comparisons of difficulty between tasks. However, comparisons of training gains between patients and controls are less affected. That gains, though smaller, occur in schizophrenia is the major contribution of the analyses.

We hope future cognitive remediation studies analyze progression on trained tasks to complement more common studies of training effects on non-trained tasks. Understanding how patients improve in training exercises has valuable implications for developing cognitive interventions.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.11.021.

Contributors

Sophia Vinogradov, Morris Bell, and Bruce Wexler designed and executed the original studies collecting the data in this manuscript. Toral Surti performed the analyses and wrote the first draft of the manuscript. All authors have contributed to and approved the final manuscript.

Declaration of competing interest

Dr. Wexler was a paid consultant for Posit Science Corporation at the time some of the data reported were collected and has had stock options in this company. All other authors declare they have no conflicts of interest.

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