Using Tools of Neuroscience to Make Personalized Care a Reality in Schizophrenia

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BRAIN & BEHAVIOR RESEARCH FOUNDATION
Awarding NARSAD Grants

SIDNEY R. BAER, JR. FOUNDATION
Are we studying and treating schizophrenia correctly?

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1. Introduction

With increasing pace, findings are revealing the structural and functional properties of limbic cortical and subcortical circuits that are conveyed through programmed cell migration, pre- and post-natal synaptic reorganization and apoptosis across normal development (cf. Tau and Peterson, 2010). Current models for the etiology of the schizophrenias (e.g. Bigos et al., 2010; Kleinman et al., 2011) suggest that this intricate weaving is turned to chaos by predisposing genes and epigenetic events; the resultant or compensatory changes are then hard-wired by tightly choreographed, inter-dependent developmental pro-
Cognitive impairment underlies functional outcome in SZ

MODEST IMPROVEMENTS IN COGNITION

CLINICALLY RELEVANT IMPROVEMENTS IN OUTCOMES
No Effect of Commercial Cognitive Training on Brain Activity, Choice Behavior, or Cognitive Performance

Joseph W. Kable, M. Kathleen Caulfield, Mary Falcone, Mairead McConnell, Leah Bernardo, Trishala Parthasarathi, Nicole Cooper, Rebecca Ashare, Janet Audrain-McGovern, Robert Hornik, Paul Diefenbach, Frank J. Lee, and Caryn Lerman

Journal of Neuroscience 2 August 2017, 37 (31) 7390-7402; DOI: https://doi.org/10.1523/JNEUROSCI.2832-16.2017

Lumosity to Pay $2 Million to Settle FTC Decepitive Advertising Charges for Its “Brain Training” Program

Company Claimed Program Would Sharpen Performance in Everyday Life and Protect Against Cognitive Decline
Testing the Information Processing Cascade Model

Thomas et al. (2017)
Disentangling Multivariate Relationships: Testing the Information Processing Cascade Model

MMN is Sensitive to Initial Exposure to Memantine: 1 pill

Swerdlow NR, Bhakta SG, Chou HH, Talledo JA, Balvaneda B, Light GA (2015), *Neuropsychopharmacology*
Testing the Information Processing Cascade Model

Early Auditory Information Processing (MMN) supports a 1-uV change.

Cognition supports d>0.78 change.

Clinical Symptoms and Daily Functioning require time-course & requirements for change?

Time-course & requirements for change? Cognitive Training?

Thomas et al. (2017), JAMA Psychiatry.
“Experimental Medicine” Trial with a Nonpharmacologic Intervention: An Example using Auditory Targeted Cognitive Training (TCT)

- Computerized approach to cognitive remediation
- Aims to improve the accuracy and fidelity of auditory sensory information processing
- Capitalizes on “neuroplasticity based” learning mechanisms via exercises that are: intensive, adaptive, rewarding
- Place progressive demands on higher-order cognitive domains
- Efficacious for improving cognition in psychosis patients at the group level

Tarasenko M, Perez VB, Pianka ST, Vinogradov S, Braff DL, Swerdlow NR, Light GA (2016), Schizophrenia Research
Previous Studies have Demonstrated *Efficacy* of TCT in Sz

- **TCT improves verbal learning and memory in adult SZ outpatients.**

- **TCT improves verbal learning/memory in recent onset SZ outpatients.**

- **TCT improves verbal learning/memory in adolescents and young adults at clinical high risk for psychosis.**

- **TCT improves verbal learning/memory and auditory hallucinations in treatment refractory schizophrenia inpatients.**

  *Top Research Finding of 2018, Brain & Behavior Research Foundation*
Challenges to overcome

- TCT has largely been tested in academic labs
- TCT is time-intensive and requires resources
- TCT does not help all patients
Are EEG measures acutely sensitive to the neural systems engaged by 1h of TCT exercises?

Does 30h of cognitive training “work” in treatment refractory schizophrenia Inpatients?

Do EEG changes following initial exposure to TCT predict future therapeutic benefit?
Auditory Targeted Cognitive Training: Brain Fitness Auditory Exercises

1. Sound Sweeps
2. To-do List Training
3. Memory Grid
4. Fine Tuning
5. Syllable Stacks
6. Rhythm Recall
Auditory Targeted Cognitive Training

Click the arrow pointing in the direction of the second sweep sound you heard. The correct arrow is highlighted.
Auditory Targeted Cognitive Training
Are EEG measures acutely sensitive to the neural systems engaged by 1h of TCT exercises?

Does 30h of cognitive training “work” in treatment refractory schizophrenia Inpatients?

Do EEG changes following initial exposure to TCT predict future therapeutic benefit?
Changes in Source Contributions after 1h of Cognitive Training

Perez VB et al (2017), *Neuropsychopharmacology*

Are EEG measures acutely sensitive to the neural systems engaged by 1h of TCT exercises?

Does 30h of cognitive training “work” in treatment refractory schizophrenia Inpatients?

Do EEG changes following initial exposure to TCT predict future therapeutic benefit?
<table>
<thead>
<tr>
<th></th>
<th>Treatment as Usual</th>
<th>Targeted Cognitive Training</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Sample Size</td>
<td>22</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>35.73 (13.00)</td>
<td>34.54 (12.13)</td>
<td>0.75</td>
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<tr>
<td>Gender: Male</td>
<td>9 (41%)</td>
<td>13 (54%)</td>
<td>0.55</td>
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<tr>
<td>Hispanic</td>
<td>6 (27%)</td>
<td>4 (17%)</td>
<td>0.61</td>
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<tr>
<td>Race</td>
<td></td>
<td></td>
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<tr>
<td>African American</td>
<td>3 (14%)</td>
<td>5 (21%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (9%)</td>
<td>1 (4%)</td>
<td></td>
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<tr>
<td>Caucasian</td>
<td>12 (55%)</td>
<td>13 (54%)</td>
<td></td>
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<tr>
<td>More than one race</td>
<td>5 (23%)</td>
<td>3 (12%)</td>
<td></td>
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<tr>
<td>Native American</td>
<td>0 (0%)</td>
<td>2 (8%)</td>
<td></td>
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<tr>
<td>Education</td>
<td>11.95 (2.17)</td>
<td>11.71 (1.99)</td>
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<tr>
<td>Chlorpromazine Equivalents</td>
<td>982.54 (758.10)</td>
<td>1329.42 (972.78)</td>
<td>0.82</td>
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<tr>
<td>Illness Duration</td>
<td>15.23 (12.78)</td>
<td>16.12 (13.67)</td>
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<tr>
<td>SAPS</td>
<td>4.45 (5.14)</td>
<td>5.12 (4.00)</td>
<td>0.62</td>
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<tr>
<td>PSYRATS-AH</td>
<td>7.32 (11.10)</td>
<td>8.79 (11.64)</td>
<td>0.66</td>
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<tr>
<td>SANS</td>
<td>6.18 (3.97)</td>
<td>7.75 (4.50)</td>
<td>0.22</td>
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<tr>
<td>MCCB-NC Composite</td>
<td>23.95 (13.71)</td>
<td>23.12 (12.14)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Thomas et al., (2018)
TCT Enhances Verbal Learning in Severely Disabled SZ inpatients

$d = 0.82$

$p < 0.01$

Thomas et al, (2018)
TCT Reduces Hallucinations in Severely Disabled SZ inpatients

Thomas et al, (2018)
TCT Improves Engagement in SZ inpatients

+ 1.34 groups activities/wk
+ 0.58 ADLs/wk
+ 0.84 rehabilitation activities/wk

~1 extra total week of rehabilitation
Are EEG measures acutely sensitive to the neural systems engaged by 1h of TCT exercises?

Does 30h of cognitive training “work” in treatment refractory schizophrenia Inpatients?

Do EEG changes following initial exposure to TCT predict future therapeutic benefit?
Amplitude Changes After 1h Predicts Improvements in Verbal Learning After 30h

Hochberger et al (2019), Neuropsychopharmacology
Amplitude Changes After 1h Predicts Reductions in Auditory Hallucinations After 30h

Hochberger et al (2019), Neuropsychopharmacology
EEG Biomarkers Predict Individual Benefits

Hochberger et al (in press)
Swerdlow NR, Bhakta SG, Light GA (2018), *Schizophrenia Research*

Revised Neuroscience-Informed Experimental Medicine Approach

“IMPRECISE MEDICINE”

- Clinical Phenotype
- Intervention

12.5% "Responders"  
87.5% "Non-Responders"

TREATMENT FAILURE

“PRECISION MEDICINE”

- Clinical Phenotype
- SCREEN FOR "BIOMARKER"
- Intervention

100% "Responders"

TREATMENT SUCCESS

Swerdlow NR, Bhakta SG, Light GA (2018), *Schizophrenia Research*
Lessons Learned and Caveats

• This particular form of cognitive training is effective for improving cognitive, clinical, and psychosocial functioning of patients, even those with long-standing illness.
• Patients with greater severity of deficits benefited the most
• Biomarkers measured

• The exercises are not that much fun
• Our sample size was small, others demonstrating similar effectiveness larger
• Not all patients benefited
• *Complaints* of daily cognitive problems were not improved, even among those with larger gains
• Specific cognitive exercises and dose probably matters
• Context of delivery and who administers it probably matters
• Clinical stabilization first
• Get the context right first – embedded within enriched psychosocial experiences.
Ongoing Studies and Future Directions

– Accelerating drug development via translational neuroscience
– Predicting development of illness in at risk individuals
– Tracking progression of deficits across course of illness
– Novel Analytics: Neural mechanisms, temporal dynamics, multivariate composite indices

• Biomarker-guided assignment to treatments?

• Biomarker in early and later phase clinical trials

• Assessing early response to pharmacologic interventions: PACT
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