Promoting Cognitive and Neural System Recovery in Early Psychosis

Sophia Vinogradov, MD
Department of Psychiatry & Behavioral Sciences,
University of Minnesota

Disclosures

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<th>Source</th>
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<th>Grant Support</th>
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Learning Objectives

At the conclusion of this continuing medical education activity, the participant should be able to:

1. Describe the typical profile of cognitive deficits in early phases of psychotic illness.
2. Discuss the principles of neuroscience-informed cognitive training.
3. Identify the effects of targeted cognitive training in early phases of psychotic illness.
Thoughts/Feelings/Actions result from the flow of information through the neural systems of the brain.

Adapted from Ahissar et al. 2009.
Psychiatric illnesses result from abnormal information flow through brain systems

- In depression, attentional bias to negatively-valenced stimuli is a core feature
- In psychotic illness, both early perceptual processes and higher-order cognitions are disrupted, even prior to illness onset

The “Symphony” of brain information flow is impaired in psychosis

Healthy Prefrontal Cortex
High gamma neural oscillations

Alex Herman et al. J Neurosci 2013
Corby Dale et al. Schiz Bull 2015
But brain systems are plastic

The brain adapts to salient experiences by representing the relevant sensory stimuli and action outputs with disproportionately larger and more coordinated populations of neurons.

Merzenich & Jenkins, 1993; Buonomano & Merzenich, 1998; Merzenich & DeCharms, 1996; Merzenich, 2001

Can we harness these plasticity processes to “repair” impaired brain systems?

- Significant neuroplastic changes occur across the lifespan in response to salient learning events.
- Thus, we should be able to engineer intensive, progressive, heavily rewarded, perceptual and cognitive training experiences that improve the accuracy, fidelity, and efficiency of targeted brain systems.

Merzenich et al 1999
Improvements in brain system function should translate to improved quality of life

- Work
- Social
- Mood
- Motivation
- Attention
- Learning and Memory
- Social/Emotional Cognition
- Speed of Information Processing
- Accuracy of Information Processing
- Reward Responses to Salient Info.

Can cognitive training serve as a “vaccine” to pre-empt cognitive deterioration in early psychosis? What should be our neural targets?

Restoration of brain system function

Neural System Target 1:
Auditory/Verbal Processing in Schizophrenia

- **Rationale:** Schizophrenia is characterized by widespread disturbances in verbal memory systems that are present prior to the first episode and have prognostic significance (Hil et al 2004).
Cognitive training of auditory systems performed at home on laptops in young recent-onset individuals

Melissa Fisher, PhD  
Rachel Loewy, PhD  
Cam Carter, MD  
Dan Ragland, PhD

AT Group  
Total randomized: 78  
Completed 20-40 hours: 52  
Completed < 20 hours: 3  
Withdrew: 22  
Excluded due to increase in benztrapine dose: 1

CG Group  
Total randomized: 80  
Completed 20-40 hours: 45  
Completed < 20 hours: 3  
Withdrew: 17  
Excluded due to increase in benztrapine dose: 1

Total Enrolled: 172  
Withdrew During Baseline Assessment: 28  
Total Randomized: 144

6 Month Follow-Up  
Completed: 37

Analyzed N = 55  
Analyzed N = 48

Baseline Cognitive Performance

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<th>AT (N=55)</th>
<th>CG (N=48)</th>
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<td>Global Cognition</td>
<td>-2.50</td>
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<tr>
<td>Speed of Processing</td>
<td>-2.00</td>
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<tr>
<td>Working Memory</td>
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<tr>
<td>Verbal Learning and Memory</td>
<td>-1.00</td>
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<tr>
<td>Visual Learning and Memory</td>
<td>-0.50</td>
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<tr>
<td>Problem Solving</td>
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Targeted cognitive training drives significant gains in cognitive outcome measures

Repeated Measures ANOVA group x time interactions significant for Global Cognition, Verbal Learning and Memory, and Problem Solving. Verbal Learning and Memory post hoc tests: Gain in AT subjects $p = .04$, decline in CG subjects $p = .11$. Results remain significant controlling for age and hours of training.


Improved cognition endures at 6 months

Baseline to 6 month follow-up change in symptoms

Positive Symptoms* Negative Symptoms Symptoms of General Psychopathology PANSS Total
Thalamic volume shows training-induced plasticity in young early psychosis individuals

Ramsay et al. Neuropsychopharm 2017

As does thalamotemporal connectivity

Dan Mathalon Susann Fryer

Left Superior Temporal Gyrus ROI

Correlation with Change in Global Cognition

A left superior temporal gyrus ROI (Z=10) showed a group x time interaction (F=12.12; p<0.001), characterised by increased thalamotemporal connectivity in the targeted cognitive training (TCT) group, and decreased in the CG group.

Slopes difference between groups correlating change in connectivity and change in global cognition (t=2.85; p=0.007), characterised by a positive correlation in the TCT group (r=0.59; p=0.02), and a non-significant negative correlation in the CG group (rn=–0.34; p=0.14).

Early Psychosis = catastrophic failure to achieve developmental milestones for social efficacy and motivated behavior
Target 2: Social Cognition Training in Early Schizophrenia

Study participants:
- n=17 recent-onset schizophrenia patients
- 13 males, 4 females
- Mean age: 23.8±3
- 17 age, gender and education-matched healthy controls (comparison group)

Baseline Assessments

Social cognitive training:
- 24 1h sessions, 3-5 times/week, 6-10 weeks

Post-Training Assessments


Participants show significant improvements in untrained measures of social cognition

Vocal Emotion

Facial Recognition

Emotional Proxody Identification (PROID): p=0.01
Facial Recognition (Penn Facial Memory Test): p=0.007, p=0.03
They also show improvement in measures of motivated behavior and functioning

What Do We Know So Far?

- Targeted cognitive training can be carried out via portable computing device in people with schizophrenia, even at the earliest stages of the illness.
- Cognitive training results in significant gains in verbal memory, processing speed, global cognition, and social cognition.
- After training, we observe associations between neural system plasticity and behavioral change.
- Behavioral and brain system changes are associated with enduring functional gains.
• Lots of Open Questions to Be Investigated:
  – How do pre-existing pathological brain system functions constrain plasticity responses?
  – Do training-induced gains endure? Which training components are driving the improvements?
  – How can we personalize training to target the specific profile of deficits of a given individual?
  – How do we enhance motivation and engagement?
  – Can we develop a “cognitive vaccine” that can prevent or mitigate the cognitive and neural system deterioration of schizophrenia?

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