# Promoting Cognitive and Neural System Recovery in Early Psychosis

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## Disclosures

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<th>Source</th>
<th>Advisory Board</th>
<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

Perceptions are integrated to generate higher-order representations

Predictive/comparing operations influence lower-level perceptions

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

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<th>Healthy High gamma neural oscillations</th>
<th>Schizophrenia</th>
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<td>Prefrontal Cortex</td>
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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
Sunday, October 2

Improvements in brain system function should translate to improved quality of life

Life Function

Cognitive Function

Brain Function

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?
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 (Hill et al 2004).
AT Group
Total randomized: 78
Completed 20-40 hours: 52
Completed < 20 hours: 3
Withdrew: 22
Excluded due to increase in benztropine dose: 1

CG Group
Total randomized: 66
Completed 20-40 hours: 45
Completed < 20 hours: 3
Withdrew: 17
Excluded due to increase in benztropine dose: 1

Baseline Cognitive Performance
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

![Bar graph showing changes in symptoms](image)

Thalamic volume shows training-induced plasticity in young early psychosis individuals

![Graph showing thalamic volume changes and correlation](image)

Ian Ramsay, PhD

Ramsay et al. Neuropsychopharm 2017
As does thalamotemporal connectivity

A left superior temporal gyrus ROI (Z=10) showed a group x time interaction ($F=12.12; p=.0008$), characterized by increased thalamo-temporal connectivity in the targeted cognitive training (TCT) group, and decreased in the CG group.

Correlation with Change in Global Cognition

Slopes difference between groups correlating change in connectivity and change in global cognition ($t=2.85; p=.007$), characterized by a positive correlation in the TCT group ($r=.50; p=.02$), and a non-significant negative correlation in the CG group ($r=-.34; p=.14$).

Early Psychosis = catastrophic failure to achieve developmental milestones for social efficacy and motivated behavior

Critical windows

- EXPERIENCE-EXPECTANT NEUROPLASTICITY
  - Primary sensor-motor functions
  - Language
- EXPERIENCE-DEPENDENT NEUROPLASTICITY
  - Higher cognitive and socio-affective functions

AUTONOMY
COMPETENCE
SELF-EFFICACY
INTEGRATED SOCIAL SELF

23

24
RCT of Targeted Cognitive Training + Social Cognition Training vs Targeted Cognitive Training Alone

**BASELINE ASSESSMENTS**
fmRI during the Monetary Incentive Delay Task (subset)

- **TCT+SCT**
  - 80 hours, 14 weeks
  - N = 57

- **TCT-Only**
  - 80 hours, 14 weeks
  - N = 54

**POST TRAINING ASSESSMENTS**
Completed Training & Assessed: 29 TCT+SCT, 32 TCT-Only
Repeat fMRI during the MID Task

**SIX MONTH FOLLOW UP ASSESSMENTS**
Assessed: 18 TCT+SCT, 16 TCT-Only

Study Participants
- 111 Randomized participants with diagnoses of schizophrenia, schizoaffective disorder, or psychosis NOS
- Mean Age 43 ± 13
- Mean education 14 yr ± 2.2

ITT Analysis of 57 TCT+SCT and 54 TCT-only participants

Fisher et al., Psychiatric Rehabilitation Journal, 2017
TCT+SCT improves prosody identification and reward responsivity immediately following treatment but TCT-only does not

Improvements in prosody identification are durable at 6-months
Improvements in reward responsivity are also durable at 6-months and are associated with improvements in social functioning.

Miley et al., in revision

Improved accuracy on the MID task and enhanced mPFC activation during reward anticipation are seen in the TCT-SCT group compared to TCT-only.

Enhanced mPFC activation during reward anticipation in TCT-SCT is associated with increased self-reported reward responsivity.

Subramaniam et al., under review
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?
  – What compensatory processes some into play?
  – 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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