## Promoting Cognitive and Neural System Recovery in Early Psychosis

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## Disclosures

| Source | Advisory Board | Grant Support | In-kind Support | Research Support |
|---|---|---|---|---|
| Alkermes | X | | | |
| Lynne and Andrew Redleaf Foundation | | X | | |
| NIMH | | | | X |
| Office of Naval Research | | | | X |
| One Mind PsyberGuide | X | | | X |
| Stanley Medical Research Institute | | | | X |
| PositScience Inc. | | | X | |
| | | | | |

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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.

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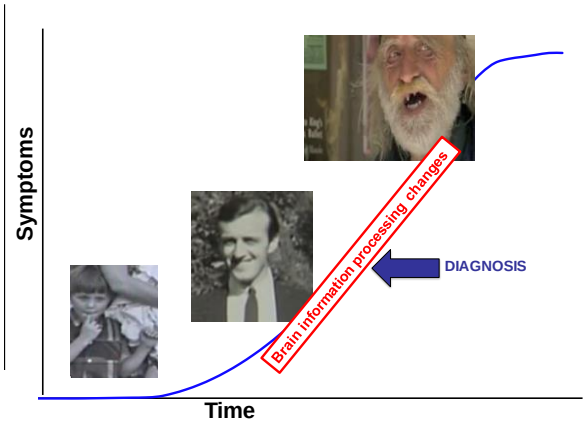
Symptoms
Time
Brain information processing changes
DIAGNOSIS

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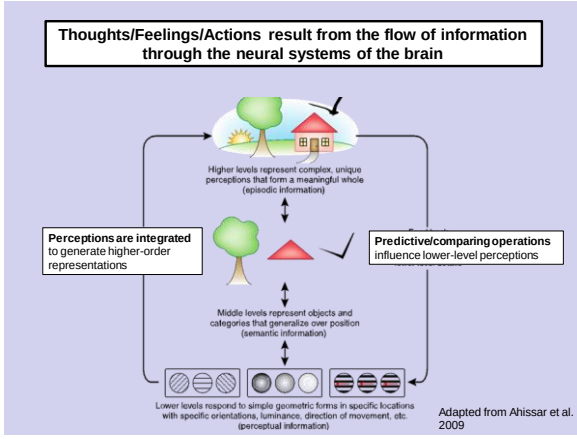
Thoughts/Feelings/Actions result from the flow of information through the neural systems of the brain
Higher levels represent complex, unique perceptions that form a meaningful whole (episodic information)
Perceptions are integrated to generate higher-order representations
Predictive/comparing operations influence lower-level perceptions
Middle levels represent objects and categories that generalize over position (semantic information)
Lower levels respond to simple geometric forms in specific locations with specific orientations, luminance, direction of movement, etc. (perceptual information)
Adapted from Ahissar et al. 2009

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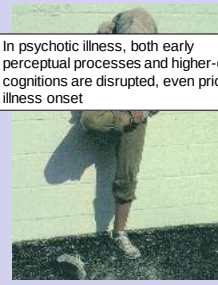
**Psychiatric illnesses result from abnormal information flow through brain systems**

- 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

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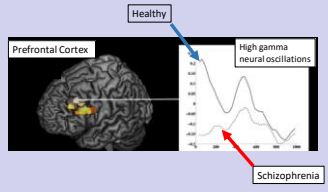
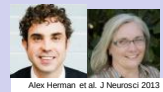
**The "Symphony" of brain information flow is impaired in psychosis**



Alex Herman et al. J Neurosci 2013
Corby Dale et al. Schiz Bull 2015

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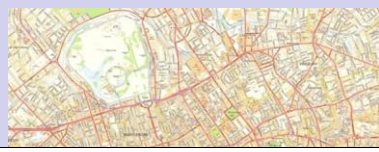
**But brain systems are plastic**



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; Buomomano & Merzenich, 1998; Merzenich & DeCharms, 1996; Merzenich, 2001

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**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

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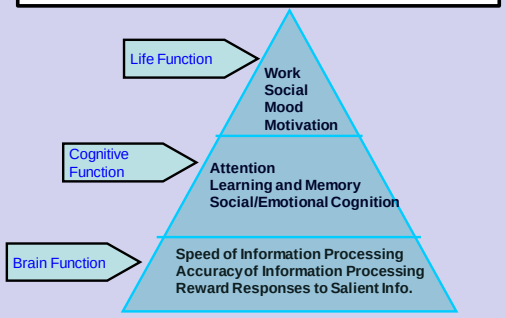
**Improvements in brain system function should translate to improved quality of life**

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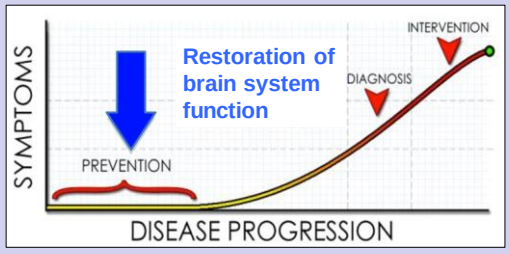
**Can cognitive training serve as a "vaccine" to pre-empt cognitive deterioration in early psychosis?**
**What should be our neural targets?**

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**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).

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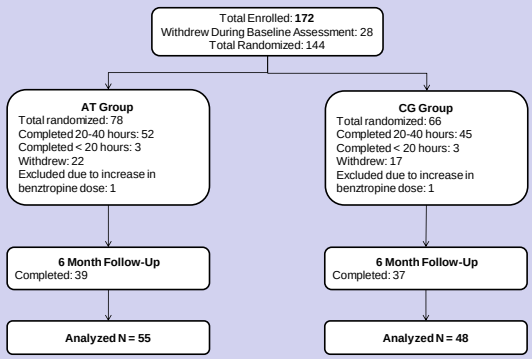
## Study design

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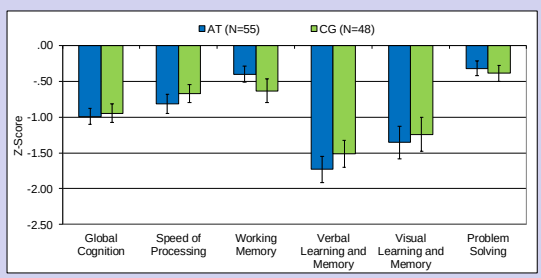
## Baseline Cognitive Performance

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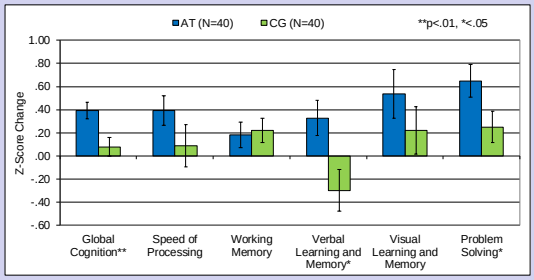
## Targeted cognitive training drives significant gains in cognitive outcome measures




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.

Fisher, Loewy, Carter, Ragland. Niendam, Vinogradov, Schiz Bull 2014

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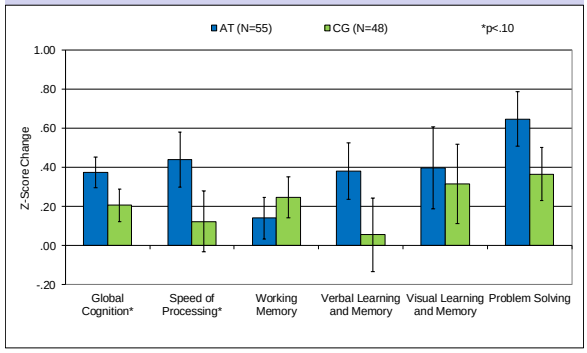
## Improved cognition endures at 6 months

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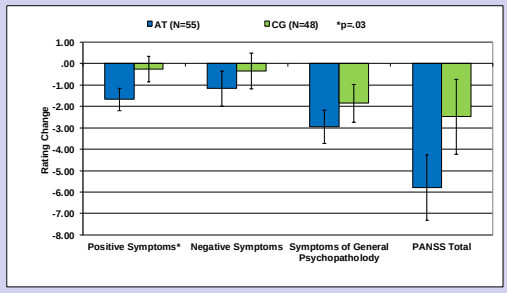
## Baseline to 6 month follow-up change in symptoms

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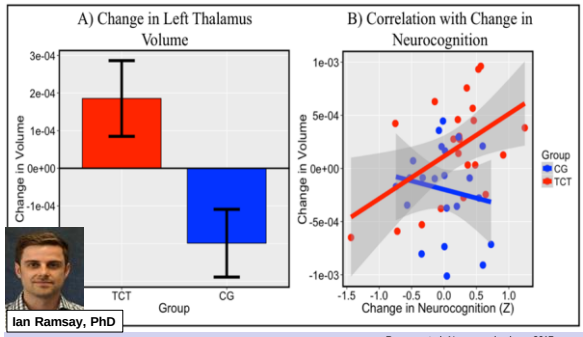
**Thalamic volume shows training-induced plasticity in young early psychosis individuals**




Ian Ramsay, PhD

Ramsay et al. *Neuropsychopharm* 2017

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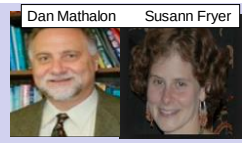
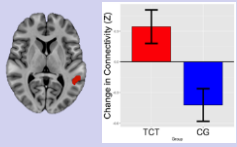
**As does thalamotemporal connectivity**



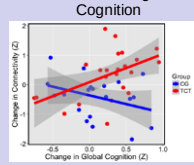
Dan Mathalon Susann Fryer

Left Superior Temporal Gyrus ROI




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).

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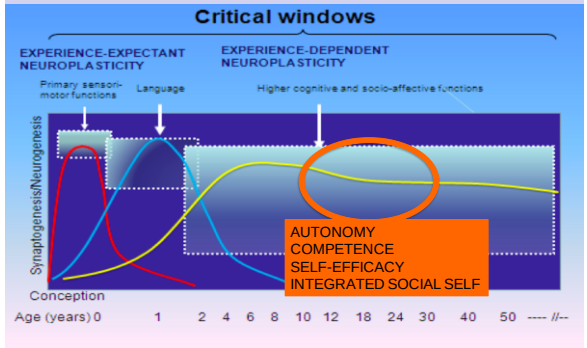
**Early Psychosis = catastrophic failure to achieve developmental milestones for social efficacy and motivated behavior**

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**Target 2: Social Cognition Training in Early Schizophrenia**

Baseline Assessments

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

Post-Training Assessments

**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)

Nahum et al., *Schiz Res: Cognition*, 2014

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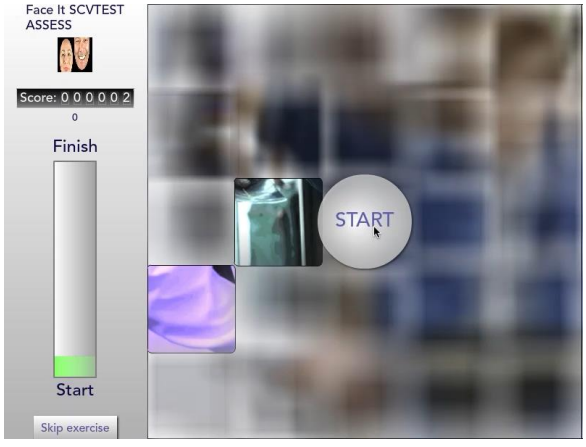


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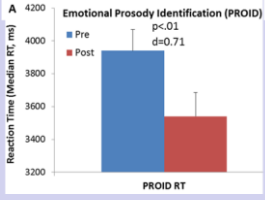
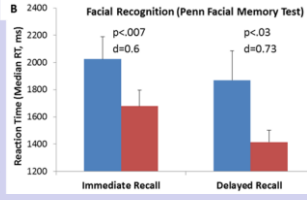
**Participants show significant improvements in untrained measures of social cognition**

Vocal Emotion




Facial Recognition

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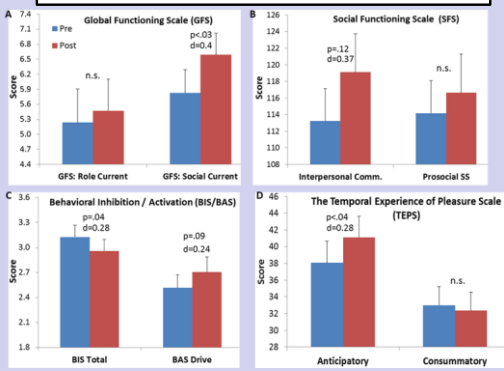
**They also show improvement in measures of motivated behavior and functioning**

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## 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.

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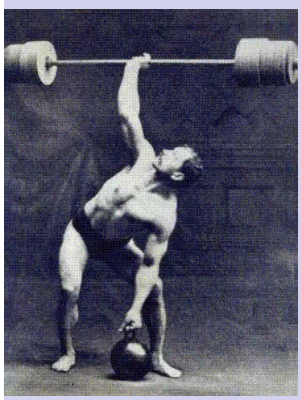

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- **Lots of Open Questions to Be Investigated:**
  - How do pre-existing pathological brain system functions constrain plasticity responses?
  - Do training-induced gains endure? Which training components are driving the improvements?
  - How can we 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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## Many, many thanks:

Melissa Fisher PhD
Ian Ramsay PhD
Univ of Minn

Rachel Loewy PhD
**Srikantan Nagarajan PhD**
UCSF

Cam Carter, Dan Ragland
Tara Niendam
UCD

**Michael Merzenich PhD**
Mor Nahum PhD
Positscience, Inc.

Laboratory Group:
Ariel Currie BA
Ben Brandrett, BA

Imaging Team:
Karuna Subramaniam PhD
Alex Herman MD PhD
Corby Dale PhD

**Robert Heinssen PhD (NIMH)**
**Staglin Family Foundation**
**The Tauber Foundation**
**Stanley Medical Res Inst**
**Dept of Veterans Affairs**

**Our research participants and their families!**

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