Cognitive training for young individuals with psychotic illness

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Using "neuroplasticity" to develop new treatments

Neuroplasticity:
The brain's lifelong capacity for physical and functional change in response to experience…

Presenter Disclosure

- **The following personal financial relationships with commercial interests relevant to this presentation exist:**
- The cognitive training software described in this presentation was supplied free of charge by Positscience Inc.
- Sophia Vinogradov is a paid consultant on an NIMH BRDG-SPAN grant to Brain Plasticity Inc., a company with a commercial interest in the cognitive training software described in this presentation.

The Path to Serious Mental Illness

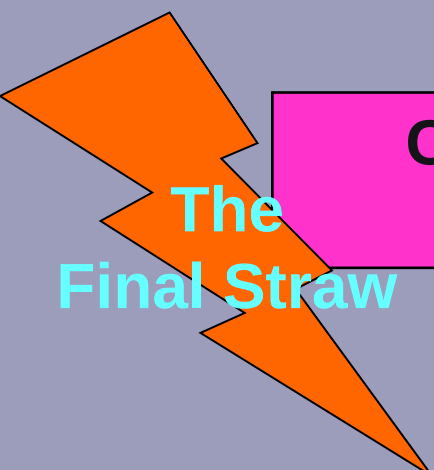
Genetic predisposition

↓ Pre/ perinatal insults

Neurodevelopmental anomalies; cognitive vulnerabilities

↓ Later environmental hits & triggers

Cognitive dysfunction; altered stress responsivity; DA dysregulation



↓

Onset of PSYCHOSIS

↓ Repeated episodes of psychosis; altered neuroplasticity

Neurodegeneration and chronicity

What do we know about early psychosis?

- Multiple cognitive deficits are present, even before the first episode. (Becker 2010; Kravariti 2009; Leeson 2009: Mesholam-Gately 2009)

- Some of these deficits worsen during the transition to psychosis. (Jahshan 2010; Keefe 2006)

- Some of these deficits predict functional outcome. (Leeson 2010; Milev 2005)

- Patients show progressive brain changes and abnormal/inefficient brain activation patterns. (e.g., Crossley 2009; Morey 2005; Sun 2009)

This suggests that…

- Cognitive dysfunction represents significant risk for psychosis, and also indicates poor prognosis.
- Early psychosis is the initial phase of a chronic neurocognitive disorder characterized by inefficient cortical processing.
- Cognitive dysfunction and underlying neural network inefficiency should be a primary target for intervention in early psychosis.

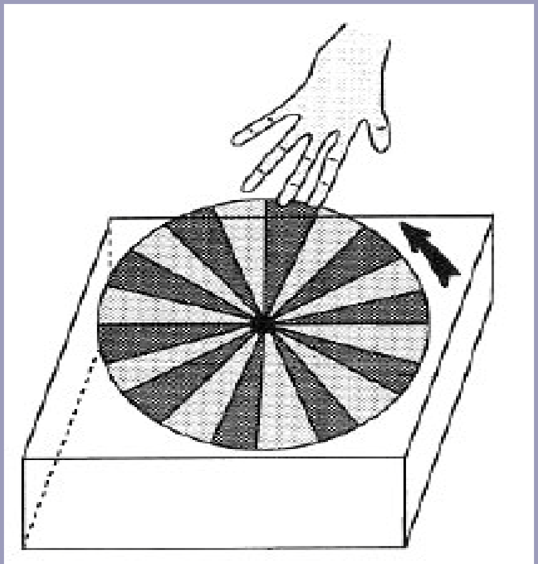
In individuals with psychosis, the cortex has difficulty with:

- The speed and fidelity of early neural responses to inputs.
- The integration of neural responses within and across cortical regions.
- The maintenance of attentional control/salience.
- The ability to associate, encode, and retrieve salient events, thoughts, and actions.

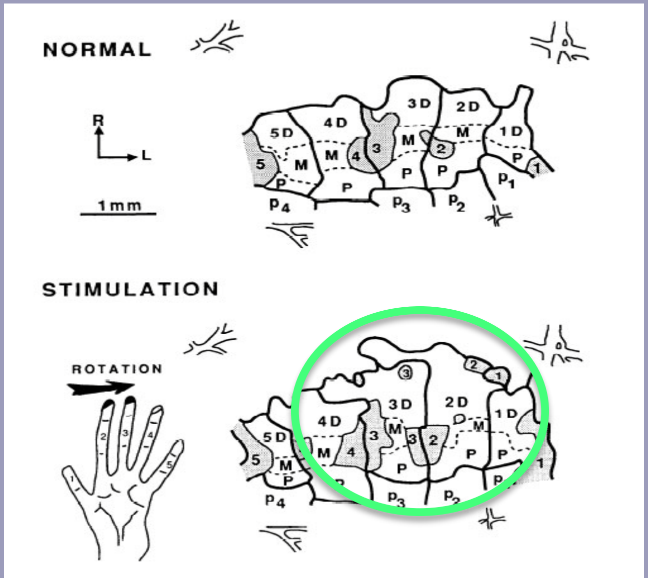
Neurons that are out of synch… fail to link…

We know from basic science that:

- The accuracy, fidelity, and efficiency of neural systems can be improved through intensive, progressive, heavily rewarded, perceptual and cognitive training. (e.g., Jenkins 1990; Merzenich 1999)



For example, monkeys trained to apply the tips of their 2nd and 3rd fingers to a rotating disc…



…show substantially enlarged cortical representations of those digits' tips.

Could this approach be used for human neurocognitive disorders?

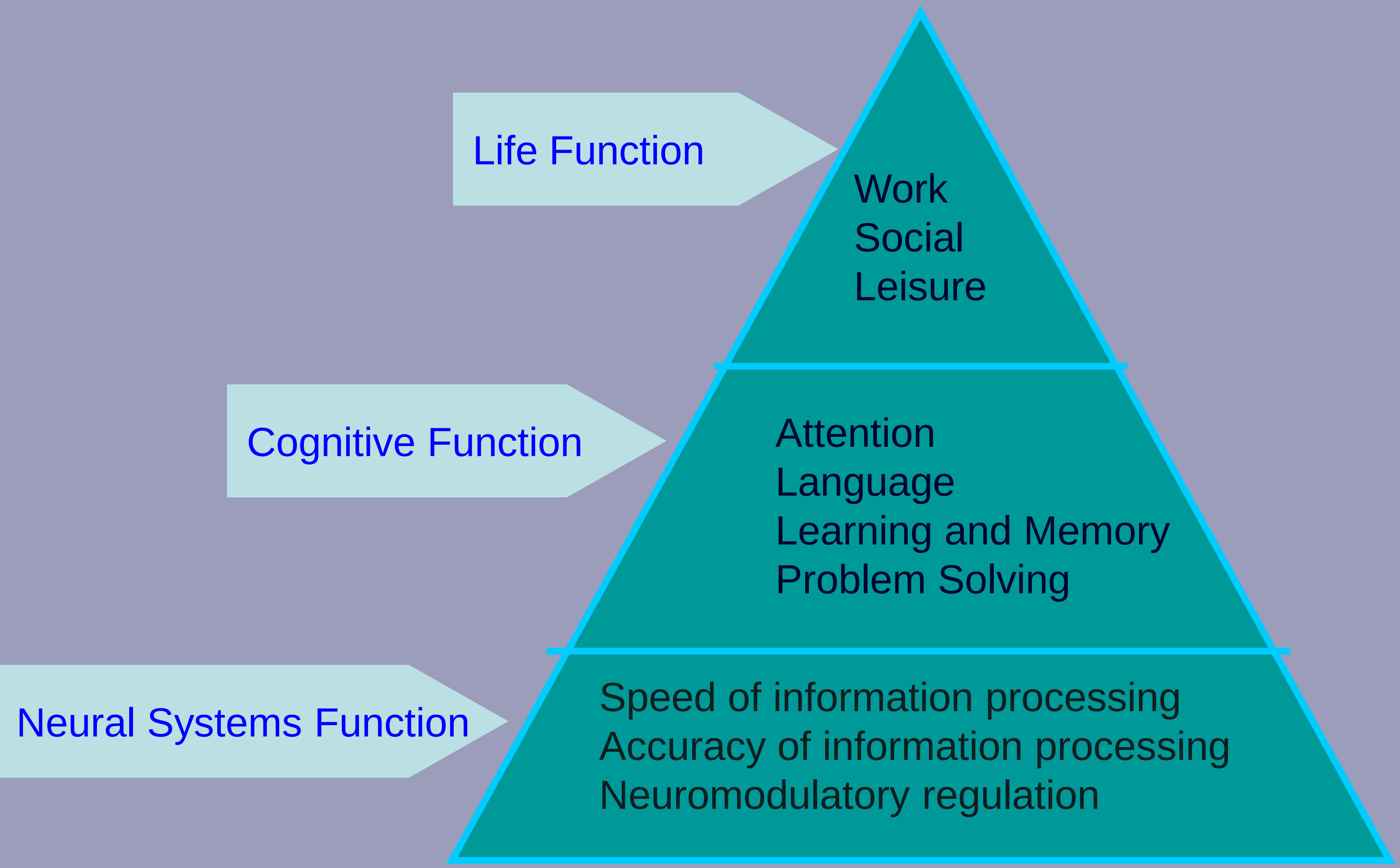
Improve speed and accuracy of information processing

Re-refine brain maps and brain activation patterns

Strengthen neuromodulatory function

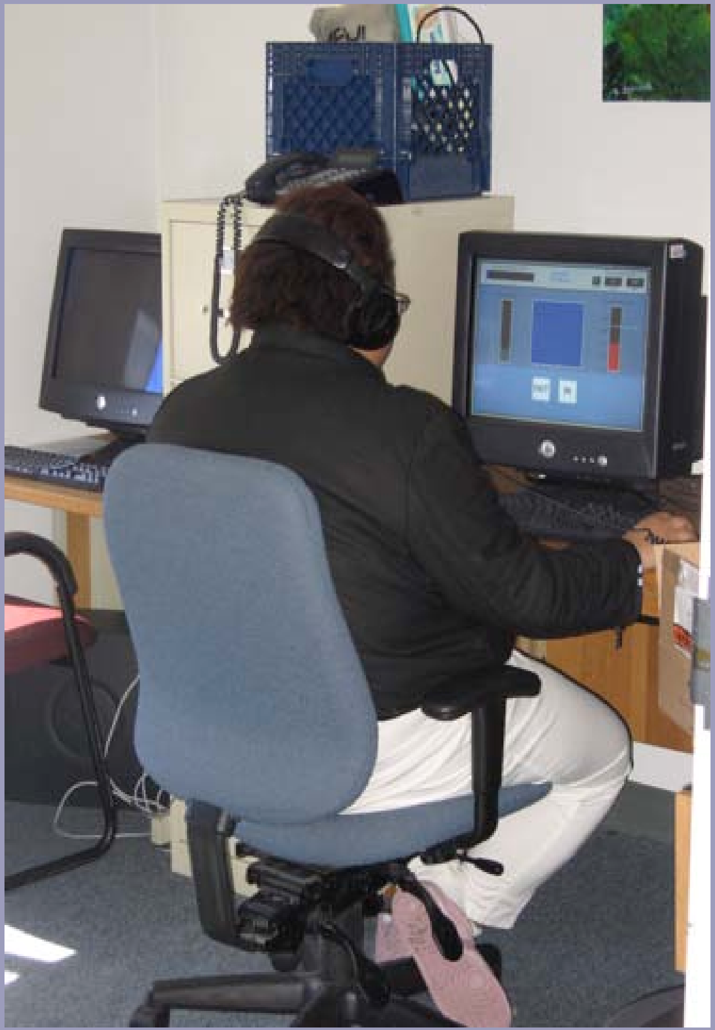
Human brain training exercises that improve these functions could have a beneficial effect

Why would this be helpful?




NITRO
Nautilus

San Francisco VA Medical Center

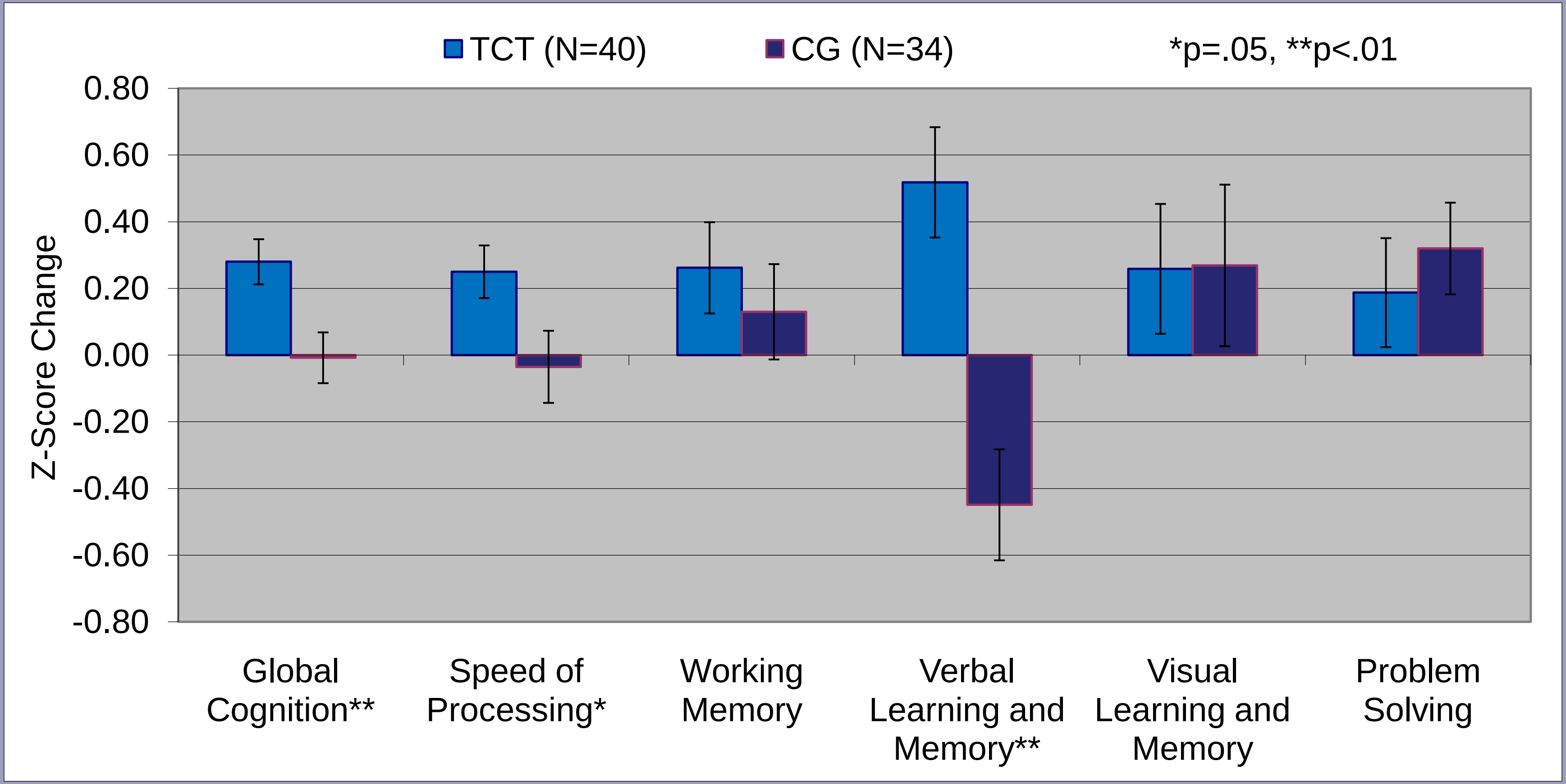


The “targeted cognitive training” consists of:

- A heavy schedule of computerized training delivered as a stand-alone treatment.
- Psychophysical training is embedded within a suite of increasingly complex auditory and verbal working memory/verbal learning exercises.
- Goal is to increase the accuracy, the temporally-detailed resolution, and the power of speech inputs feeding verbal memory processes– to induce widespread plastic changes throughout the verbal encoding network.

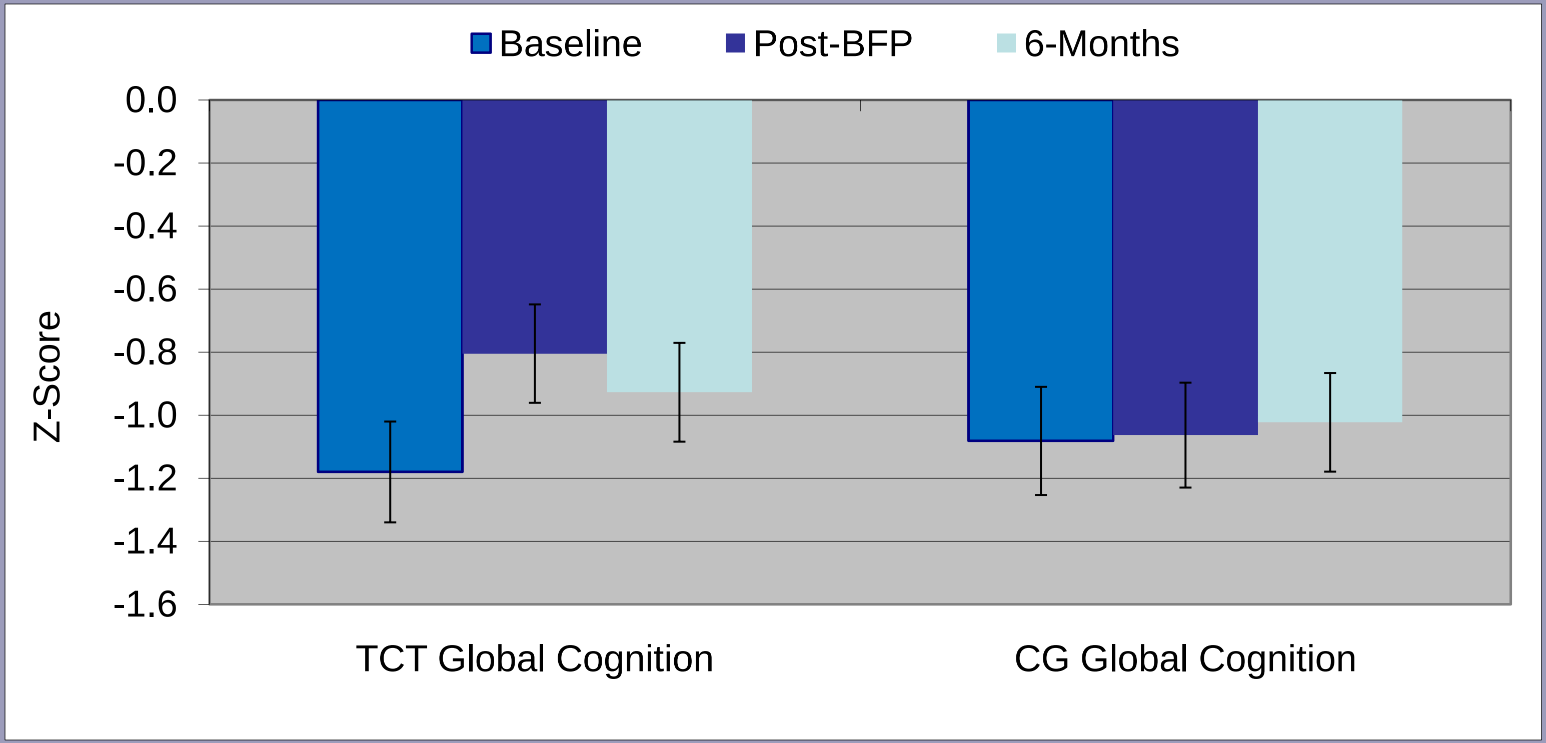
Neurons that fire together, wire together…

Cognitive improvement is seen after 10 weeks of targeted cognitive training (TCT) but not computer games control condition (CG)



Results of Repeated Measures ANCOVA controlling for age: Relative to the CG group, the TCT group shows significant gains in Global Cognition, Speed of Processing, and Verbal Learning and Memory.

Global cognition remains improved 6-months later in TCT (N=27) but not CG (N=24) subjects

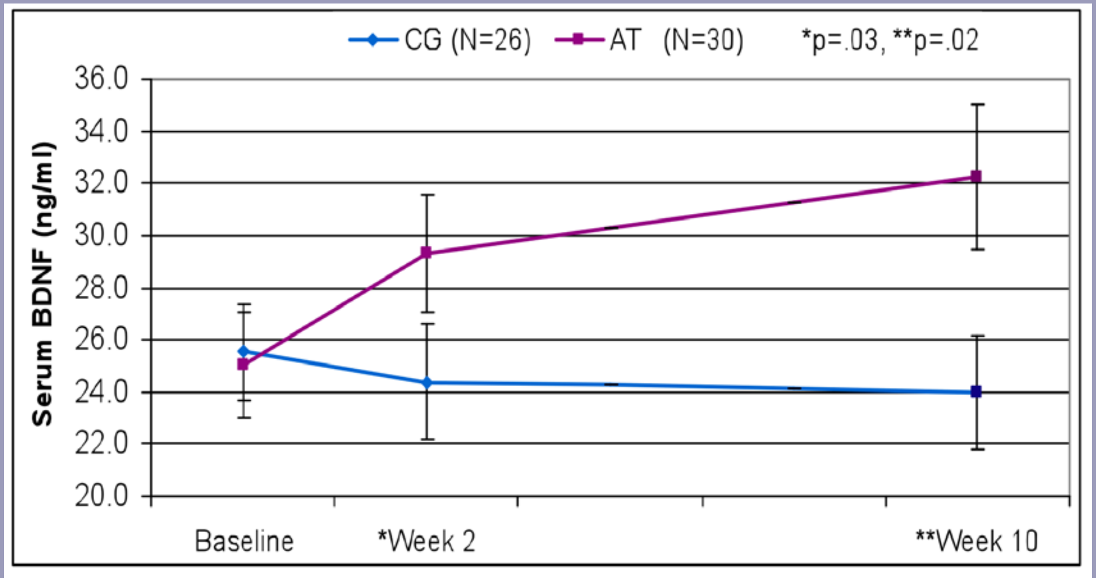


Results of Repeated Measures ANOVA: Relative to the CG group, the TCT group show significant gains in Global Cognition from Baseline to Post-Training ($p < .01$), and significant gains from baseline to 6-Months Post Training at trend level ($p=.08$).

Serum BDNF levels increase in response to targeted cognitive training

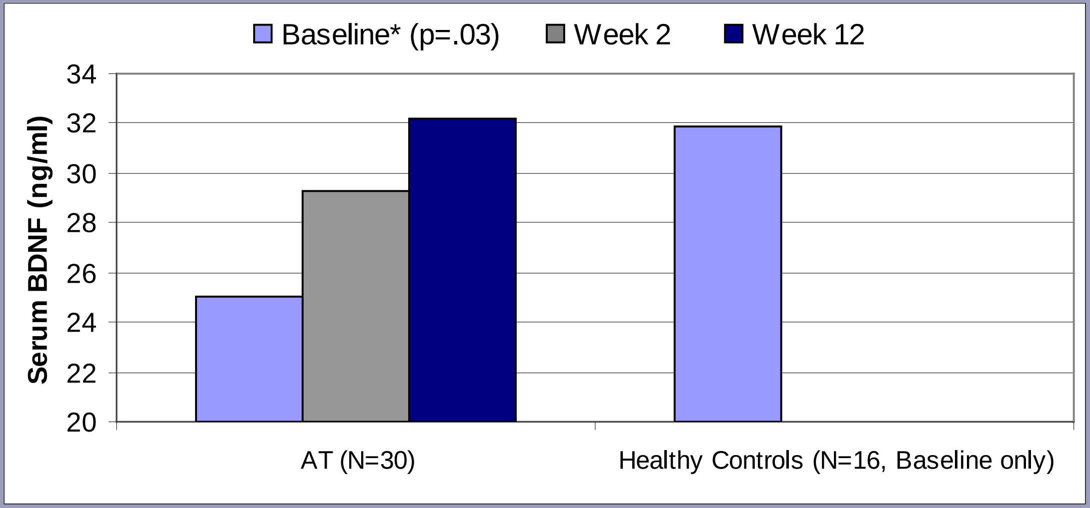
Repeated measures ANOVA with post hoc contrasts:

AT and CG subject groups differed significantly in serum BDNF from Baseline to Week 2 (p= .03) and from Baseline to post-training (p=.02).



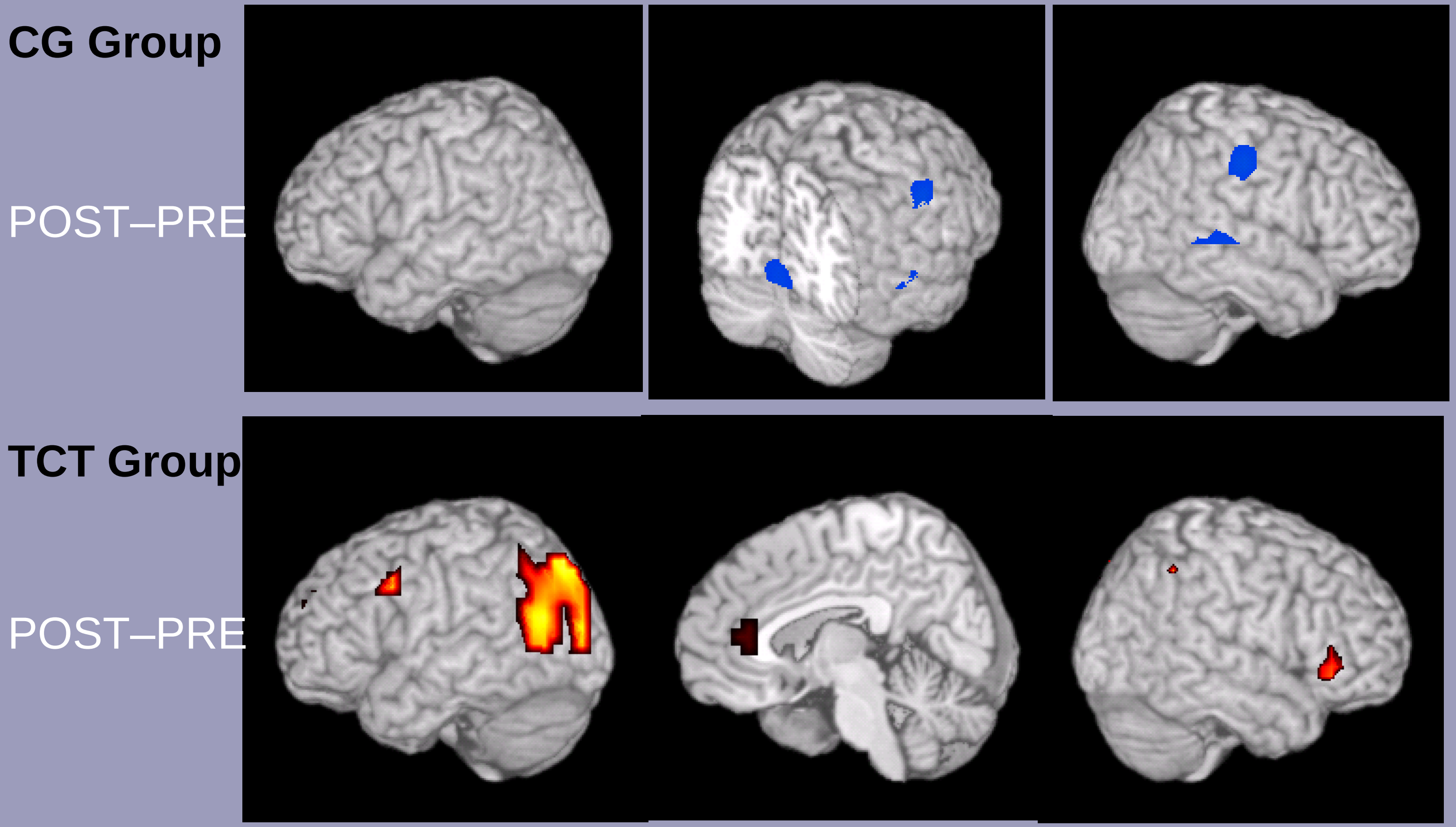
AT and Healthy Control subjects differed significantly in Baseline serum BDNF level.

By Post-Training, serum BDNF level of AT subjects is comparable to healthy control subjects.

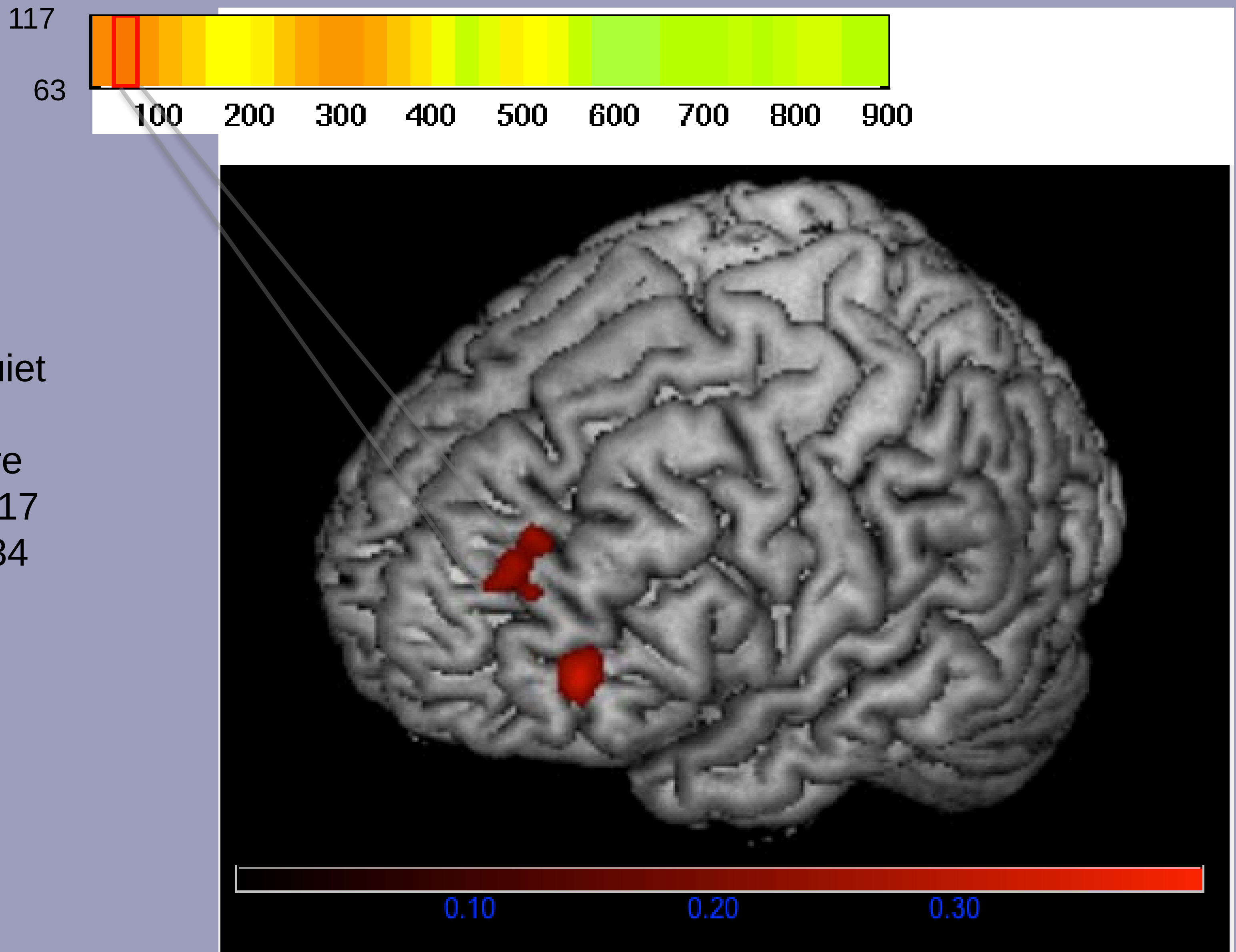


Vinogradov, Fisher, Holland, Wolkowitz, Mellon, Biol Psych, 2009

Alpha-band resting-state functional connectivity shows significant increases after targeted cognitive training



Gamma band activity in prefrontal cortex is significantly increased after training

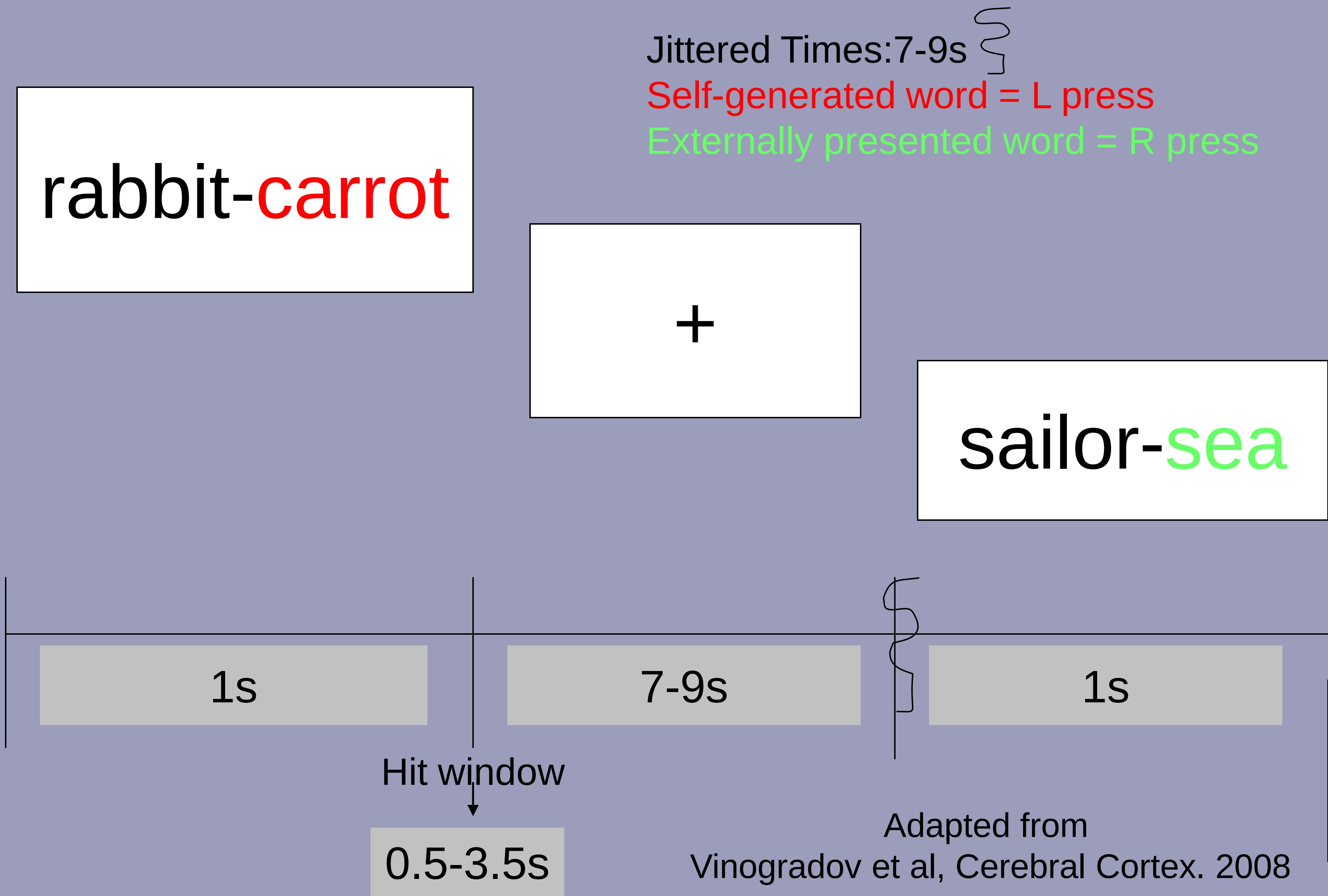


BaPa Quiet Task, Post-Pre TCT, n=17 p=0.0034

Targeted cognitive training improves performance on a complex reality monitoring task and “normalizes” brainactivation patterns

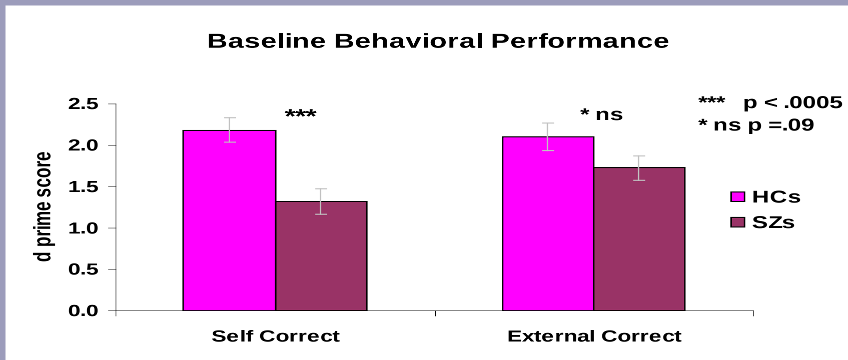
Experimental Reality Monitoring Task: Source memory for self-generated information **STUDY PHASE PRIOR TO SCANNING**
The rabbit ate the __________.
The sailor sailed the sea.
The dog chased the ________.
The girl played with the ball.

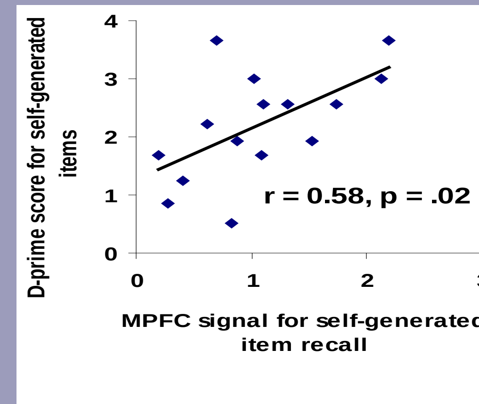
During fMRI scan: Reality-monitoring retrieval trials



Adapted from
Vinogradov et al, Cerebral Cortex. 2008

At baseline, SZ subjects show poor performance and no mPFC activation

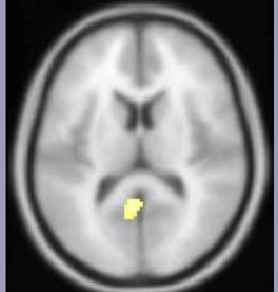


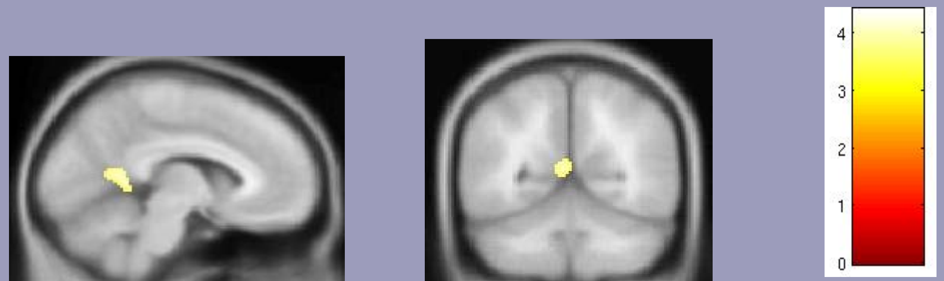


mPFC activation across 15 HCs

t = 3.79, p <.001
v = 678

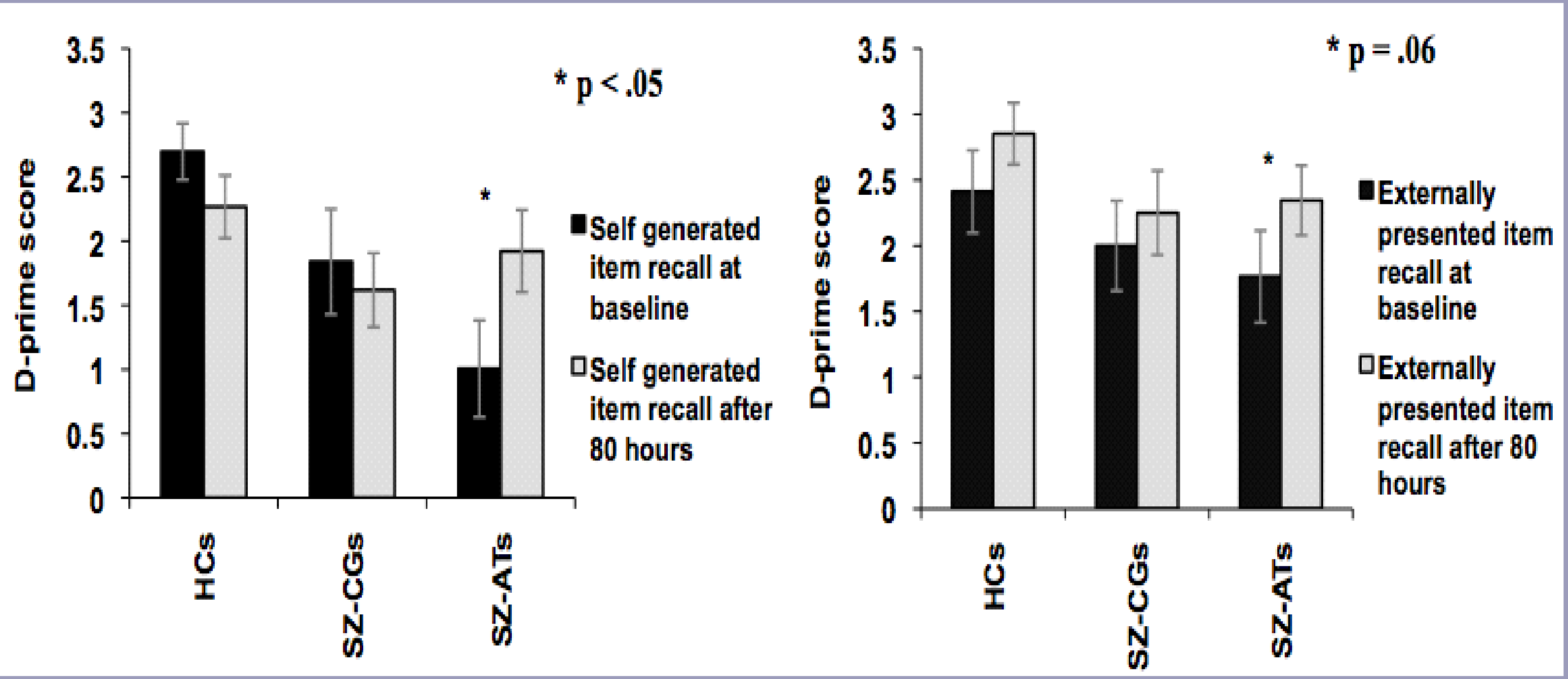
PCC activation across 31 SZ





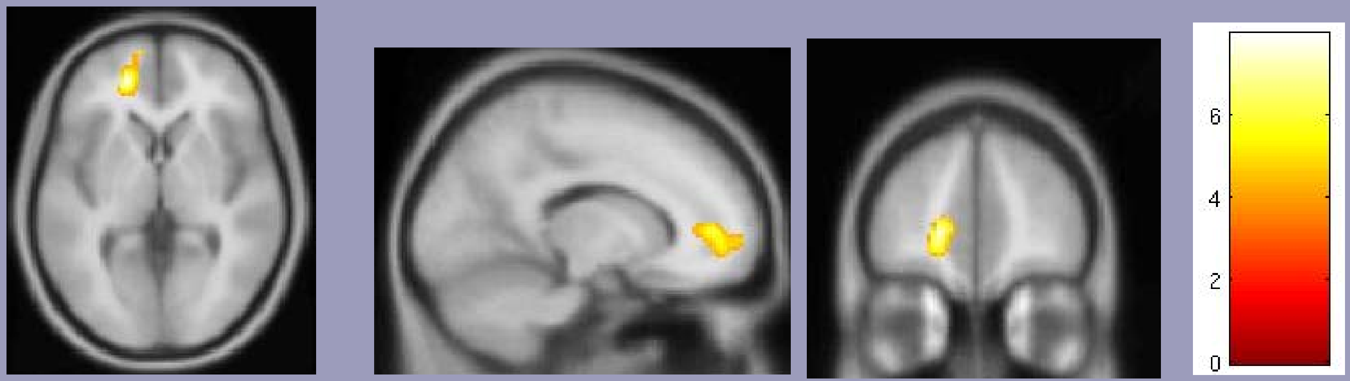
t = 3.83, p <.001
v = 201

After training, SZ subjects show significant improvement in recognizing self-generated items…

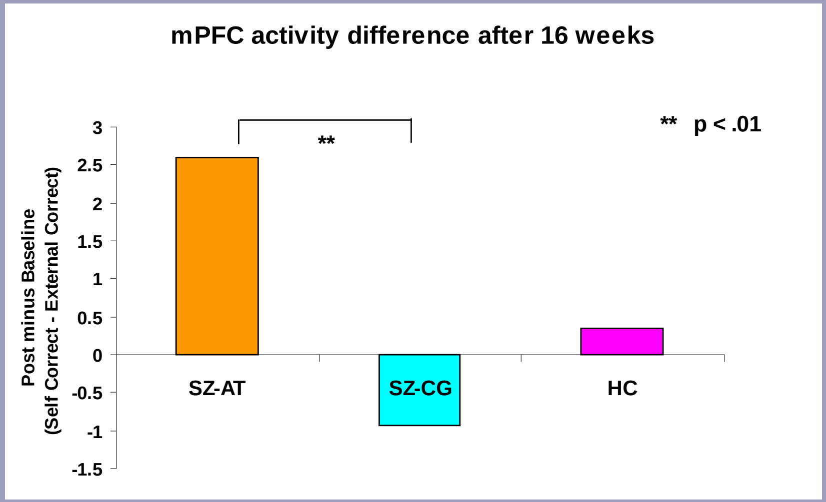


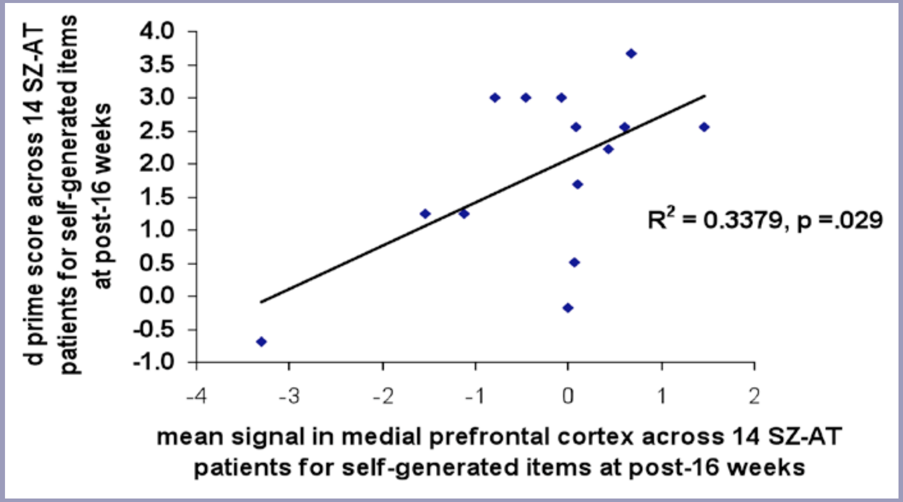
…and now show mPFC activation during task performance

(Post-intervention > Baseline)



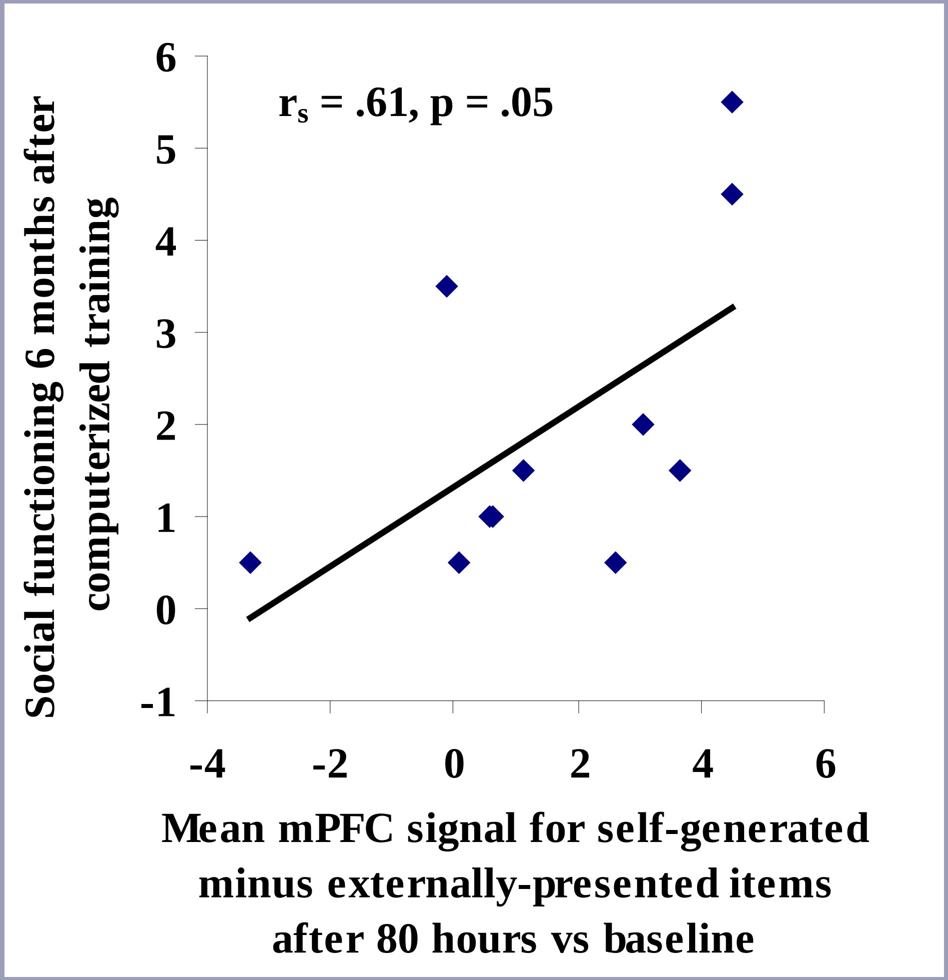
t = 7.93,p <.002 FWE corr, v=240, 10mm sphere at [-14, 52, 0]



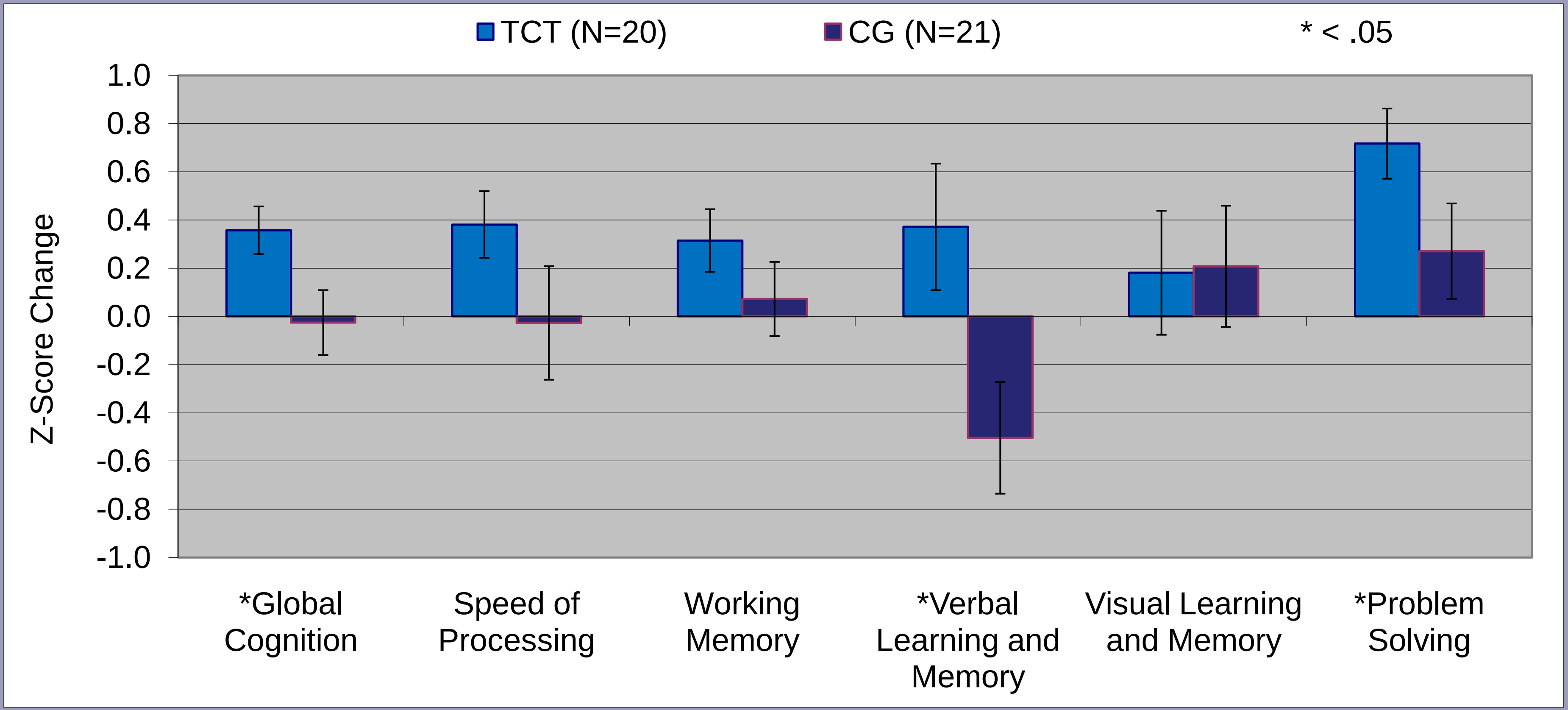


- ANOVA shows significant between-group differences ($F=4.3$, $p < .02$) on self-correct minus external-correct beta signal in mPFC after 16 weeks compared to baseline

MPFC activation after training predicts enhanced social functioning 6 months later

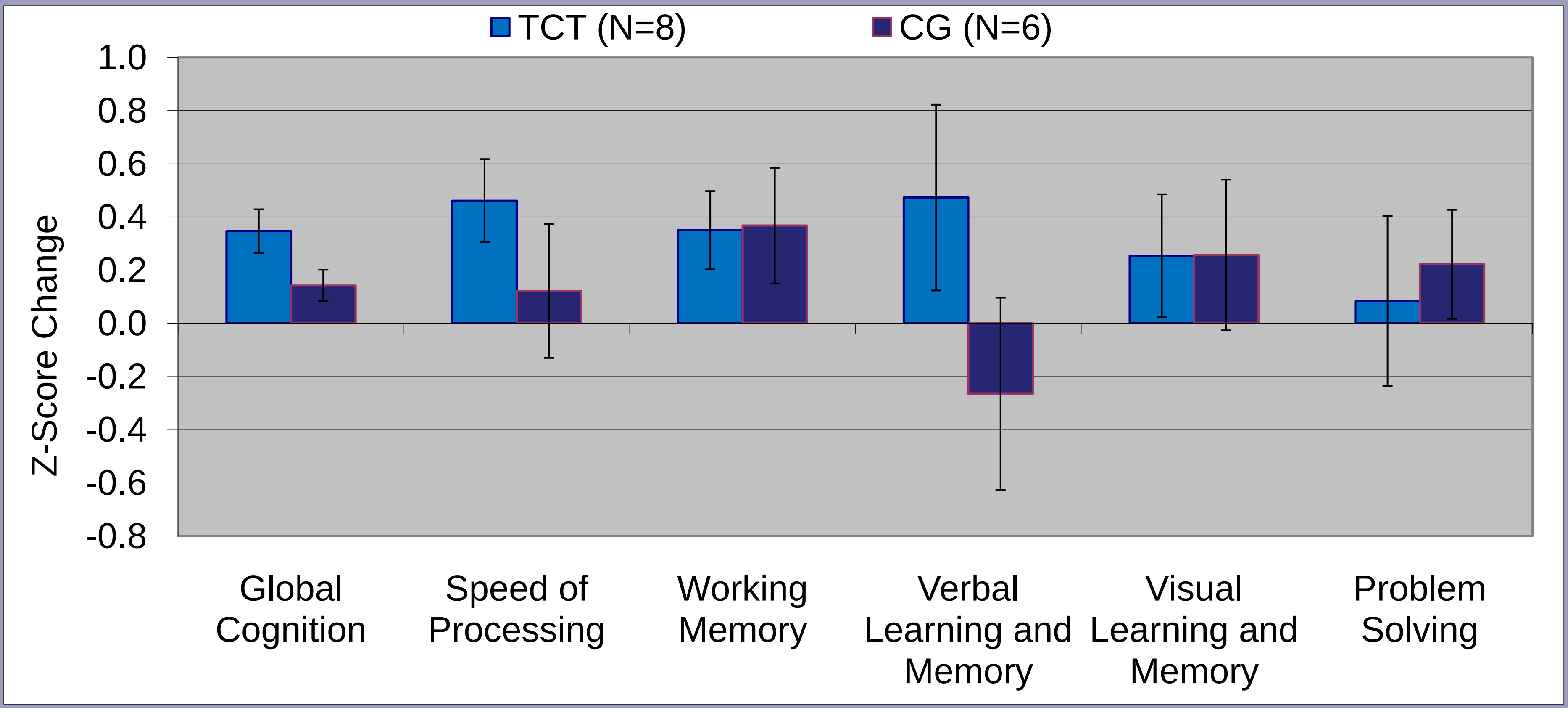


Cognitive improvement also occurs after 40 hours of TCT but not CG in young recent-onset subjects, but with a slightly different pattern of results



Results of Repeated Measures ANCOVA controlling for age, gender and IQ: Relative to the CG group, the TCT group shows significant gains in Global Cognition, Verbal Learning and Memory and Problem Solving.

Adolescents who are clinically ultra high risk also show improvement after training



Results of Repeated Measures ANCOVA controlling for education and hours of training.

Group x Time Interactions: Global Cognition p = 0.15; Verbal Learning and Memory p = 0.11

Conclusions

- “Neuroplasticity-based” cognitive training in schizophrenia results in improved cognitive performance and more normal brain activation patterns.
- Training-induced increases in brain activation patterns predict real-world functional improvement 6 months later.
- Similar patterns of improvement are observed in young recent-onset participants and in ultra-high risk adolescents.

- **Ongoing research questions:**
  - Can this approach be used to target other neural system impairments, such as motivational disorders, impulsivity, emotion regulation?
  - Can we personalize training to target the specific profile of deficits of a given individual?
  - **Will training prove to be “pre-emptive” in young individuals?**

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Adult Schizophrenia Studies

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