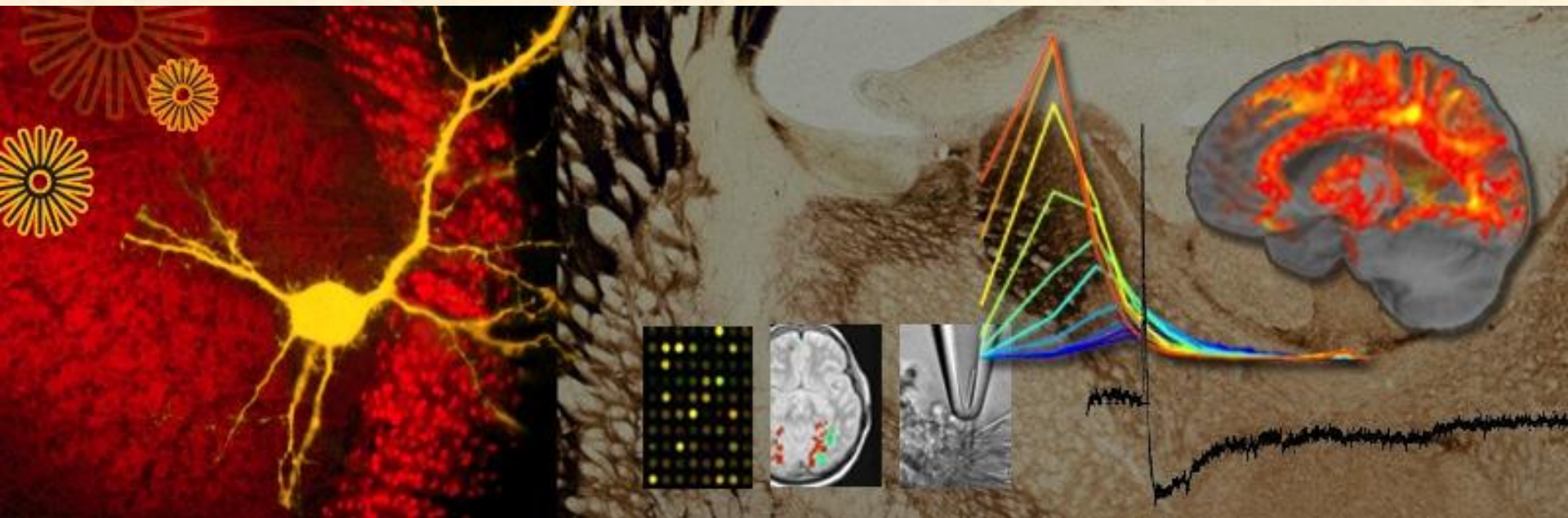


# Brain Networks in Schizophrenia and Bipolar Disorder: Targets for Novel Therapies

Cameron S. Carter, MD



# Schizophrenia and Bipolar Disorder

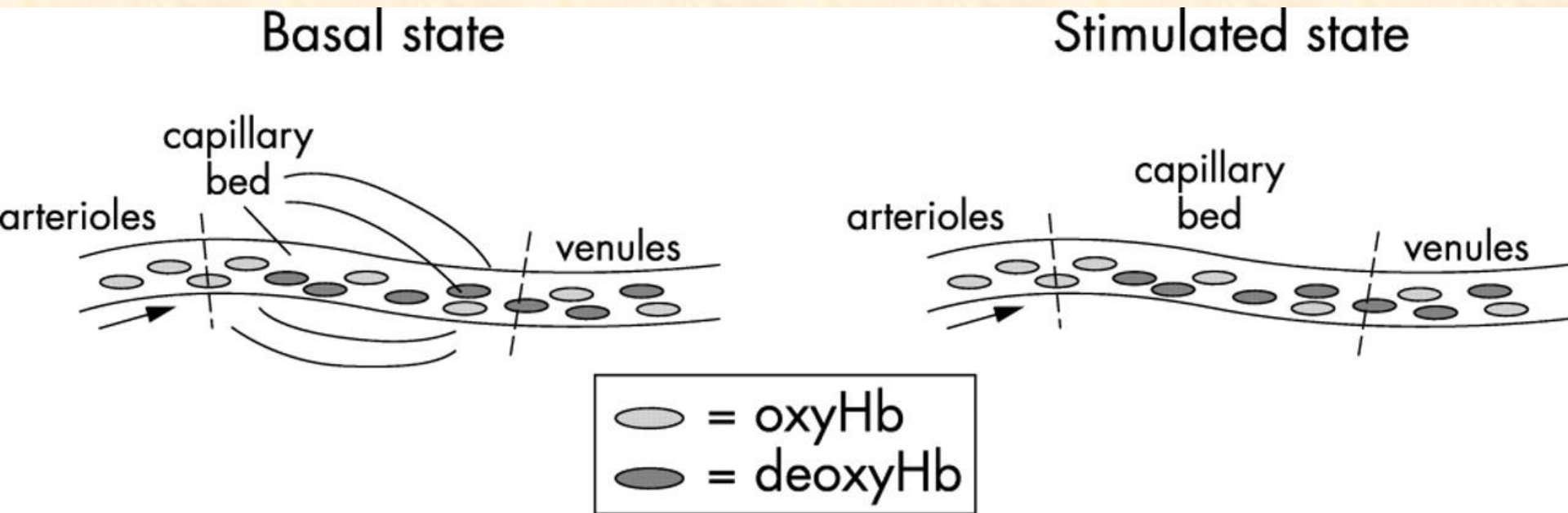
- Each affects 1% of the population world wide
- Risk is determined by genes and environmental risk factors
- Affects many aspects of mental life and behavior
- Best outcomes are with early intervention and evidence based treatments
- Negative symptoms and cognitive deficits are treatment refractory and this is a big challenge we must face

# Impaired Cognition in Schizophrenia

- Present at onset and throughout the life span
- Impaired cognition is a strong predictor of disability in schizophrenia
- Currently available treatments have little impact on cognitive disability in schizophrenia
- Perhaps the most amenable to investigation using modern, non invasive neuroscientific tools



# Effects of hemodynamic activation on BOLD signal in the brain



- Basal flow
- Basal level [deoxyHb]
- Basal CBV
- Field gradients around vessels resulting from [deoxyHb]
- Normal signal

- Increased flow
- Decreased [deoxyHb]
- Increased CBV
- Lower field gradients around vessels due to lower [deoxyHb]
- Increased signal

# Task fMRI in Clinical Neuroscience

- Identify functional neural networks linked to specific cognitive and affective processes
- Allows us to identify what cognitive and neural processes are impaired and what are intact
- Establish links between changes in neural circuitry, cognitive and emotional processing and clinical symptoms and functioning

# Higher Cognitive Functions In Schizophrenia

- Attention
- Memory
- Language Disturbances
- Emotional processing

# Cognitive Control

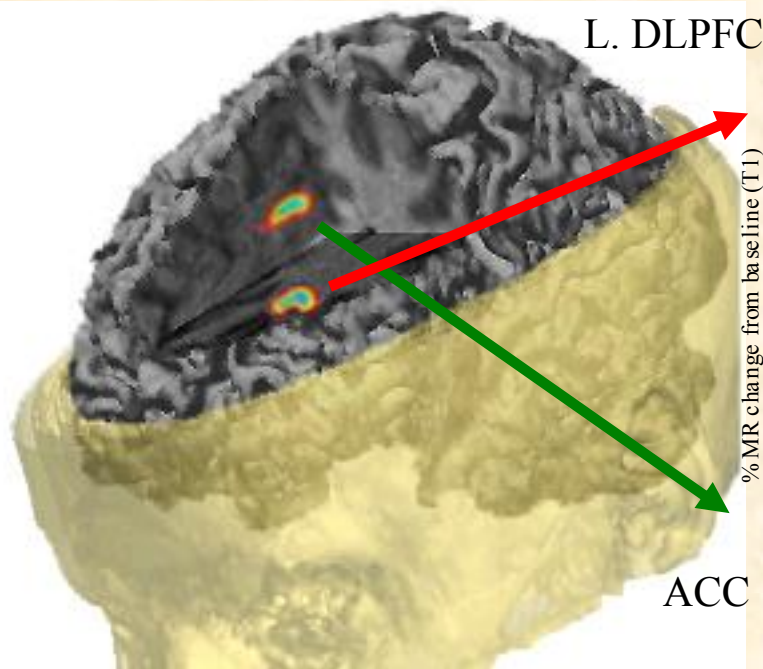
..when habitual responding won't do and you have to use a representation of a task or goal to guide behavior...





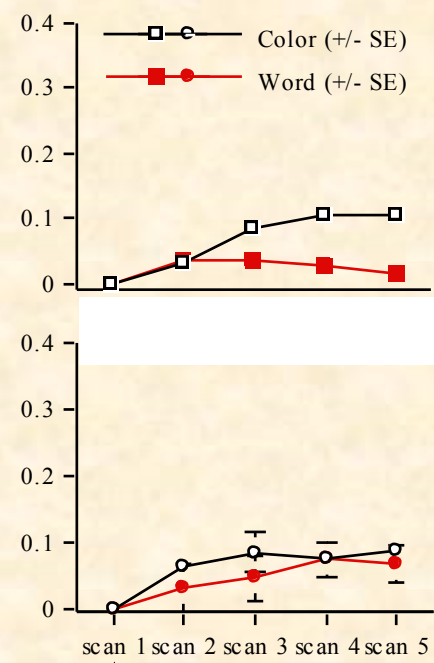
**GREEN**

# Role of the Prefrontal Cortex in Cognitive Control

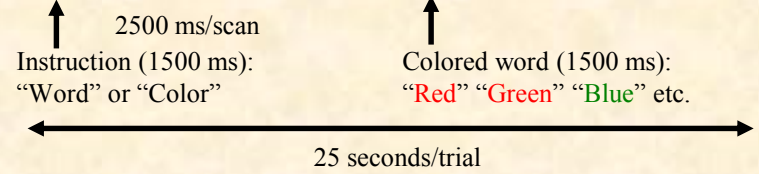
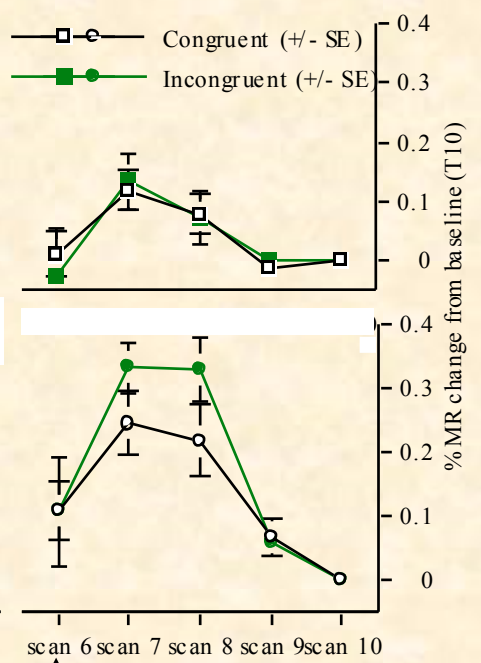


Paradigm

Instruction-related fMRI Activity



Color-naming response-related fMRI Activity

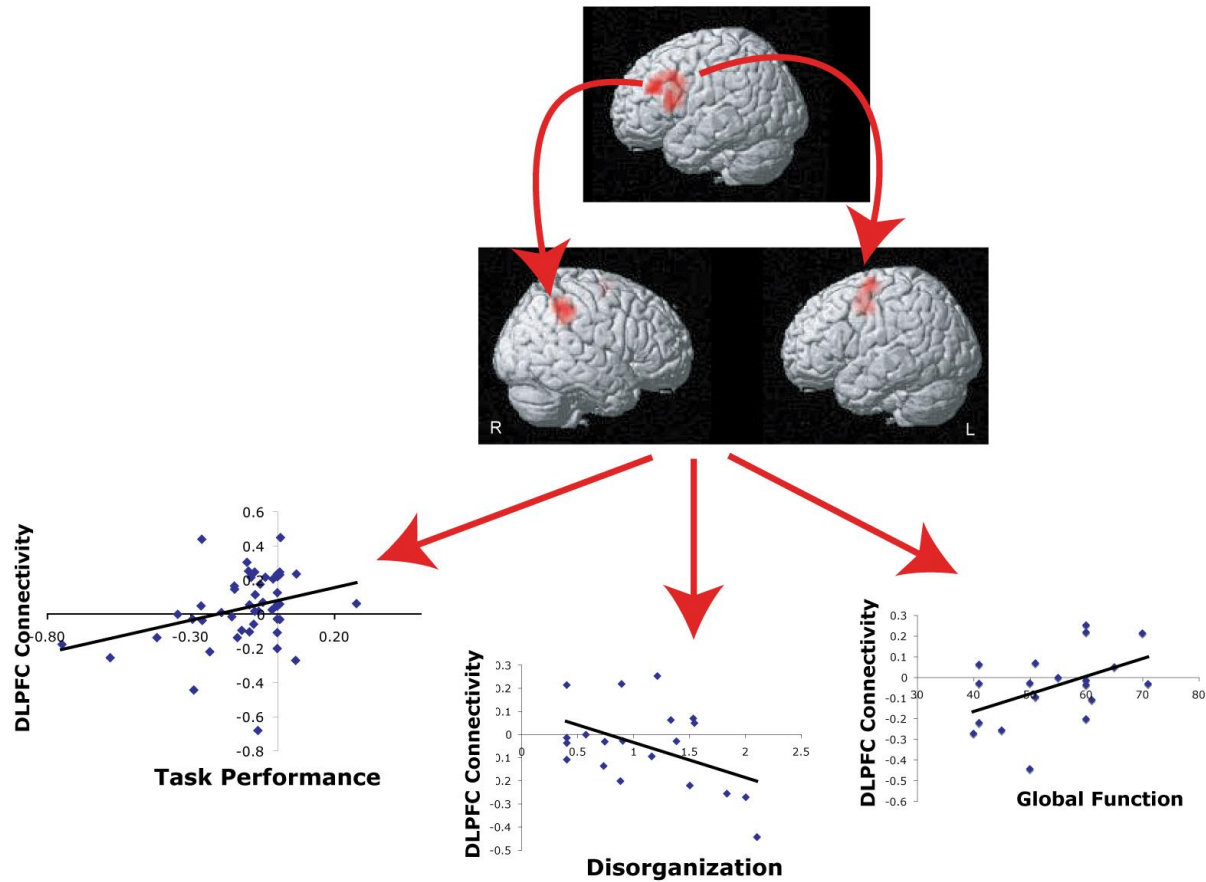


# PFC AND CONTROL ACROSS DOMAINS

## Evidence from Cognitive Neuroscience

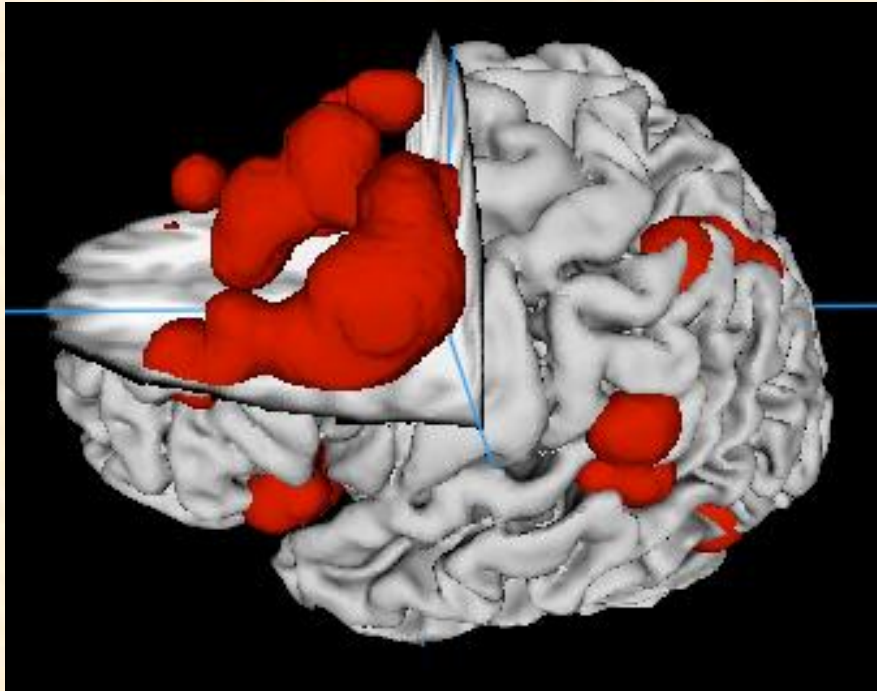
- Perceptual Decision Making (Heekeren, Marrett, Ungerleider Nat. Reviews Neuroscience 2008)
- Working Memory (D'Esposito Philos. Trans. R Soc London 2007 )
- Episodic Memory (Hannula and Ranganath 2009 Neuron)
- Cognitive control of emotions (Ochsner and Gross Trends Cogn Sci. 2005)
- Social Cognition (Beer and Ochsner Brain Res. 2006)
- Basic Cognitive Neuroscience theory and data support a domain general control related-role for the PFC

# Impairment of PFC-related connectivity in Schizophrenia

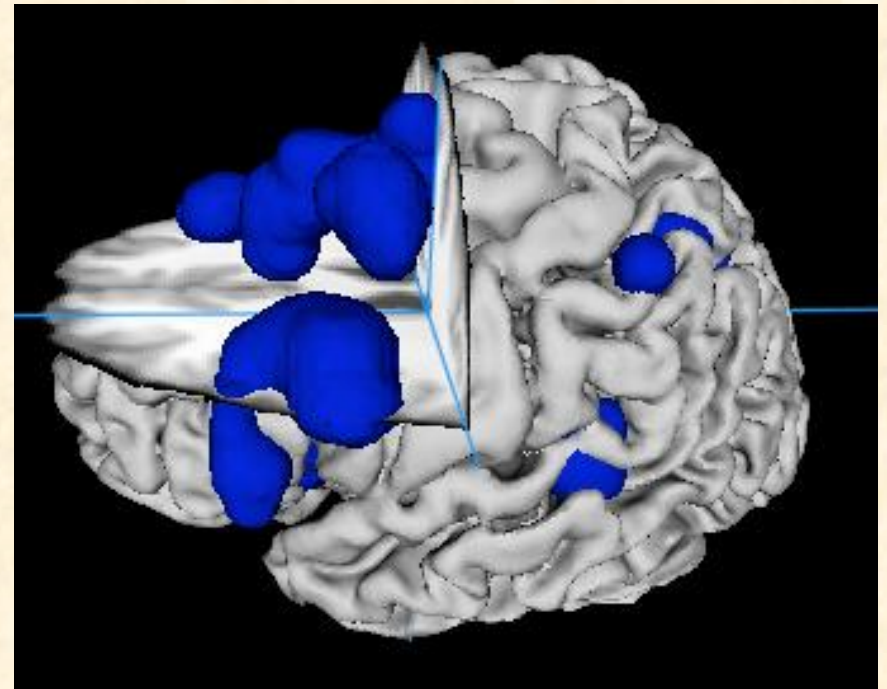


Yoon et al, American J. Psychiatry 2008

# Metanalysis of 41 fMRI Studies of Executive Functions (ALE)



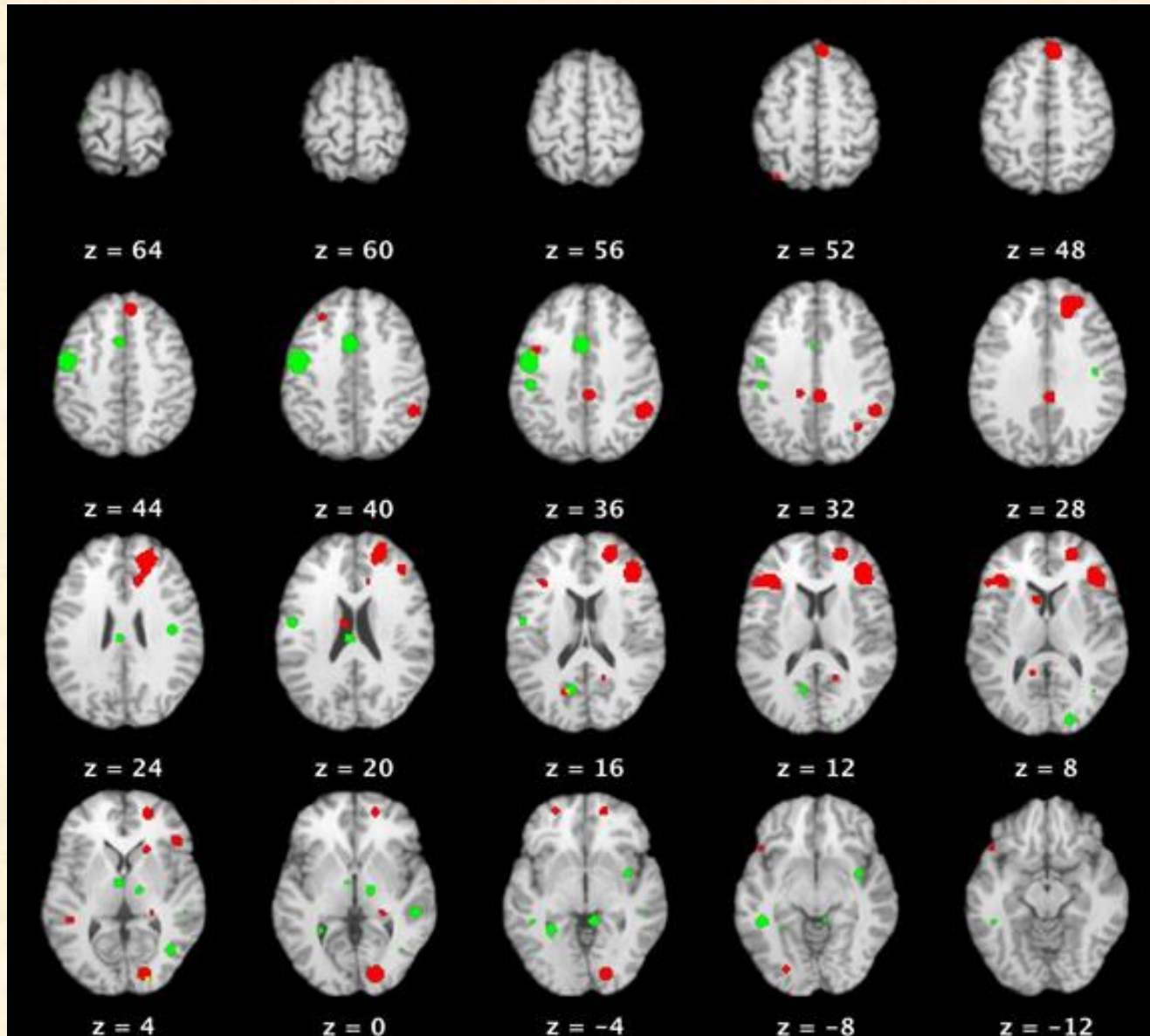
**Healthy Controls**



**Schizophrenia**

Minzenberg, Laird, Thelon, Carter and Glahn, 2009 Archives of General Psychiatry  
See also MacDonald et al 2008 reduced DLPFC correlates with disorganization

# Generality of PFC Cognitive Control Deficits: Episodic Memory



Ragland et al 2009 American J. Psychiatry

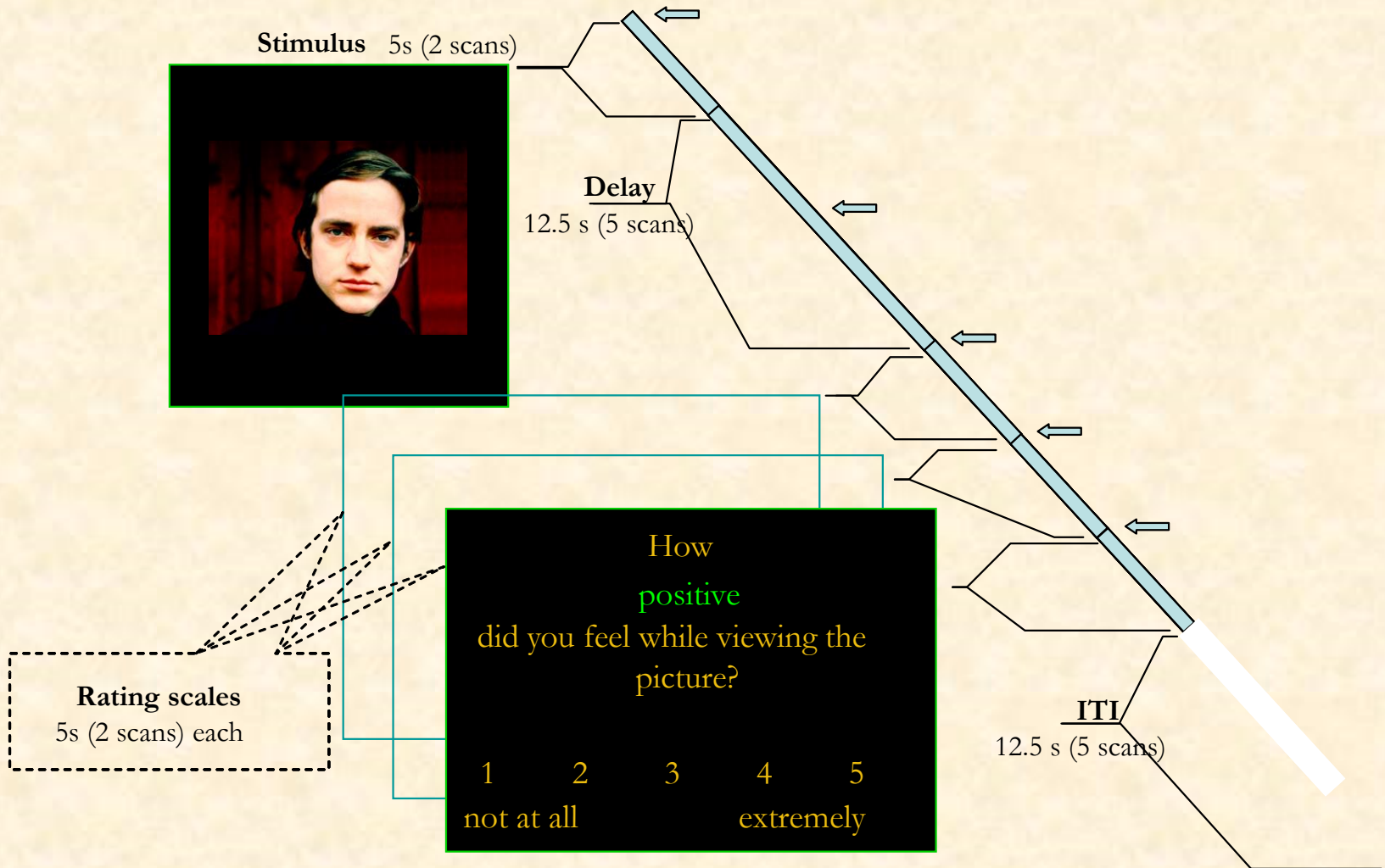
# PFC and Control in Emotion Processing

# The (Kring) Paradox of Emotion in Schizophrenia

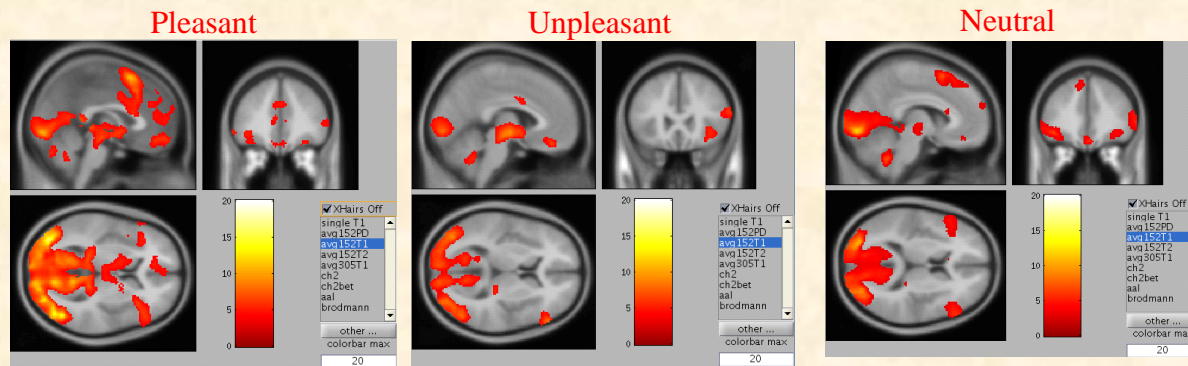
- People with schizophrenia have reduced emotional expression and impaired motivated behavior
- However emotional experienced measured using self report and experience sampling appears to be intact
- Active use of emotion to guide behavior impaired? Impaired cognition emotion interactions in schizophrenia.



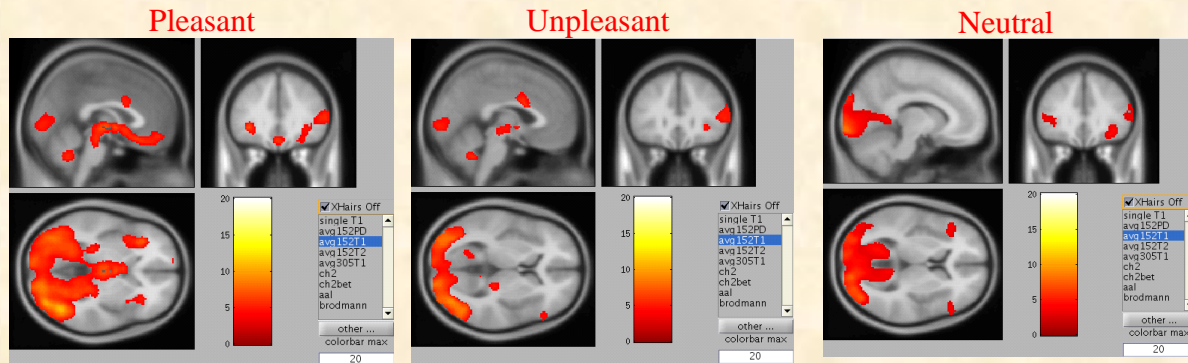
# Emotional Processing in Schizophrenia



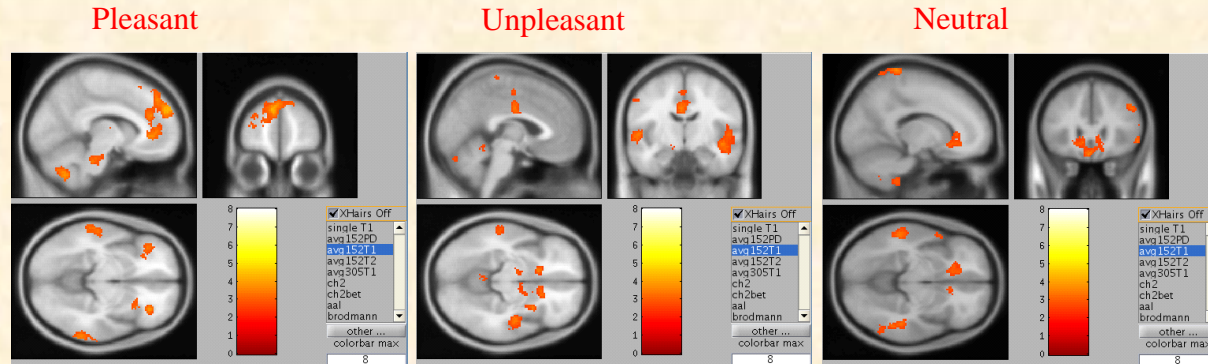
## A. Stimulus-related activity in comparison subjects (N = 20)



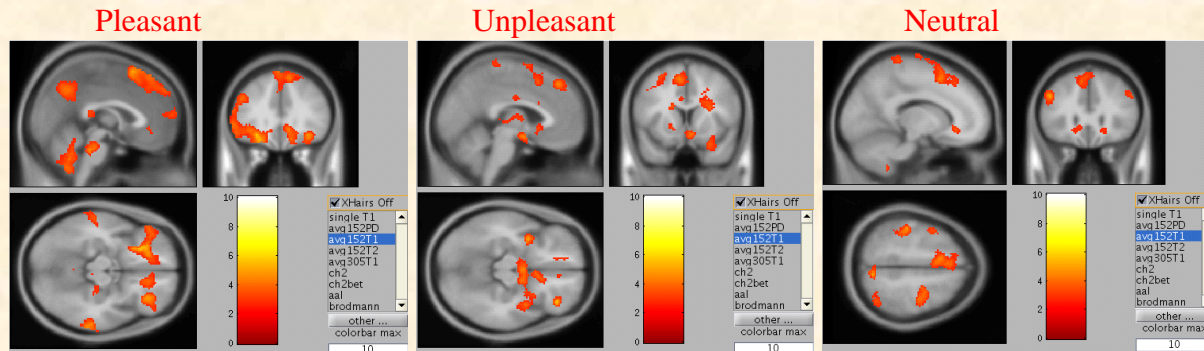
## B. Stimulus-related activity in patients (N = 20)



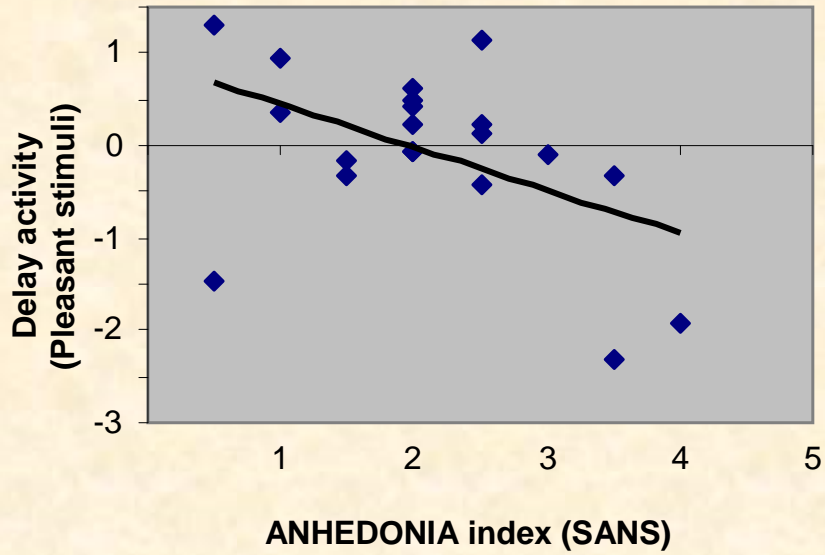
## A. Group differences (HC > SZ) in delay-related activity



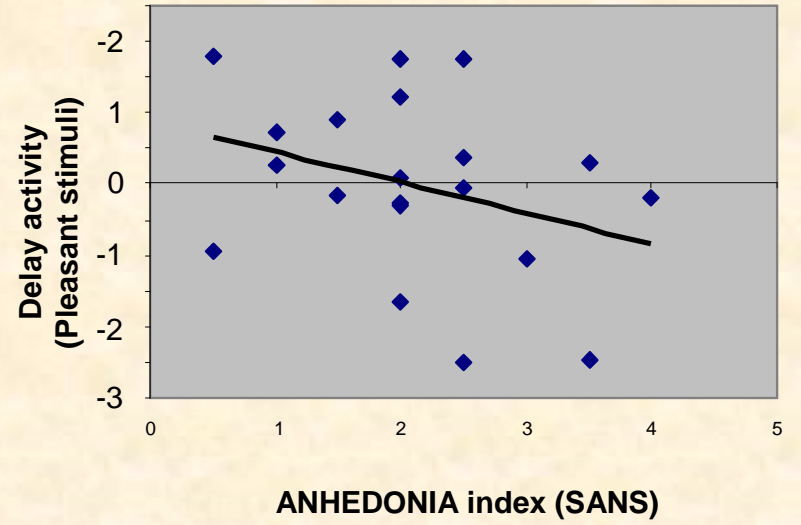
## B. Delay-related activity in healthy comparison subjects



Left DLPFC



Right DLPFC



# Summary

- Basic emotional perception and responses are intact
- Delay related activity reduced
- Altered emotional behavior reflects disrupted interactions between PFC related cognitive control and emotional processing systems
- Prefrontal cortex is a target for intervention for cognitive deficits and negative symptoms

***What is the abnormal physiological mechanism underlying dorsolateral hypofrontality in schizophrenia?***

***Hemodynamic signals most strongly correlate population activity, particularly high frequency synchronous firing (gamma 30-80 Hz)***

# What are Neuronal Oscillations?

- Neurons can fire in a variety of frequency ranges e.g. Alpha (8-15Hz), Beta (15-35Hz), Gamma (35-80Hz).
- Sometimes populations of neurons will fire at different times from each other (*asynchronously*), and sometimes they fire together (*synchronously*).

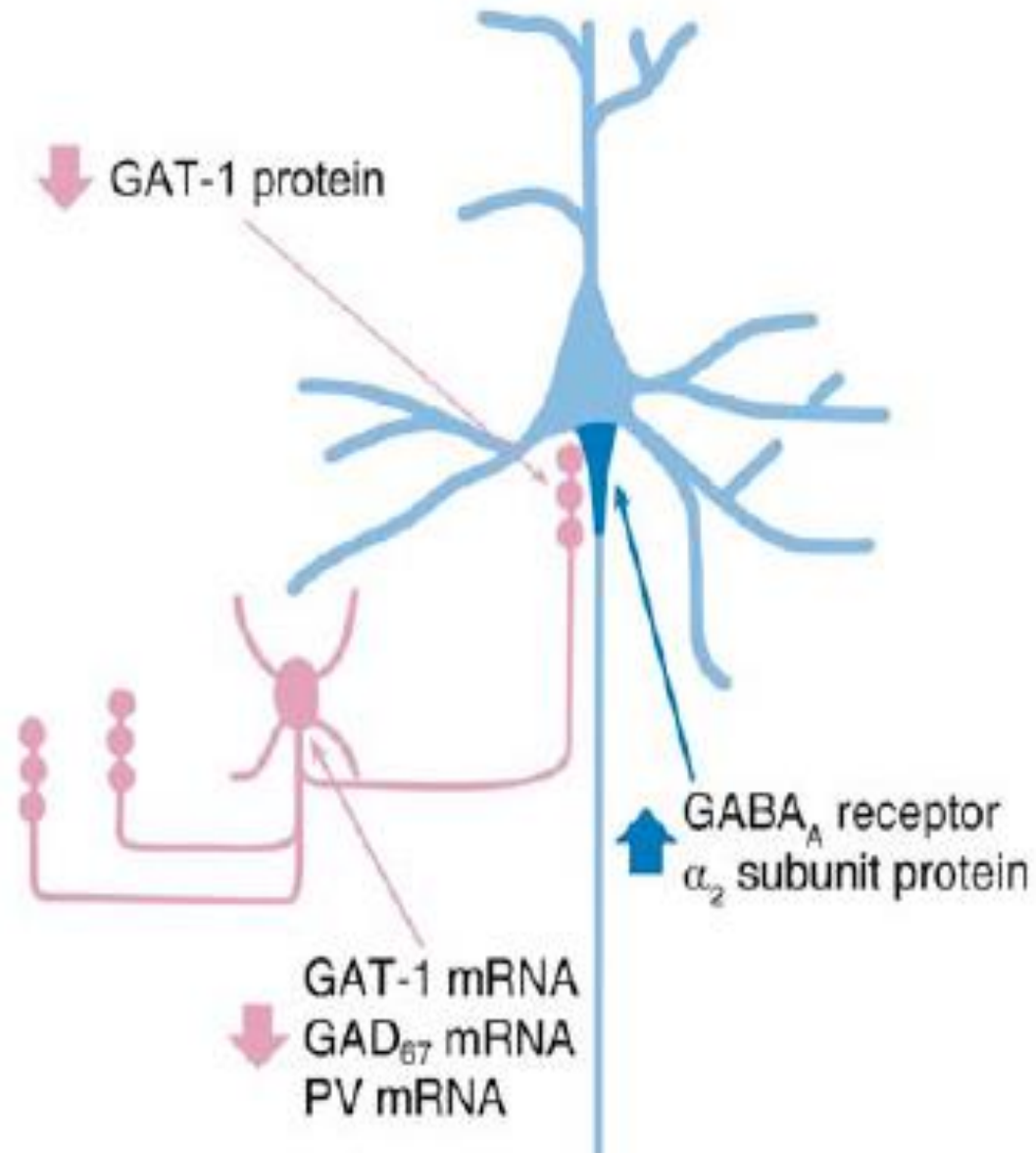


Asynchronous firing



Synchronous firing

\* Encoding and processing occurs when a population of neurons fires at the **same time AND** with the **same frequency**.







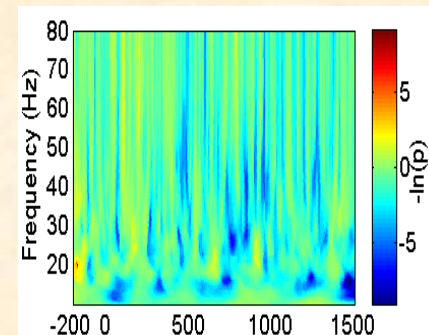
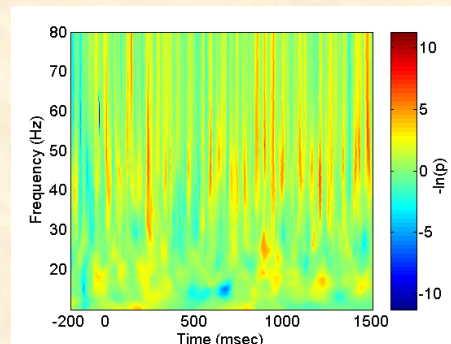
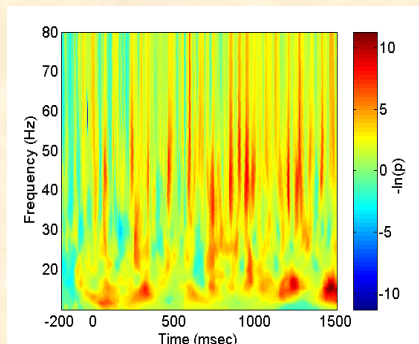
Increases in cognitive control demands elicits greater modulation of prefrontal gamma-band activity in healthy controls vs. schizophrenia subjects

**Group contrast**

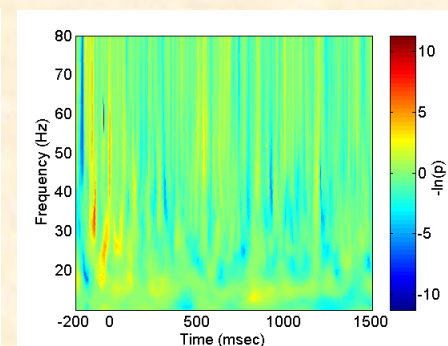
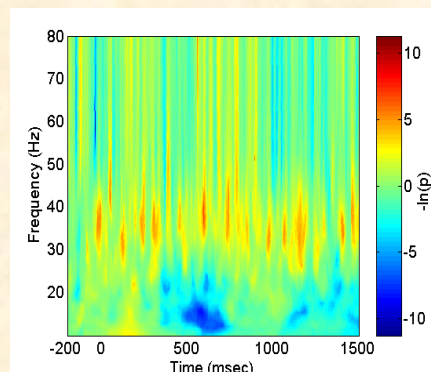
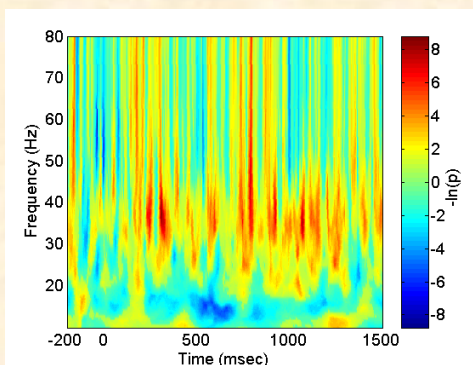
**Controls**

**Patients**

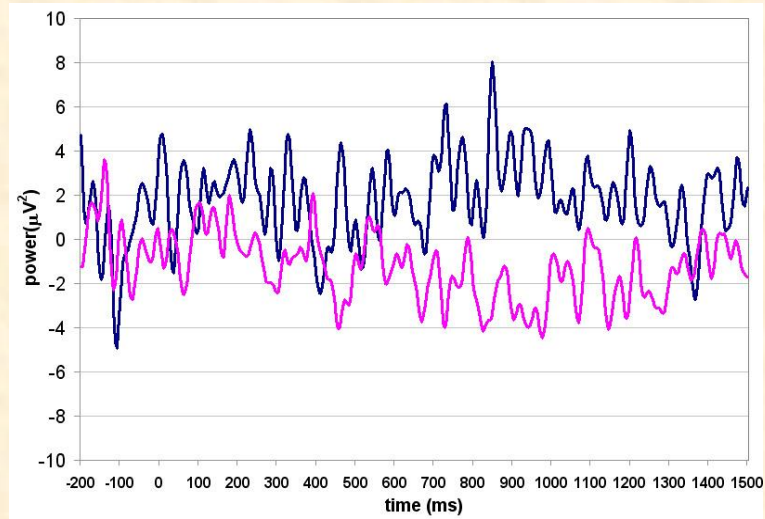
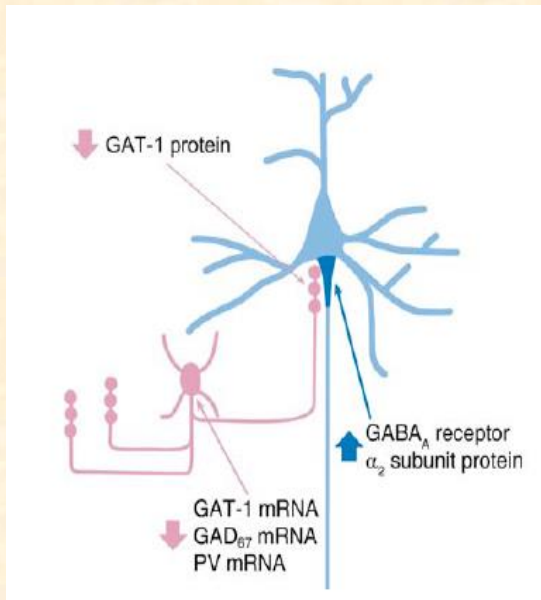
**right frontal**



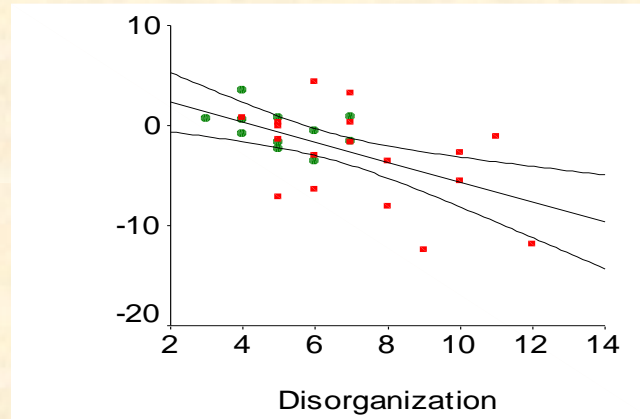
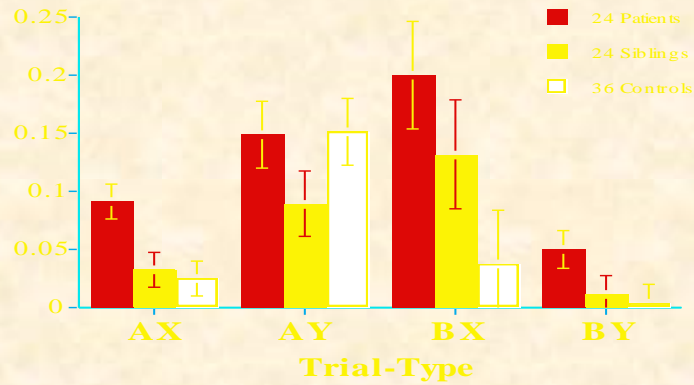
**left frontal**



**Cho, Konecky and Carter *PNAS* 2006**

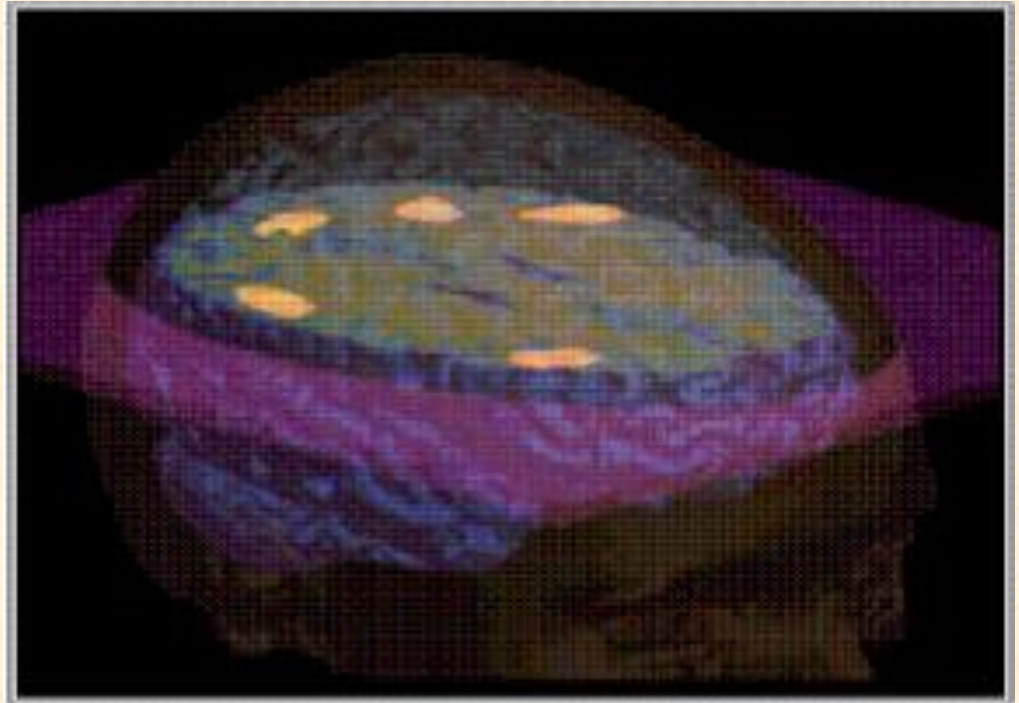


### % Errors



# Neural Systems as Treatment Targets

- Cognitive Training
- Neurostimulation



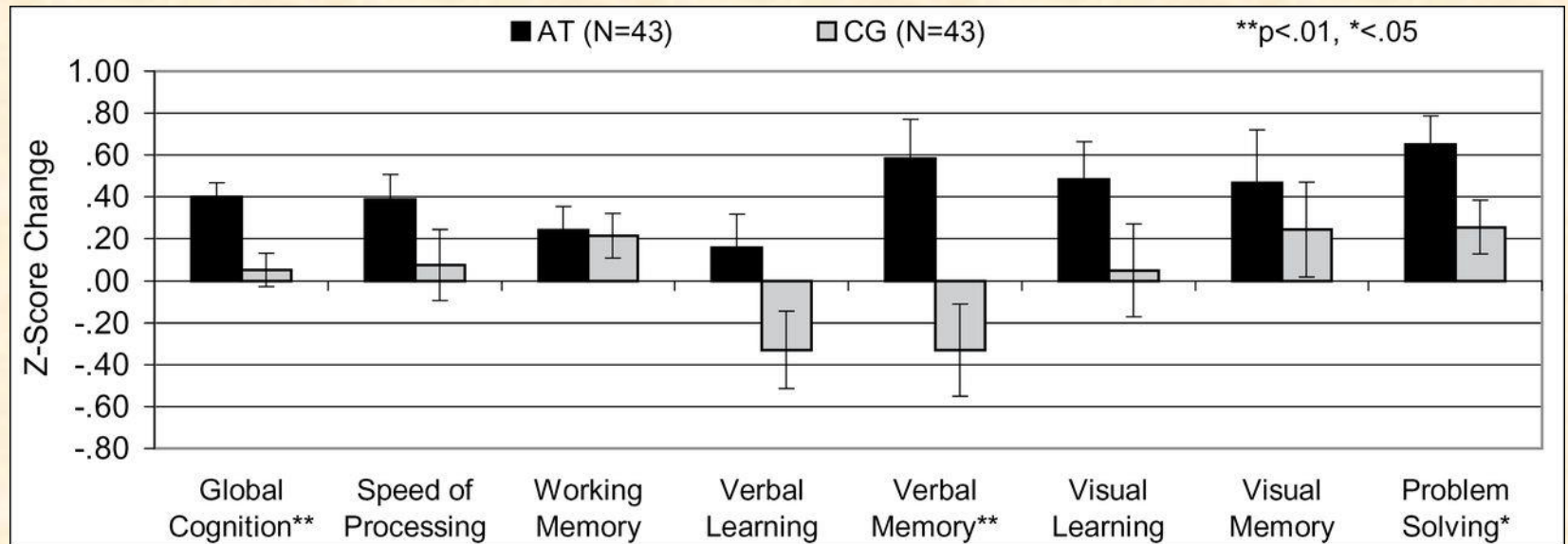
# Brain Training to Enhance Cognition in Schizophrenia



# Recent Onset Schizophrenia Patients

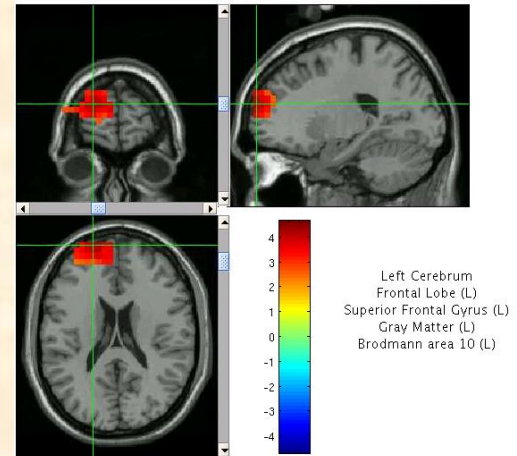
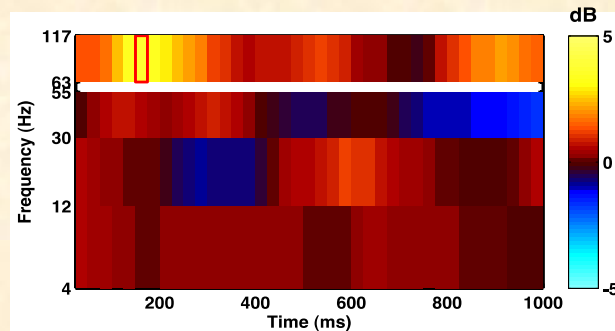
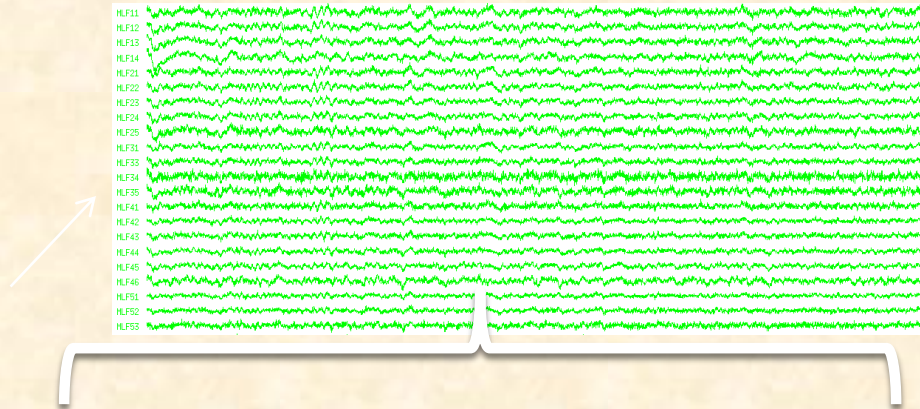
	AT (N = 43) CG (N = 43)		t	df	p	
Mean	SD	Mean				
Male/females		31/12				
Age (range 16–30)		21.70	20.74	–1.34	84	.19
Education		12.88	12.86	–0.06	84	.95
WASI IQ <sub>b</sub>		102.63	100.67	–0.66	84	.51
PANSS total <sub>c</sub>		57.95	59.60	0.55	80	.58
Strauss Carpenter		7.83	8.00	0.31	80	.76
Global role		4.79	2.47	4.71	–0.16	80
Global social		5.72	5.74	0.07	80	.95
Hours of training		32.93	36.37	8.94	84	.10
Months of illness		18.87	20.26	0.39	84	.70

## Change in cognitive performance in subjects with recent onset schizophrenia after computerized auditory training (AT) or computer games (CG).



Fisher M et al. Schizophr Bull 2014;schbul.sbt232

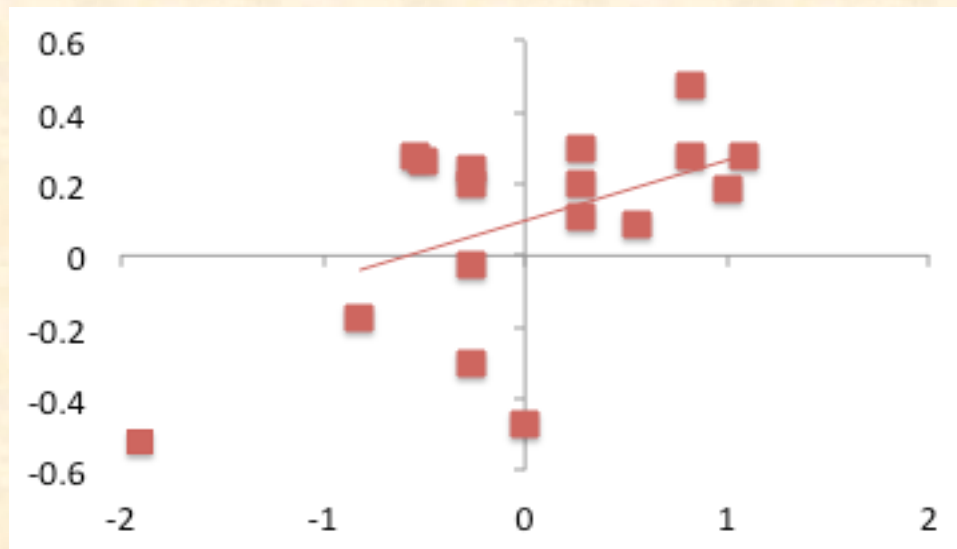
# MEG confirms changes in auditory/verbal encoding cortical networks



Neural activity assessed using 275-channel MEG in participants performing auditory tasks before and after the intervention. Time-frequency analysis done with NUTMEG and co-registered to normalized structural MRIs. Task-based high-gamma range (63-117Hz) changes analyzed.

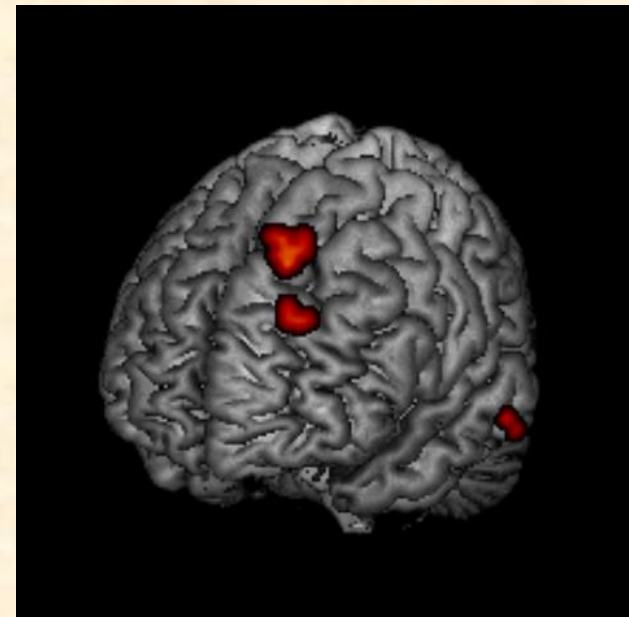


# Prefrontal high gamma is increased with training and associated with improved executive function



Change in Tower of London (normalized)

$r=.613, p=.009,$   
 $N=17$

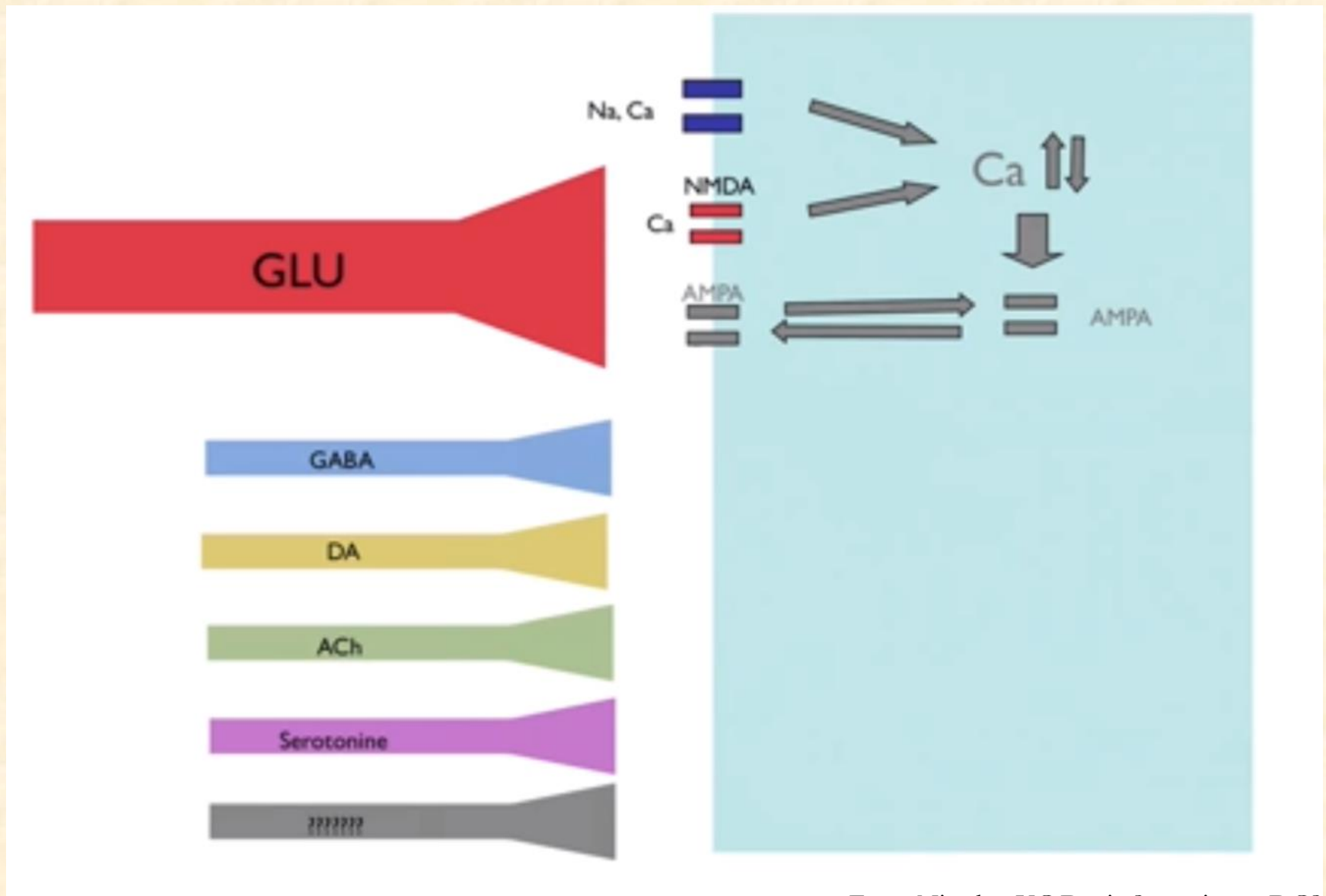


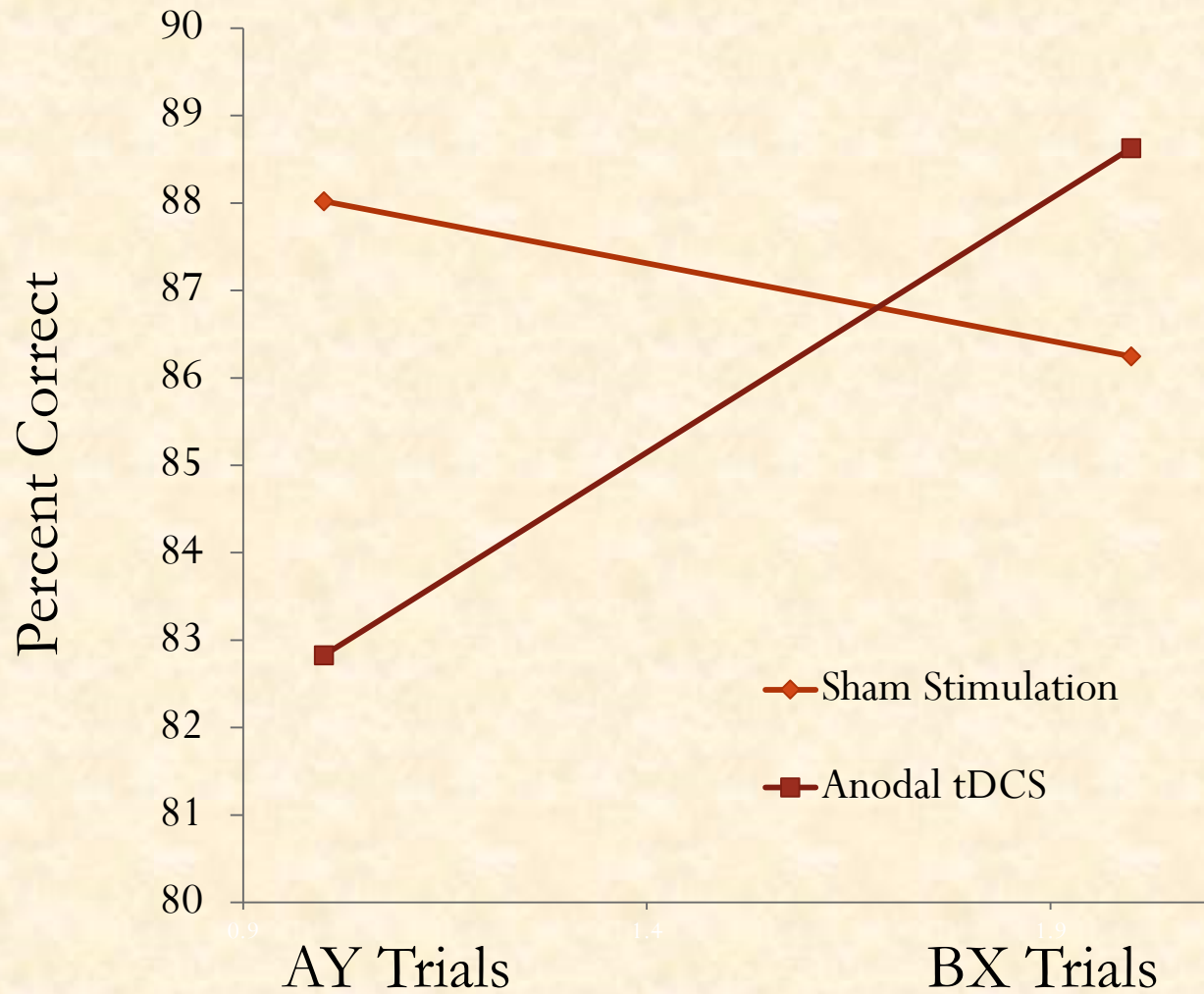
175-275 ms PFC

Dale et al. under review



# Physiological Mechanisms of tDCS





\* Stimulation Condition x Trial Type Interaction:  $F[1,38] = 4.889$ ;  $p = 0.033$

# Conclusions

- Insights obtain from neuroimaging studies of the functional circuitry changes underlying cognitive and emotion processing deficits in schizophrenia allow us to develop novel interventions to enhance the function of this circuitry.
- These circuitry based interventions are showing promise in offering new tools to address the disabling, treatment refractory symptoms in psychotic disorders.