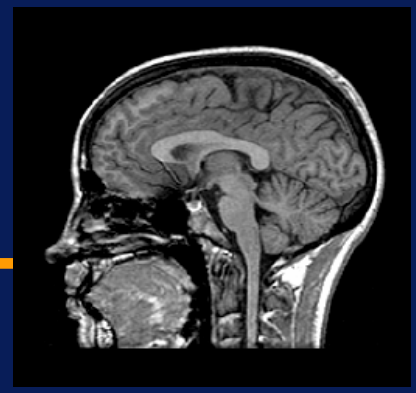


Executive Cognitive Function in Alcoholism: Insight from fMRI

Edith V. Sullivan, Ph.D.
Stanford University School of Medicine

Supported by NIAAA and NIA

Executive Function in Alcoholism

- Definition of alcoholism: Relevance to executive function
- Evidence for executive function and prefrontal structural compromise in alcoholism
- Capturing dynamic executive function and "elusive" dysfunction

Alcohol Dependence: DSM-IV

- Maladaptive pattern of substance use, leading to clinically significant impairment or distress, manifest by 3 or more of the following in a 12-month period:
  - Tolerance
  - Withdrawal
  - Increasing amounts consumed
  - Unsuccessful efforts to cut down
  - Inordinate time spent obtaining alcohol
  - Marked deterioration in life activities (work, home, recreation)
  - Continued use despite physiological or psychological problems

Good Executive Functioning

- Self-monitoring
- Multi-tasking
- Organization and efficiency
- Good judgment
- Delayed gratification
- Attentional focus
- Flexibility
- Problem solving (whole>sum of parts)

Characteristic Behaviors of Alcoholics

- impaired judgment
- blunted affect
- poor insight
- social withdrawal
- reduced motivation
- distractibility
- cognitive rigidity
- inattention

FRONTAL LOBE DYSFUNCTION

Functional Specificity despite Widespread Brain Damage

- In diseases with widespread brain damage, multiple brain structural and functional systems are affected.
- Widespread damage does not mean diffuse, nonspecific dysfunction.

Patterns of Sparing and Loss in Brain Structure and Function

- Selective brain damage-behavioral dysfunction relationships are observable with quantitative imaging and neuropsychological testing.
- Requirement: examine whole brain and test multiple component sensory, motor, and cognitive processes
- This approach provides a context for an observed deficit and to seek assurance that the brain-behavior relationships observed is not attributable to other deficits.

Considerations & Methods for Studying Executive Function

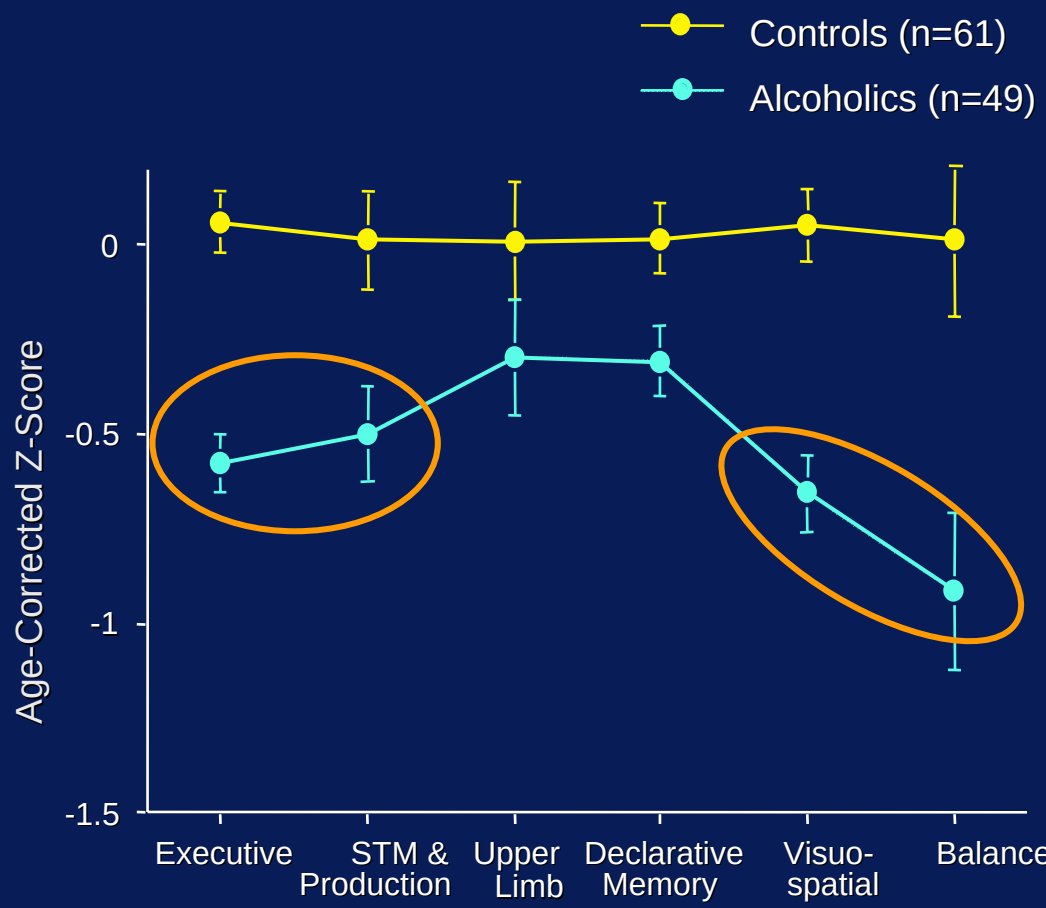
- Frontal circuitry
  - Influence from remote anatomical loci
  - Modulate the nature of compromise
  - Loci of different control processes influencing a single "compound" psychological mechanism
- Investigational Requirements
  - Whole brain analysis
  - Multiple systems or processes assessment

Alcoholism and Executive Function

- Definition of alcoholism: Relevance to executive function
- Evidence for frontal and executive function compromise in alcoholism
- Capturing dynamic executive function and "elusive" dysfunction

Alcoholism and Brain Function

- Alcoholic Cognitive and Motor Dysfunctions include:
  - Problem solving
  - Attention
  - Short-term memory
  - Visuospatial ability
  - Balance and postural stability

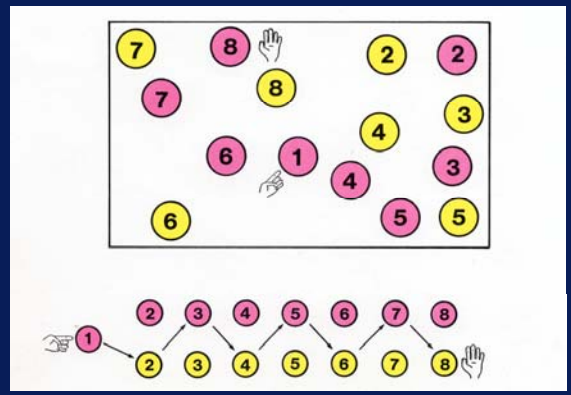


Sullivan et al. *ACER* 2000

Characteristic Behaviors of Alcoholics

- impaired judgment
- blunted affect
- poor insight
- social withdrawal
- reduced motivation
- distractibility
- cognitive rigidity
- inattention
- perseveration

Executive Functions

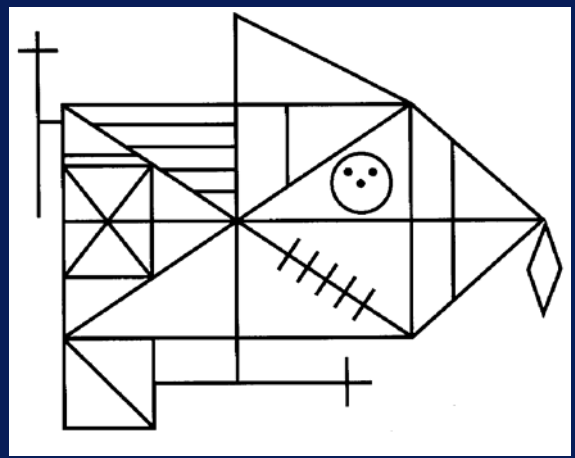


→ FRONTAL LOBE DYSFUNCTION

Characteristic Behaviors of Alcoholics

- poor sense of direction
- impaired constructional ability
- impaired spatial placement
- impaired drawing ability

} Visuospatial Abilities



→ PARIETAL LOBE DYSFUNCTION

Characteristic Behaviors of Alcoholics

- impaired timing
- impaired tracking
- impaired balance
- impaired gait
- increased falls

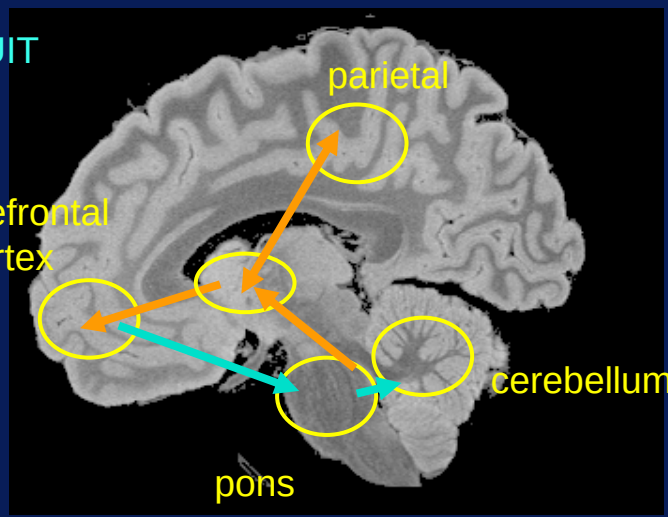
} Motor Control

→ CEREBELLAR DYSFUNCTION

Sources of Executive Dysfunction

- Posterior and inferior brain regions (e.g., parietal cortex, cerebellum, and pons) have major connections with prefrontal cortical sites.
- Non-frontal pathology in these brain regions must also be considered as potential modulators and sources of disruption of executive functioning.

FEEDFORWARD CIRCUIT

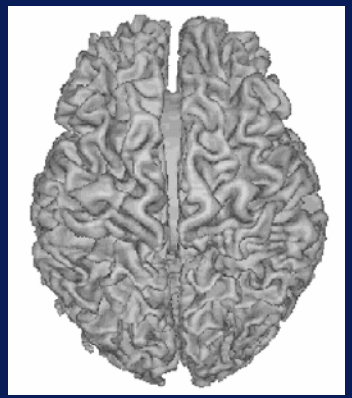


FEEDBACK CIRCUIT

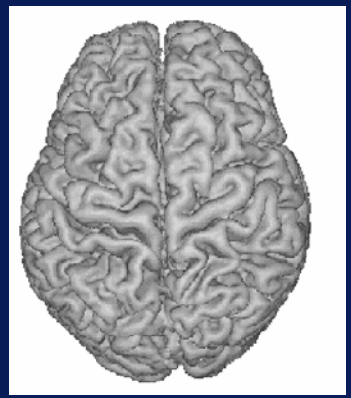
Schmahmann & Pandya 1997

Cortical Gray Matter and White Matter Volumes

Alcoholic



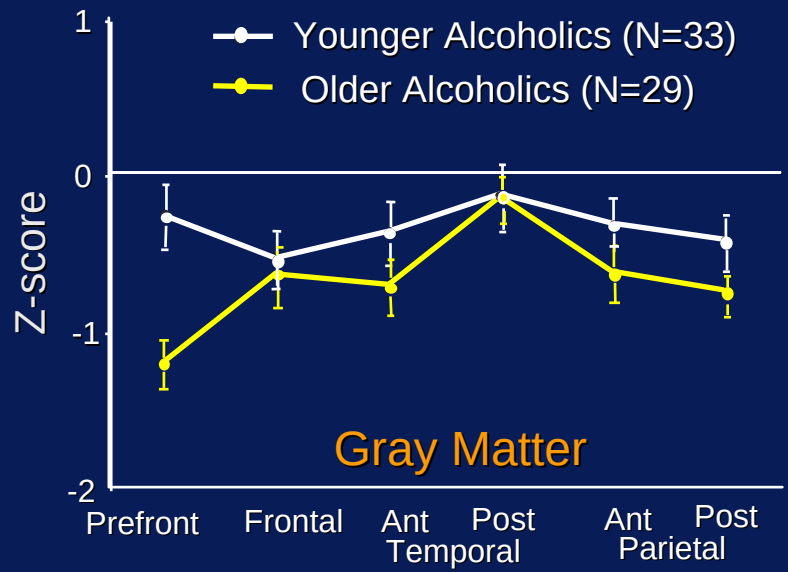
Control

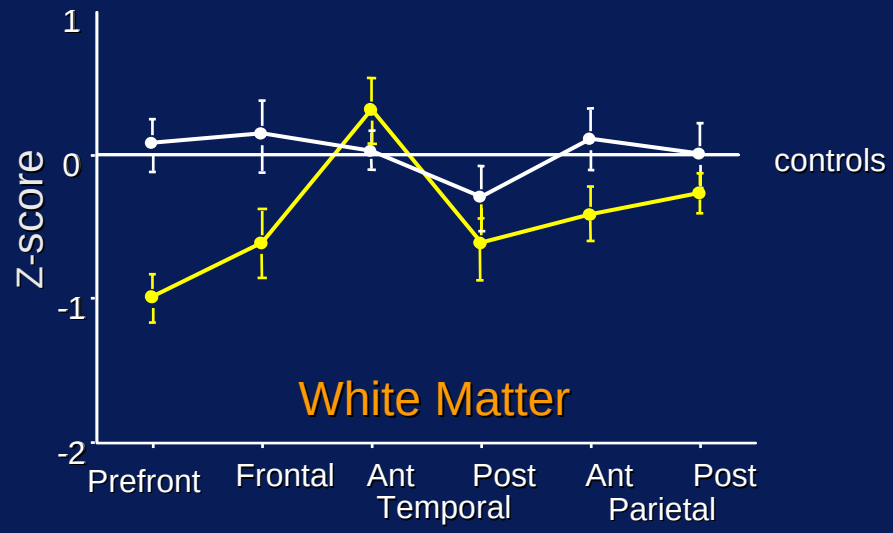


57 yr old men

Lifetime consumption of alcohol

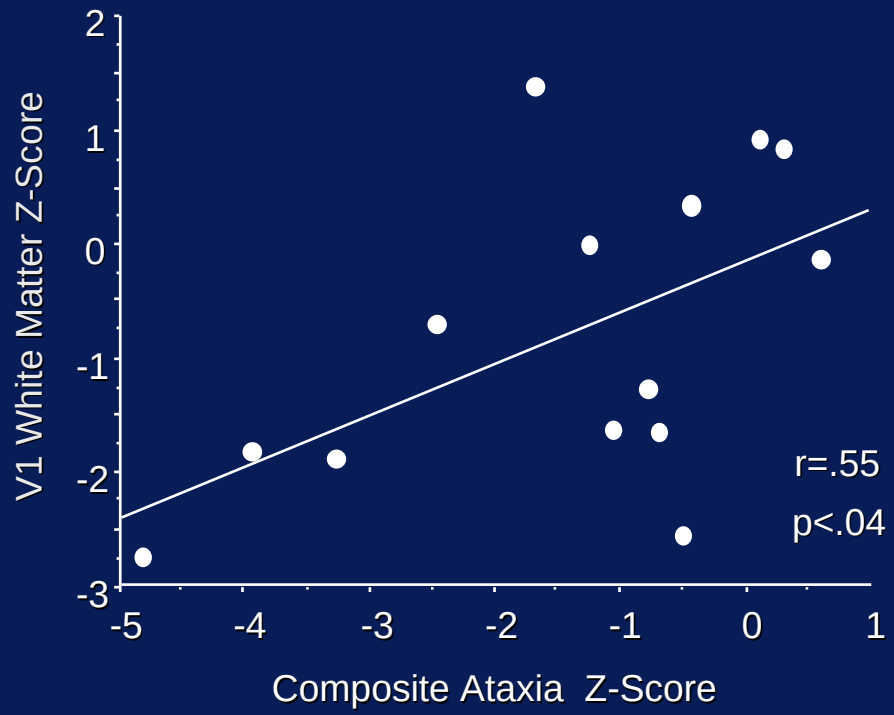
1866 kg 60 kg





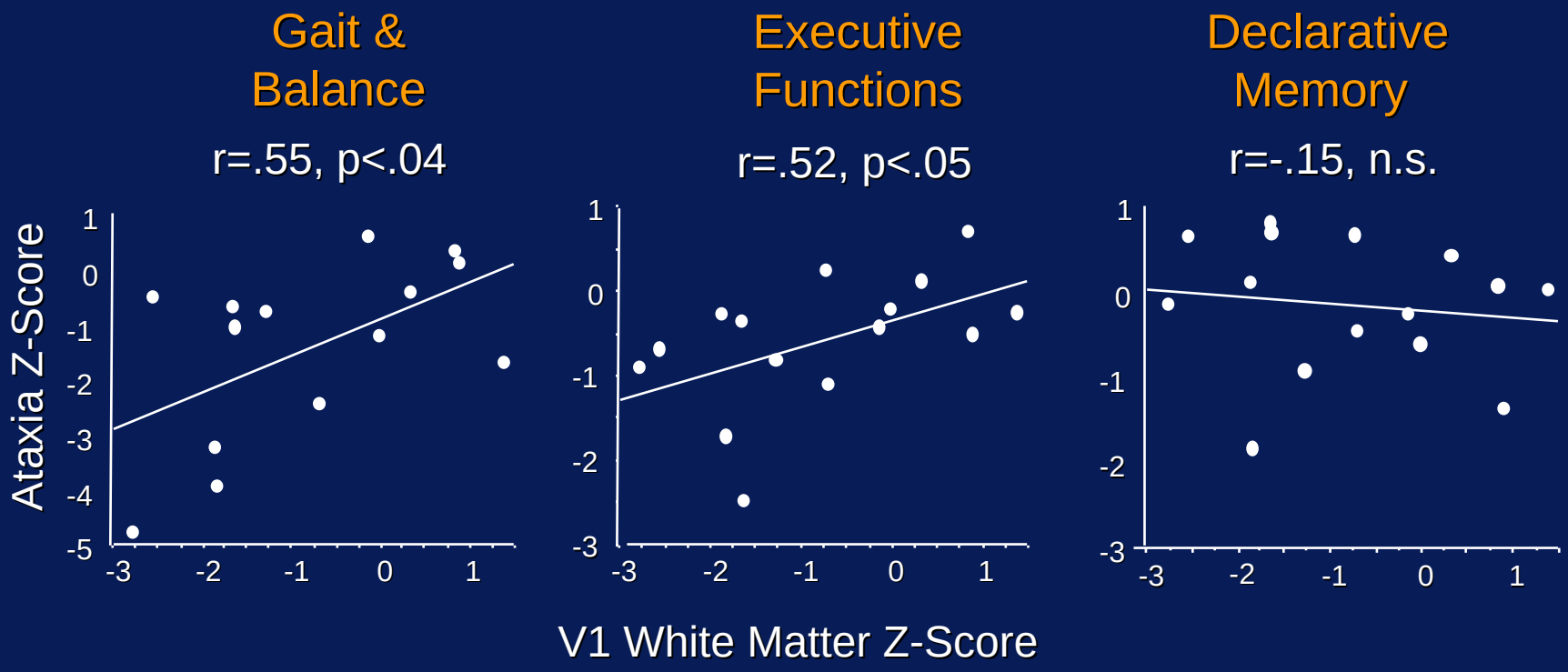
Pfefferbaum et al.
ACER 1997

Ataxia and Anterior Superior Vermis in Recovering Alcoholics



Sullivan et al.
Neuropsychology 2000

Motor and Cognitive Functions and the Vermis



Executive Functions = temporal ordering, self-ordered pointing, sequencing, set shifting, problem solving

Sullivan *ACER* 2003

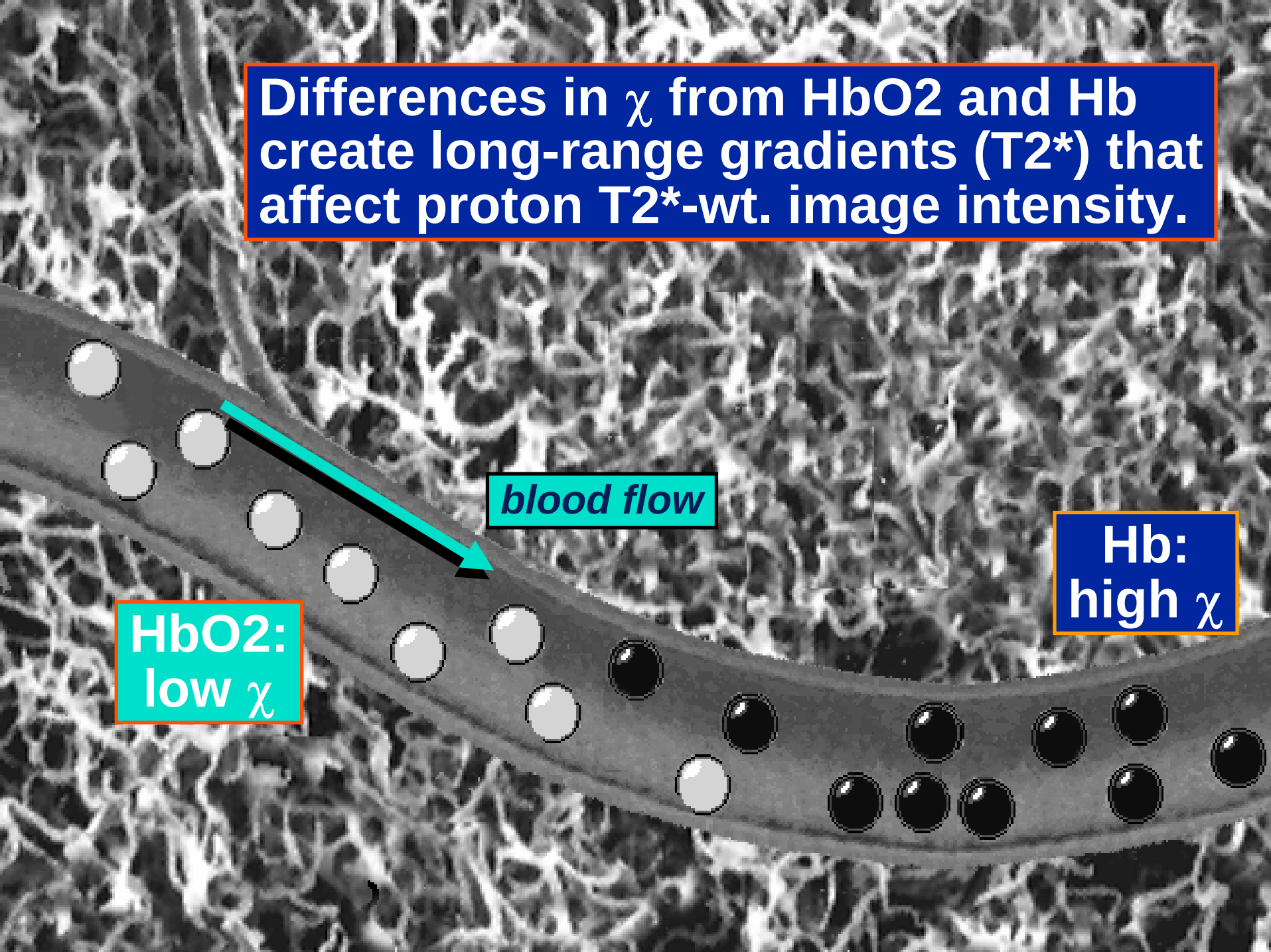
Alcoholism and Executive Function

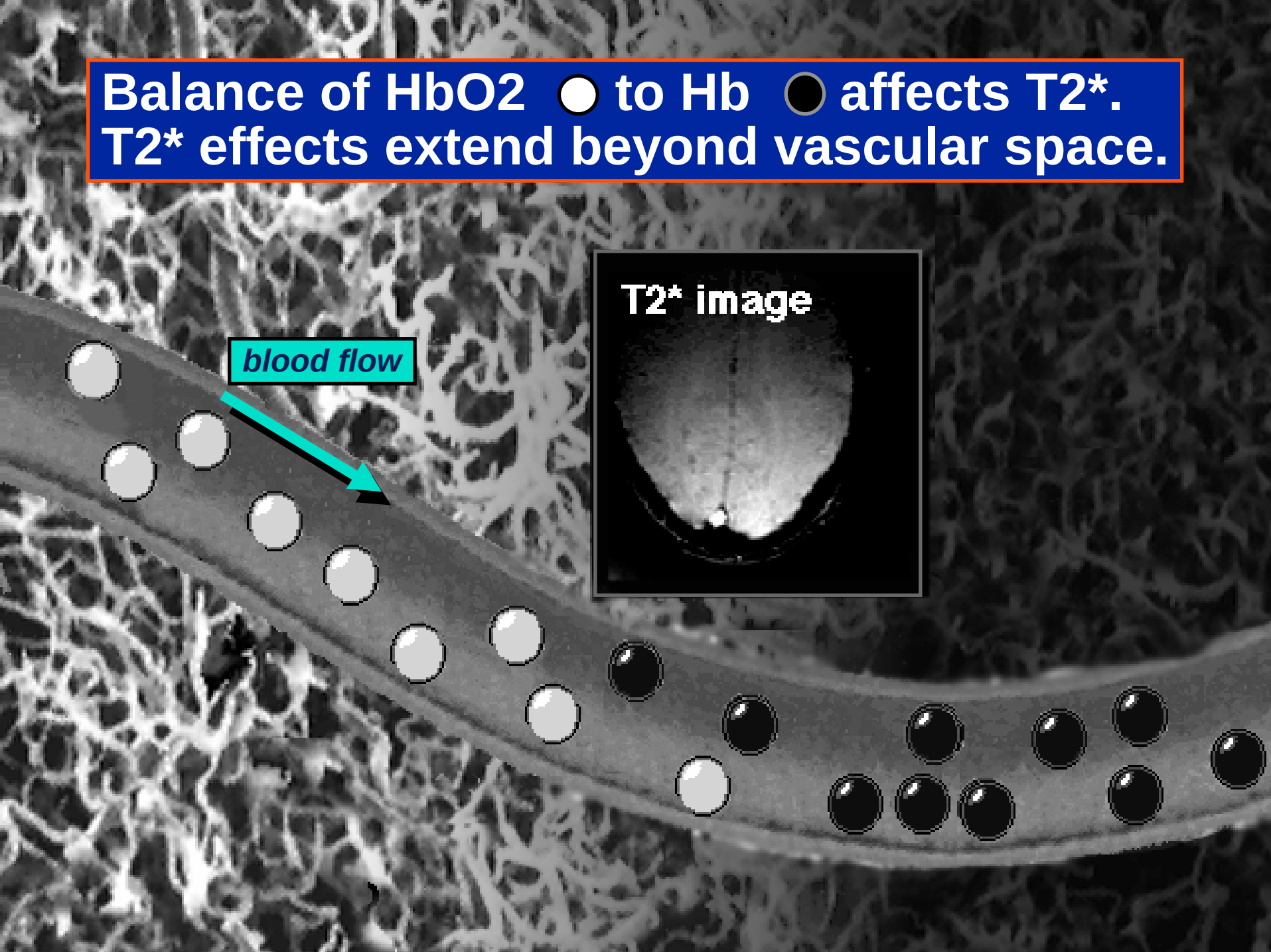
- Definition of alcoholism: Relevance to executive function
- Evidence for frontal and executive function compromise in alcoholism
- Capturing dynamic executive function and "elusive" dysfunction

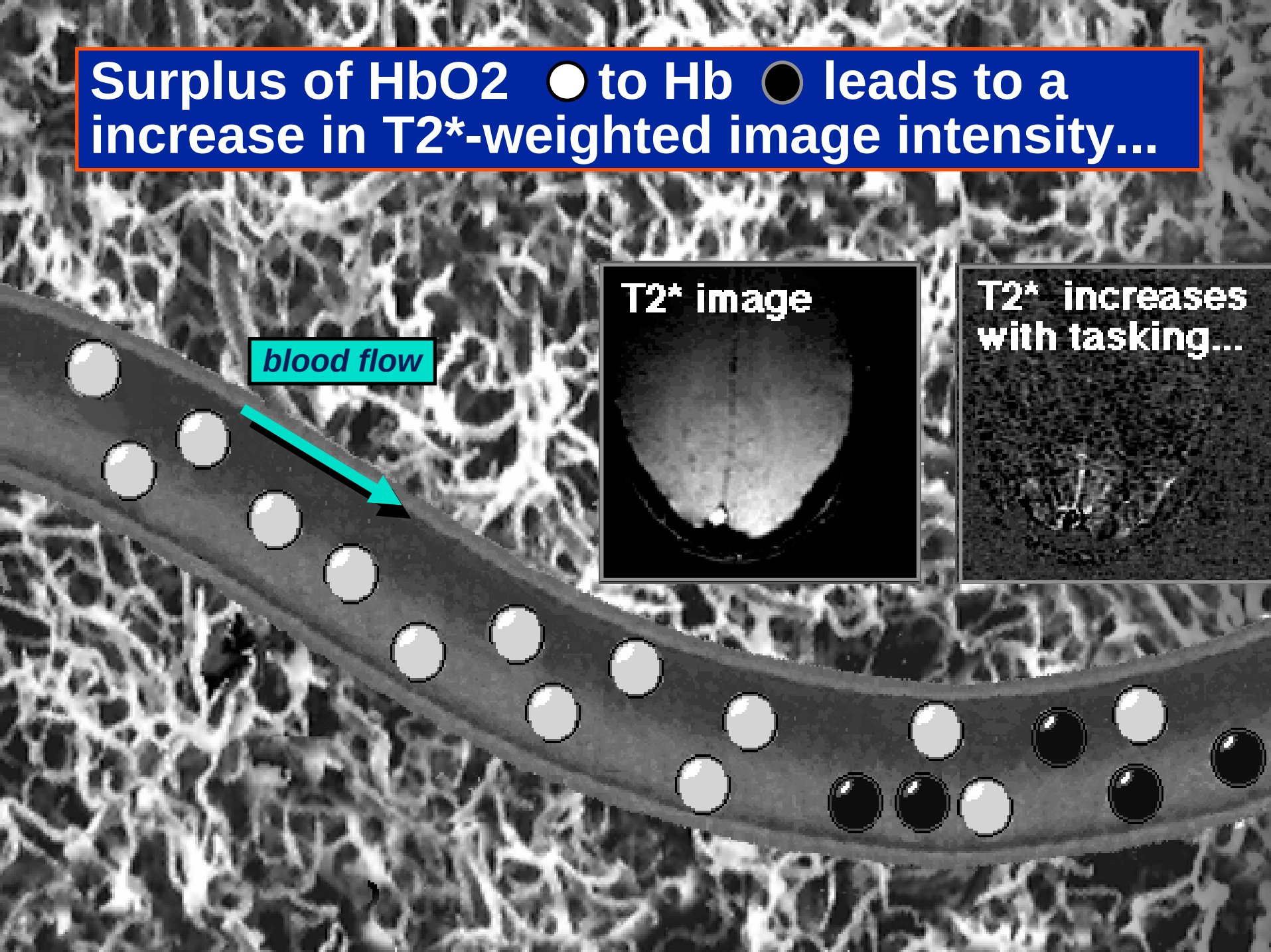
Process Inefficiency Hypothesis Tested with fMRI

- The functional outcome of these incomplete brain lesions can be apparently normal performance, but at the price of usurping reserve that reduces processing capacity for conducting multiple tasks simultaneously or efficiently.

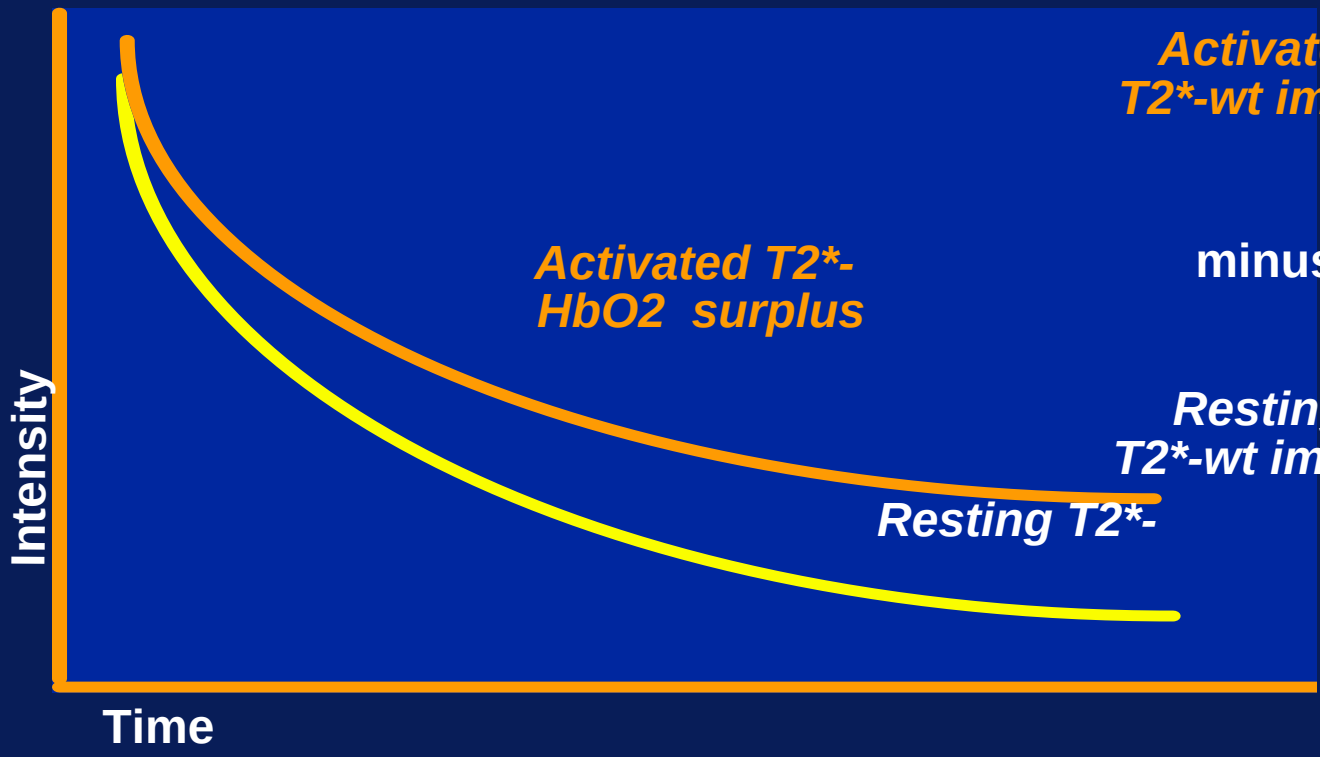
- Functional MRI (f MRI) studies of alcoholism
  - Spatial working memory
  - Verbal working memory
  - Resolution of proactive inhibition

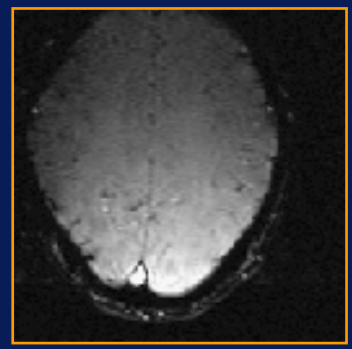

Differences in χ from HbO2 and Hb create long-range gradients (T2*) that affect proton T2*-wt. image intensity.
blood flow
HbO2: low χ
Hb: high χ

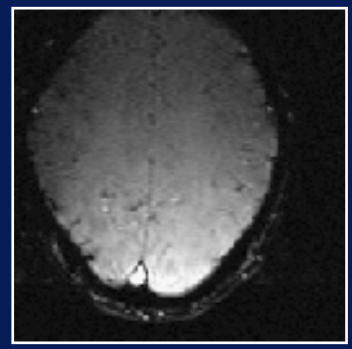

Balance of HbO2 to Hb affects T2*.
T2* effects extend beyond vascular space.
T2* image
blood flow


Surplus of HbO2 to Hb leads to a increase in T2*-weighted image intensity...
blood flow
T2* image
T2* increases with tasking...

Blood Oxygen Level Dependent (BOLD) Effect T2* Contrast







Difference is an image of activation =

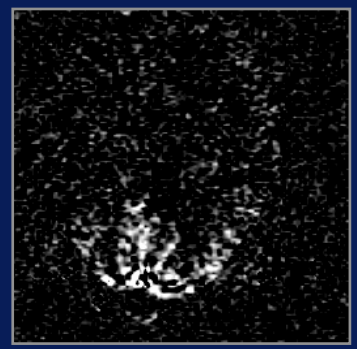
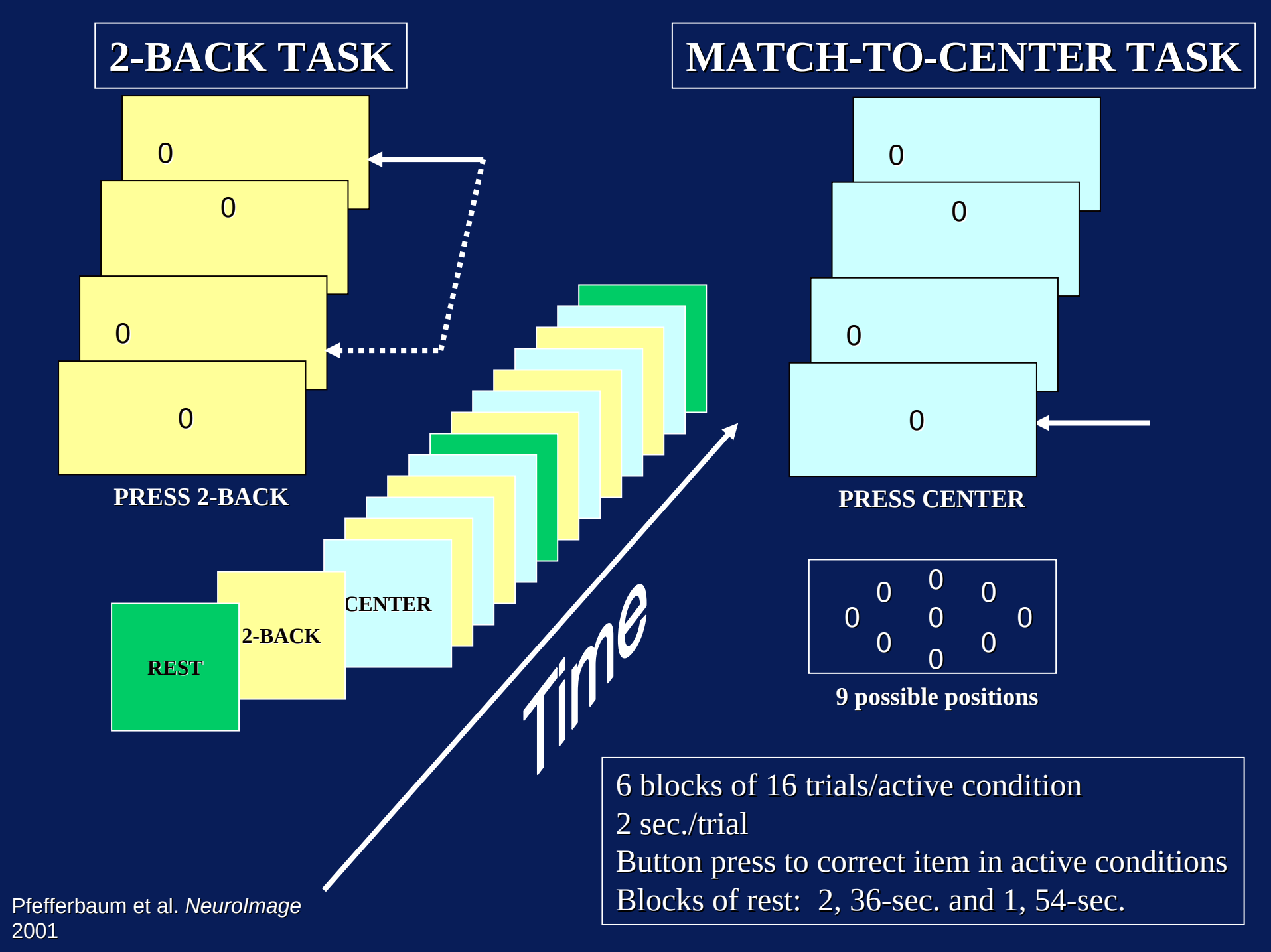


Image increases due to increased T2* in V1 during photic activation using surface coil at 1.5Tesla

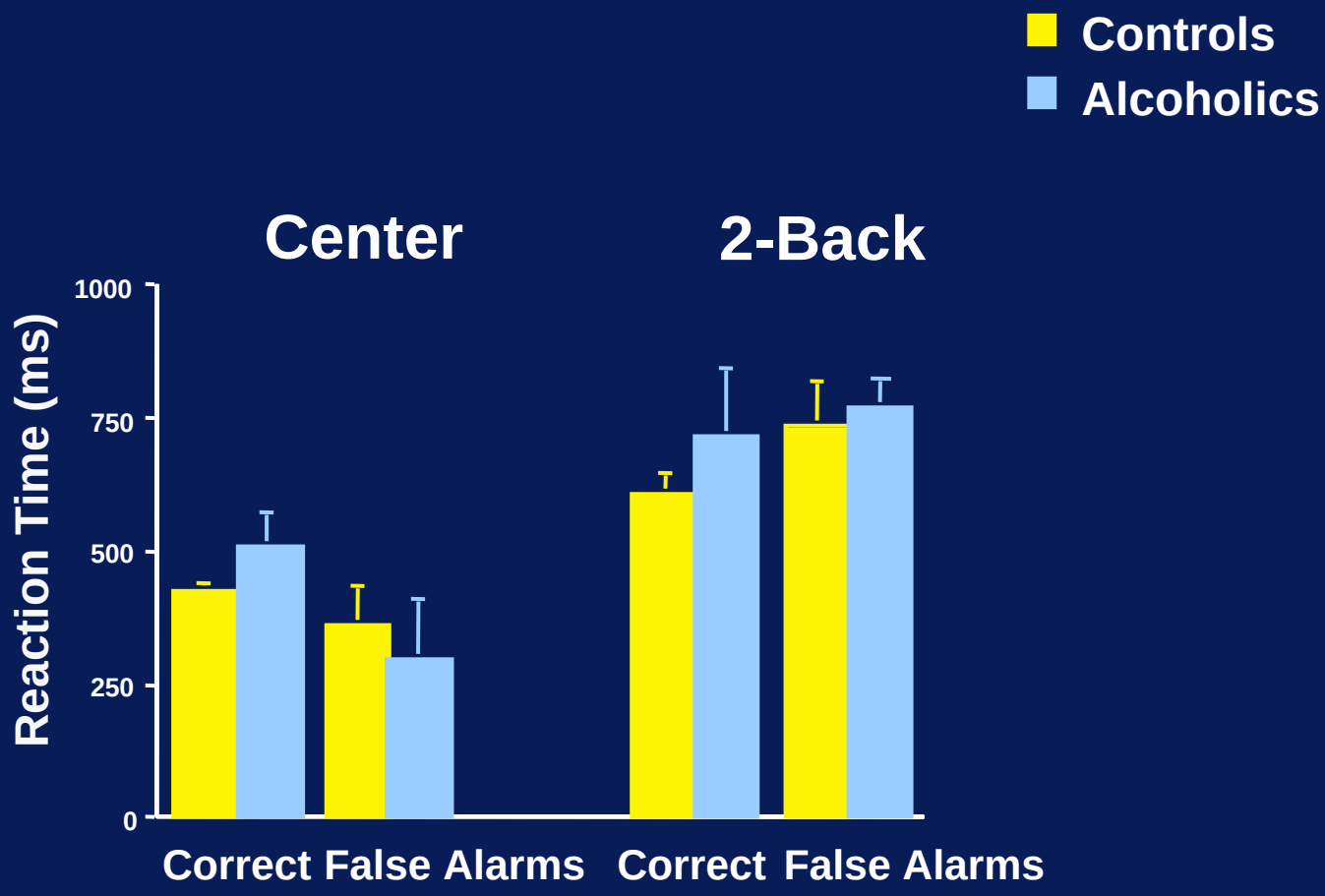
Spatial Working Memory

- When engaging in a spatial working memory and attention paradigm, in contrast to
  - controls who activated the dorsal "Where?" neural stream and dorsolateral prefrontal cortex,
  - alcoholics activated the ventral neural "What?" stream and ventrolateral prefrontal cortex.



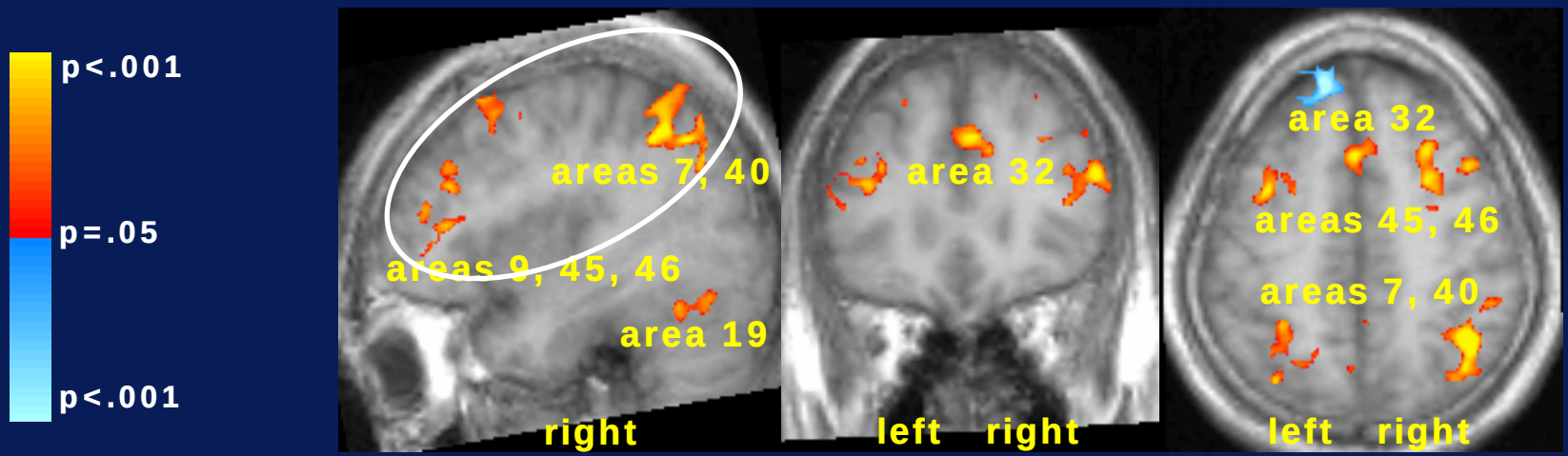
Pfefferbaum et al. *NeuroImage* 2001

Button Press Reaction Time

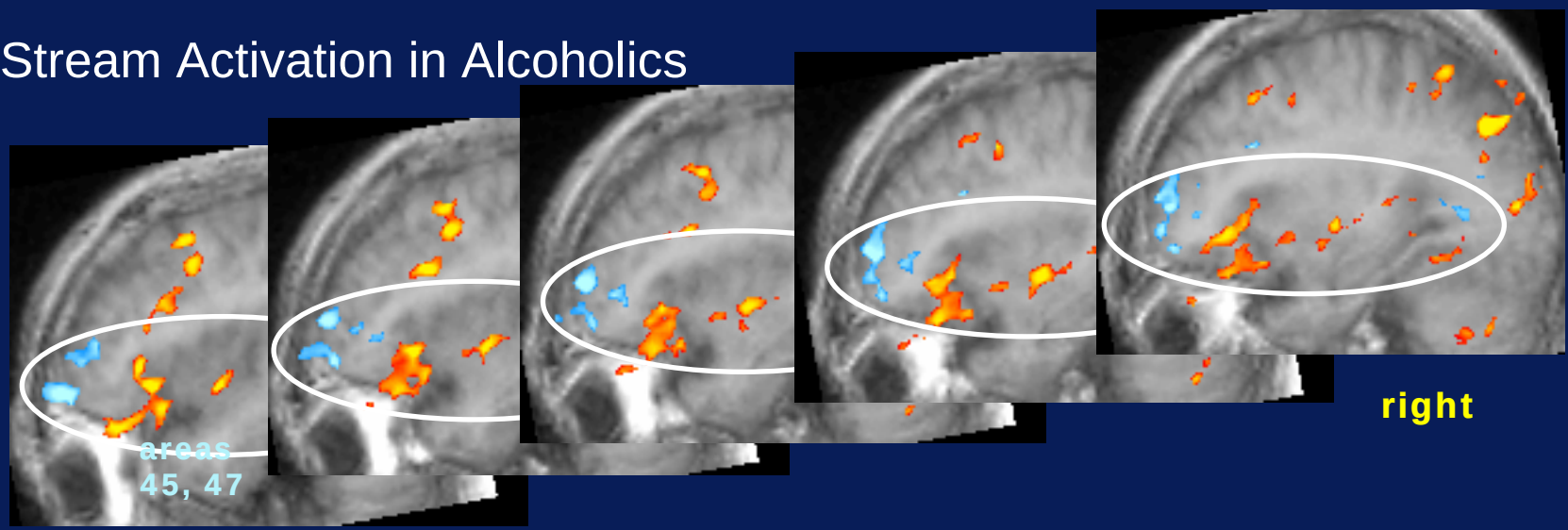


2-Back/Center Match/Rest Tasks

Dorsal Stream Activation in Controls



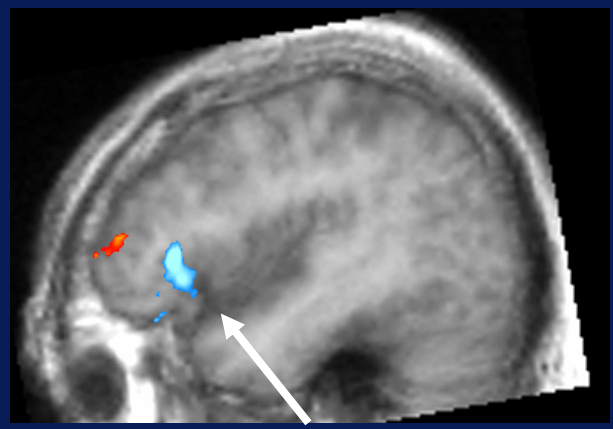
Ventral Stream Activation in Alcoholics



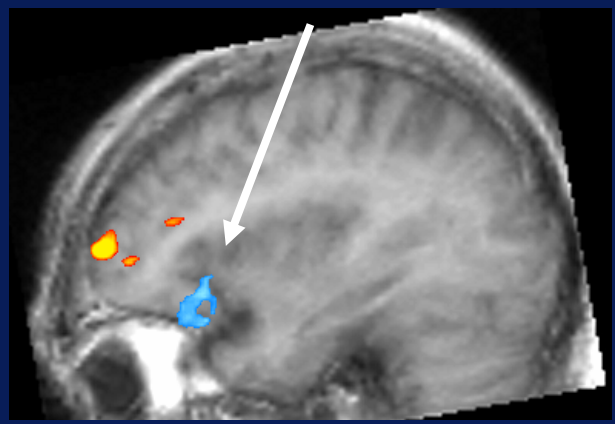
Group Differences: Center vs. Rest

areas
9, 10,
45, 46

left right

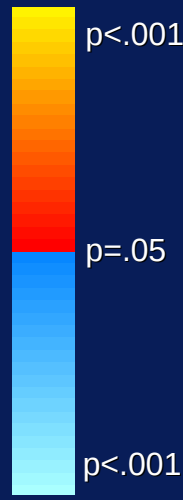


areas 45, 47



right

Controls > Alcoholics



Alcoholics > Controls

Verbal Working Memory

- In a verbal working memory setting, alcoholics recruited more widely spread areas of frontal and cerebellar brain regions than controls to achieve normal levels of performance.

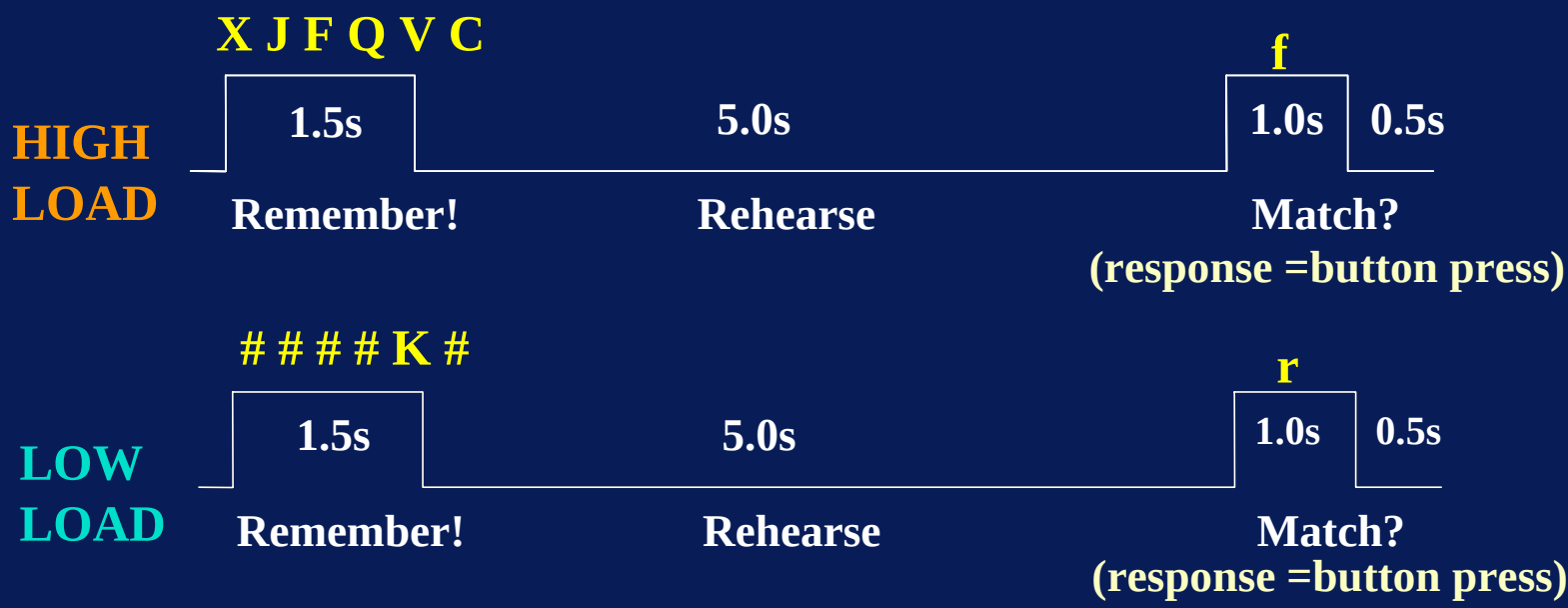
Verbal Working Memory

Short-Term Verbal Working Memory Task

(Articulatory control and phonological storage components)

Left frontal, left temporal/parietal, and right cerebellar structures

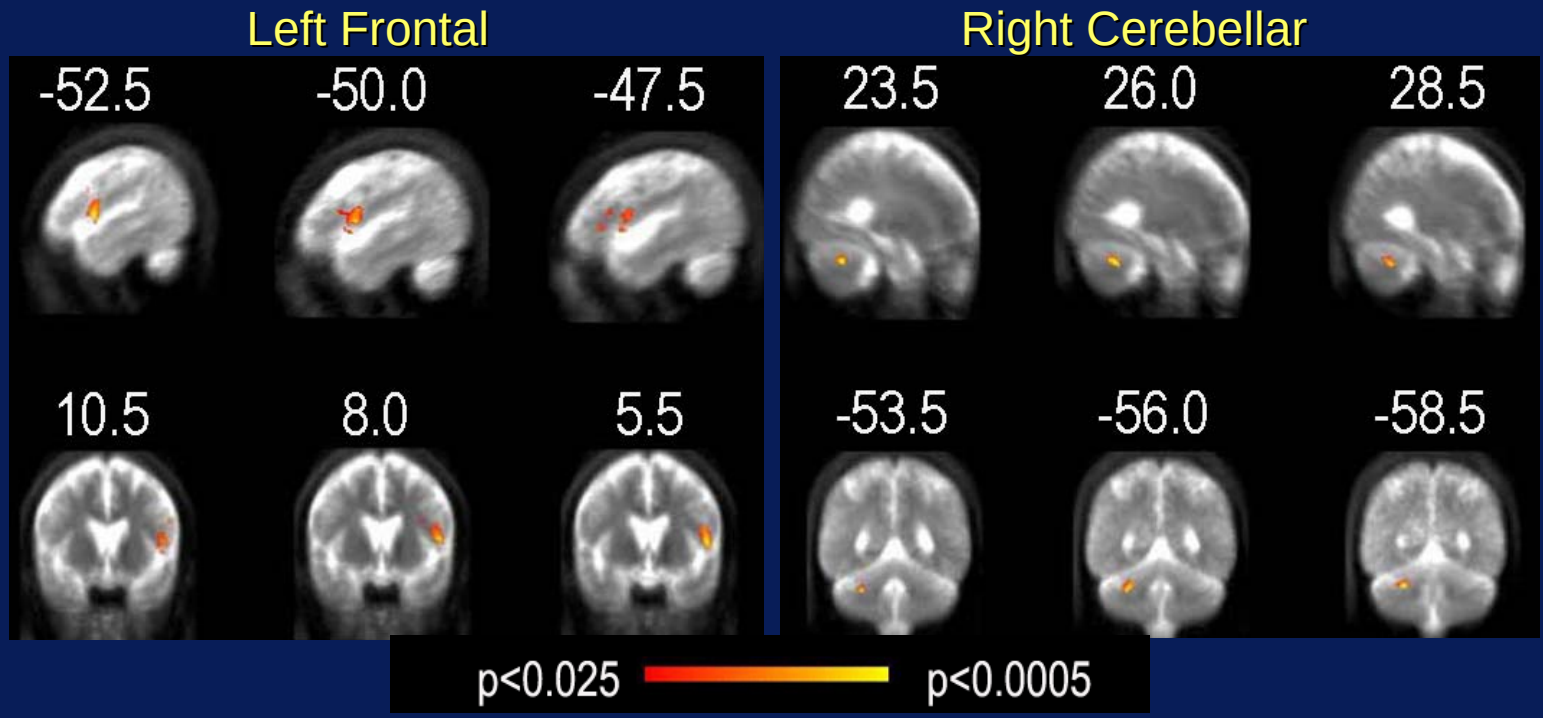
Sternberg Paradigm as Probe in an fMRI Study



Desmond et al.
NeuroImage 2003

Neuroadaptation to Alcoholic Brain Tissue Injury

Greater Activation in Alcoholics than Controls



- Alcoholics invoked more extensive brain regions to achieve normal levels of performance on a high vs. low load, verbal working memory task.

Desmond et al. *NeuroImage* 2003

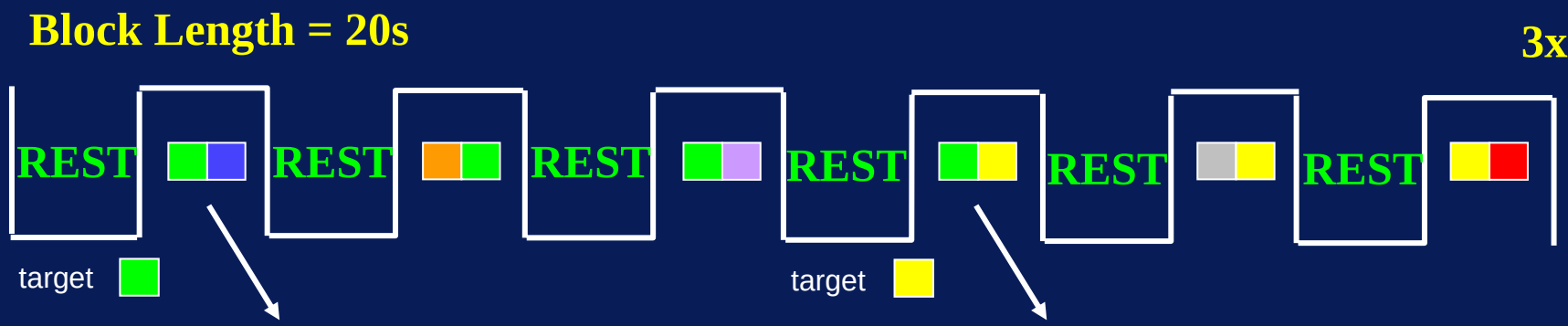
Resolution of Proactive Interference

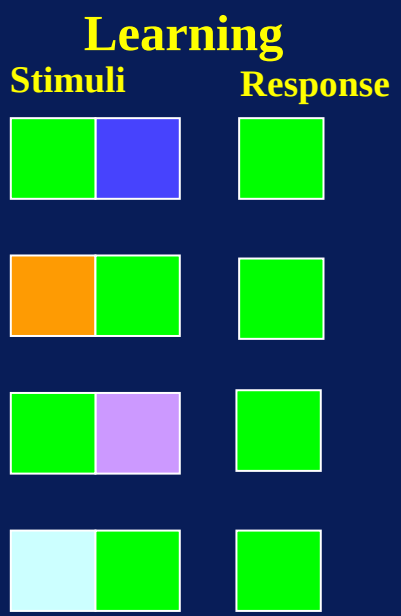
- In a task requiring resolution of proactive interference, from an animal model of PI resolution deficit following lesion to the basal forebrain cholinergic system,
  - alcoholics activated a frontally-based brain system associated with high-level executive function rather than the
  - control-activated basal forebrain system adequate for completing this low-level form of interference resolution.

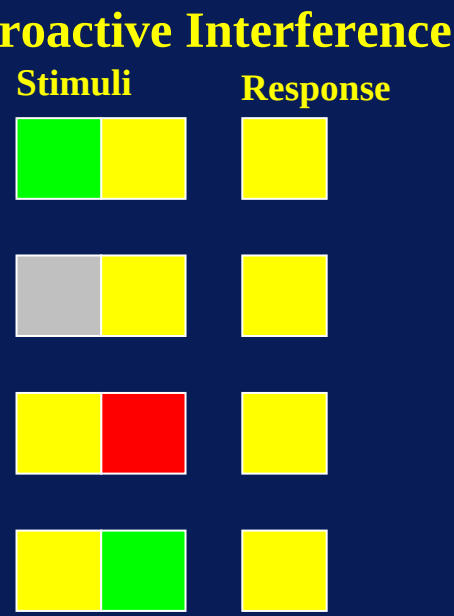
Proactive Interference (PI)

- Previously learned information reduces the ability to acquire new, related information
  - Switching computers or keyboards
  - Searching for gear shift knob, the radio buttons and the headlights in a new car

fMRI Block Design

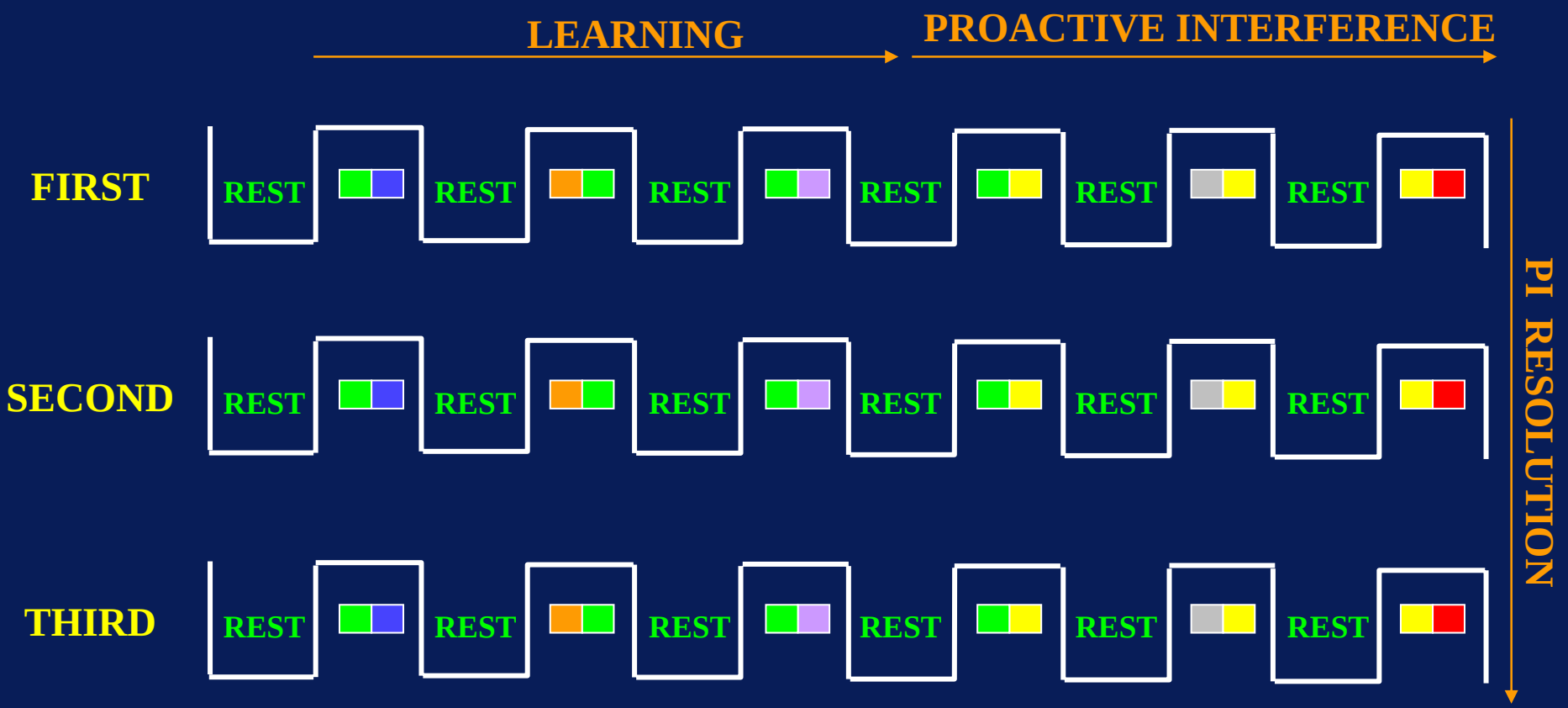






De Rosa et al. *Neuron* in press

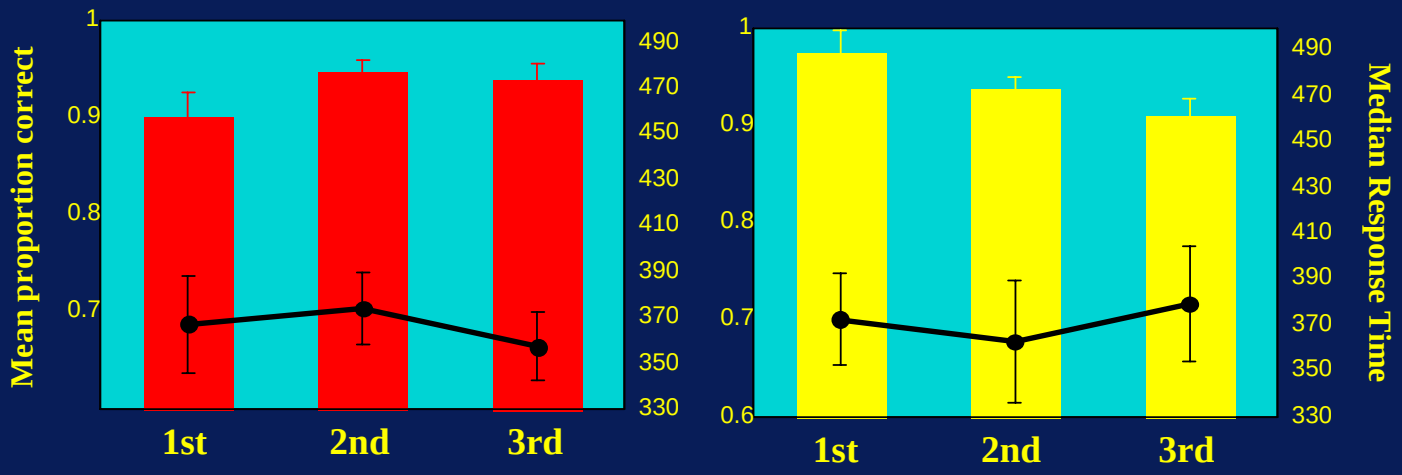
fMRI Block Design



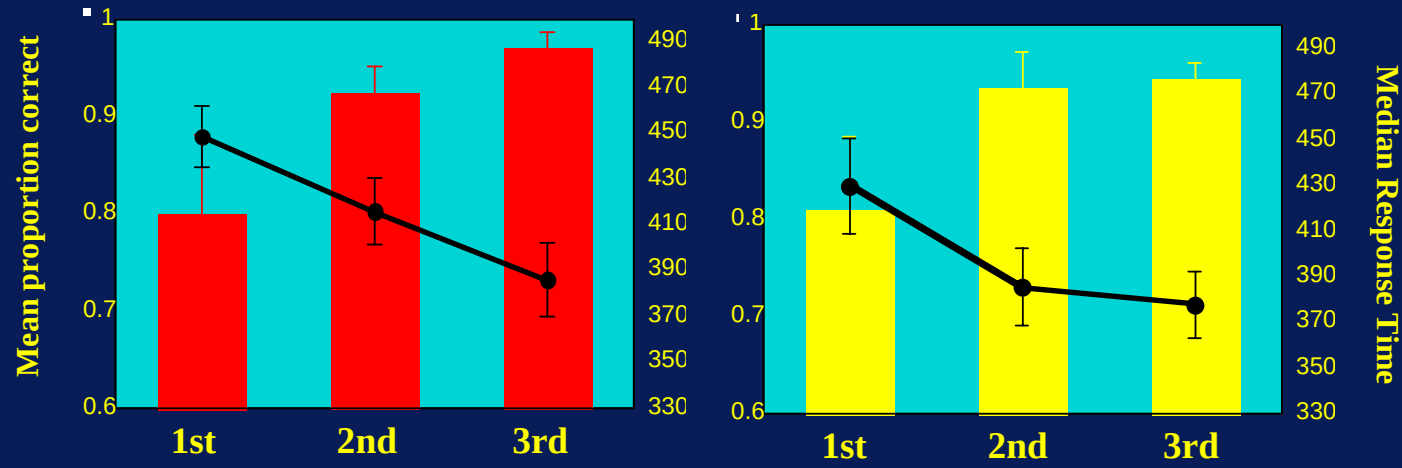
fMRI Behavior

Controls **Alcoholics**

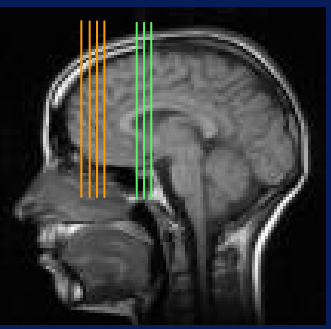
Learning



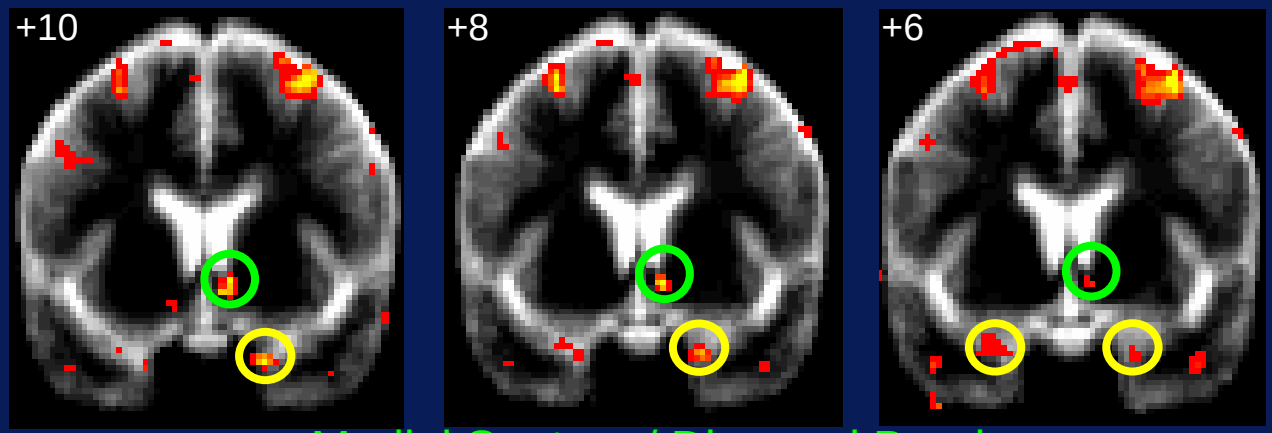
Proactive Interference



PI vs. Learning in Controls

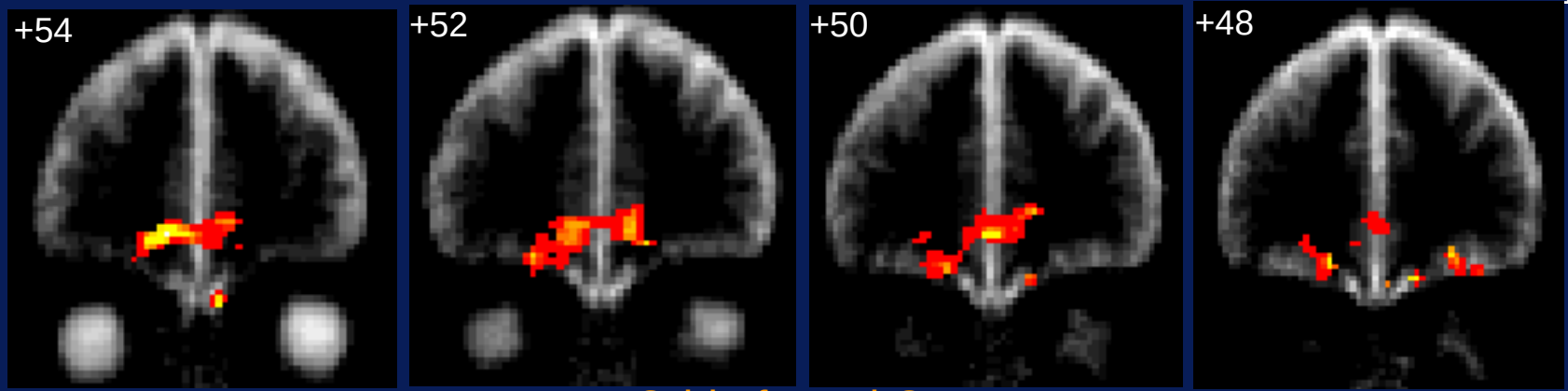


Anterior → Posterior



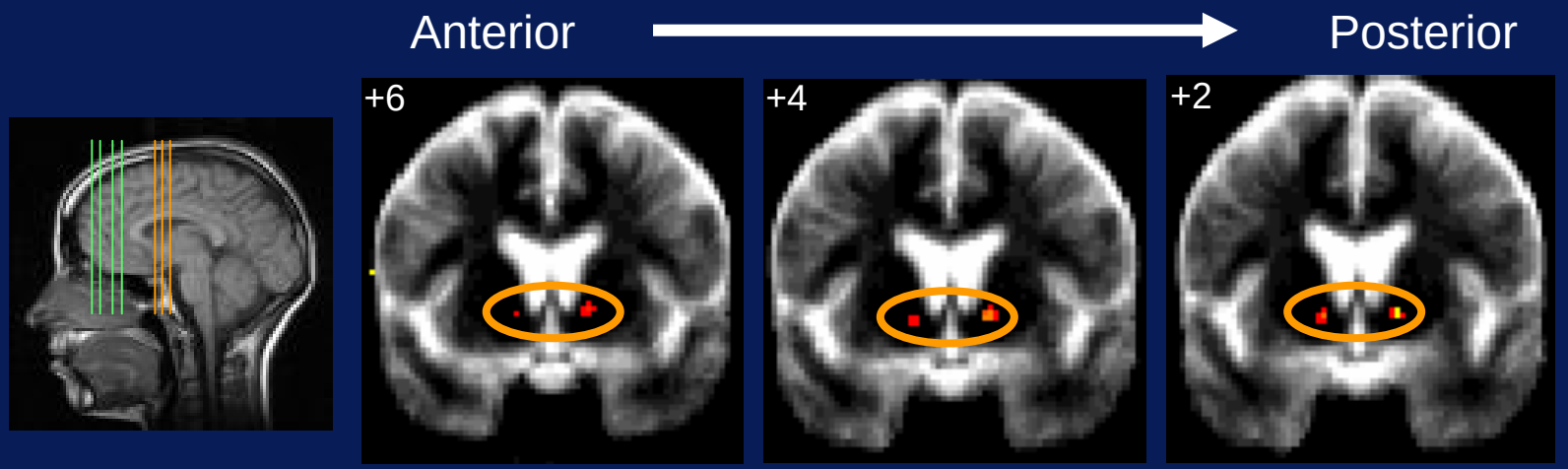
Medial Septum / Diagonal Band

Entorhinal Cortex



Orbitofrontal Cortex

PI vs. Learning in Alcoholics



Ventral Striatum

Lateral Prefrontal Cortex

Anterior Cingulate Cortex

Process Inefficiency Hypothesis Tested with fMRI

In a visuospatial working memory task,
alcoholics recruited a different neuronal circuit from controls with performance at the same level

In a verbal working memory task,
alcoholics recruited more widely spread areas of frontal and cerebellar brain regions than controls to achieve normal levels of performance

To achieve normal levels of behavior in the resolution of proactive inhibition,
alcoholics recruited areas associated with higher-order executive functions

“Incomplete Lesion” in Alcoholism

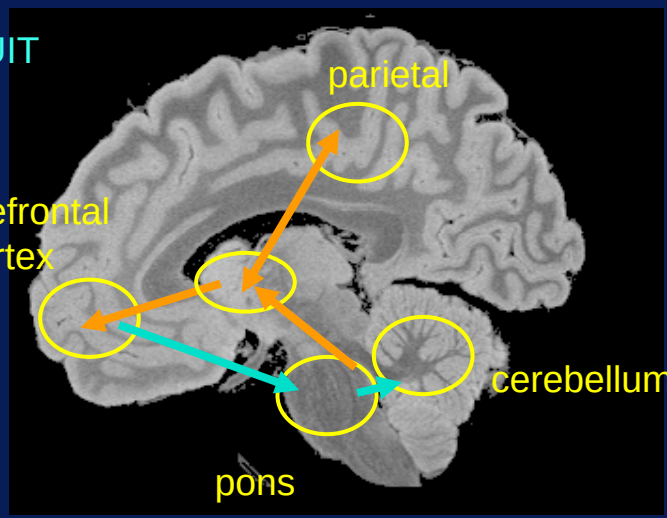
- Shrinkage or disruption of neuronal processes and not necessarily cell loss
- Resulting cognitive deficits in abstinent alcoholics may be more a compromised or distorted function than a lost function
- Attributable to either:
  - Reduced or diffuse activation of task-appropriate brain regions

    OR
  - Activation of task-inappropriate brain regions.

Sources of Executive Dysfunction

- Pathology of the full extent of frontocerebellar circuitry must be considered as potential modulators and sources of disruption of executive functioning and perpetuation of the alcohol dependence syndrome.

FEEDFORWARD CIRCUIT



FEEDBACK CIRCUIT

Sullivan *Alc: Clin Exp Res* 2003