Executive Cognitive Function in Alcoholism: Insight from fMRI

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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

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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.
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

→ 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.

Schmahmann & Pandya 1997
Cortical Gray Matter and White Matter Volumes

Alcoholic

57 yr old men
Lifetime consumption of alcohol
1866 kg

Control

57 yr old men
Lifetime consumption of alcohol
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

Gait & Balance
\[ r = 0.55, \ p < 0.04 \]

Executive Functions
\[ r = 0.52, \ p < 0.05 \]

Declarative Memory
\[ r = -0.15, \text{ n.s.} \]

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

Sullivan ACER 2003
Alcoholism and Executive Function

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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 $\chi$ from HbO2 and Hb create long-range gradients (T2*) that affect proton T2*-wt. image intensity.

- HbO2: low $\chi$
- Hb: high $\chi$

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

blood flow
Surplus of HbO2 $\bullet$ to Hb $\bullet$ leads to an increase in T2*-weighted image intensity...
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
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.
2-BACK TASK

MATCH-TO-CENTER TASK

6 blocks of 16 trials/active condition
2 sec./trial
Button press to correct item in active conditions
Blocks of rest: 2, 36-sec. and 1, 54-sec.
Button Press Reaction Time

Reaction Time (ms)

Correct False Alarms

Center

2-Back

Controls
Alcoholics
2-Back/Center Match/Rest Tasks

Dorsal Stream Activation in Controls

- areas 9, 45, 46
- area 19
- areas 7, 40
- area 32
- areas 45, 46

Ventral Stream Activation in Alcoholics

- areas 45, 47
- areas 45, 47
- area 32
- areas 45, 46
- areas 7, 40
- area 32
- left
- right
- right
Group Differences: Center vs. Rest

Areas: 9, 10, 45, 46

Controls > Alcoholics

Areas: 45, 47

Alcoholics > Controls

p < .001

p = .05

p > .05

Areas 45, 47
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

Desmond et al. *NeuroImage* 2003

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

Block Length = 20s

Learning
Stimuli  Response

Proactive Interference
Stimuli  Response

De Rosa et al. Neuron in press
fMRI Block Design

LEARNING

FIRST

SECOND

THIRD

PROACTIVE INTERFERENCE

REST

REST

REST

REST

REST

REST

REST

REST

REST

REST

REST

REST

REST

REST

pi resolution
fMRI Behavior

Learning

Proactive
Interference
PI vs. Learning in Controls

Anterior Posterior

Medial Septum / Diagonal Band
Entorhinal Cortex

Orbitofrontal Cortex
PI vs. Learning in Alcoholics

Anterior Posterior

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
  - Activation of task-inappropriate brain regions.
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.