

**Neuroimaging cognitive  
function in children diagnosed  
with ARND and ADHD**

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National Research Council of Canada

# The Team

## Co-Applicants:

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## Team members:

### NRC-IBD

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# FASD The 4-Digit Diagnostic Code

Uses a 4 digit scale to define and reflect 4 key diagnostic features of FAS [and 2 digits for pre- and post-natal co-morbidities]:

- (1) growth deficiency
- (2) facial phenotype
- (3) brain dysfunction
- (4) gestational alcohol exposure

# Alcohol Related Neurodevelopmental Disorder (ARND)

- Frequently do not demonstrate facial characteristics of FAS
- Have neurodevelopmental abnormalities: cognitive/behavioural
- Executive functions (including working memory), response inhibition and attention are affected by alcohol exposure
- Similar attention problems as ADHD

# Objectives

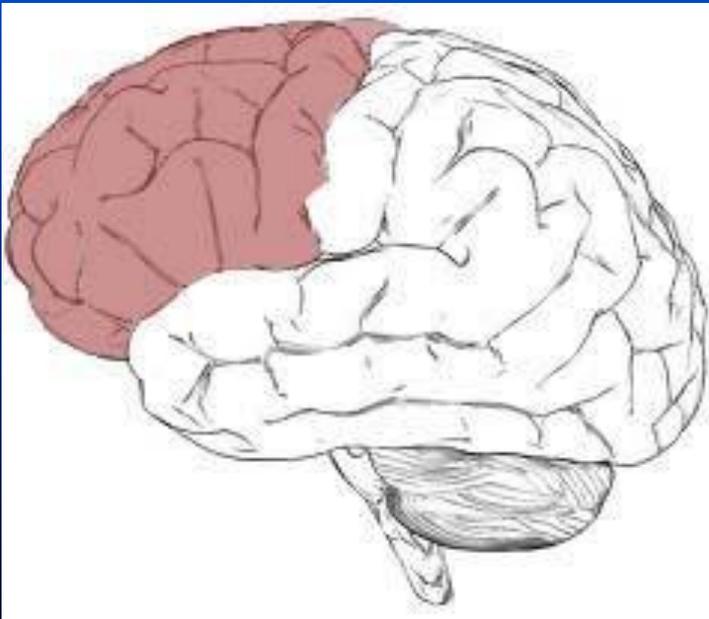
To determine differences in brain function using functional Magnetic Resonance Imaging (fMRI) between children (10-14 yrs) diagnosed with ARND and ADHD and typically developing controls (TD) in areas of:

- Working Memory
- Attention
- Response Inhibition

# Executive Functions

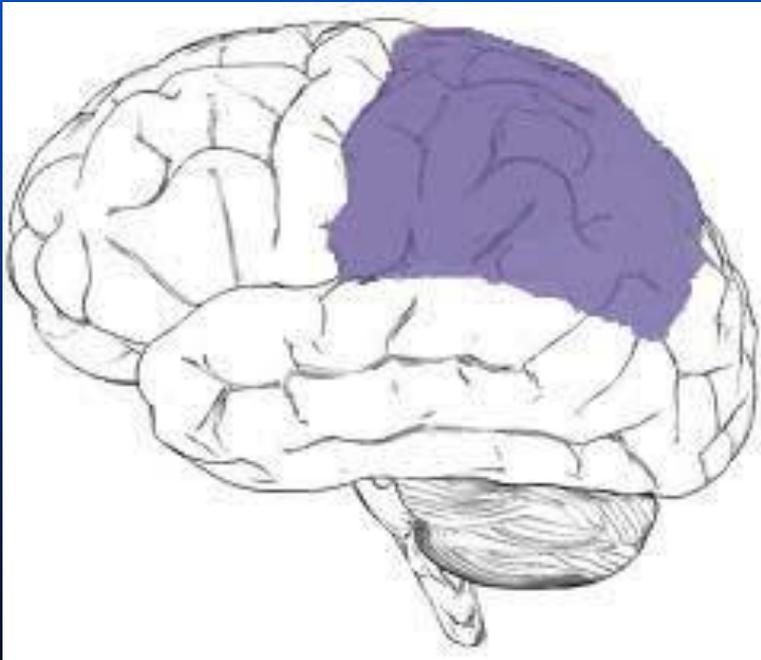
## The frontal cortex

- Working memory
- Inhibition
- Planning
- Time perception
- Internal ordering
- Self-monitoring
- Verbal self-regulation
- Motor control
- Regulation of emotion
- Motivation



# Parietal lobe Function

- Attention
- Memory
- Sensation and perception (cognition)
- Integrates sensory input (visual)
- Spatial information

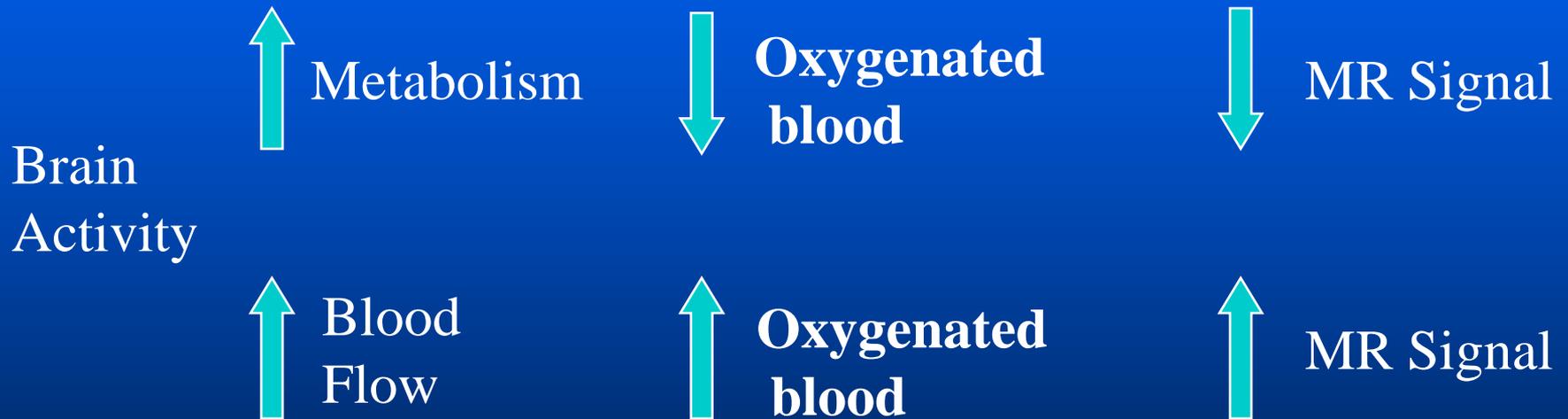


# What are we trying to do?

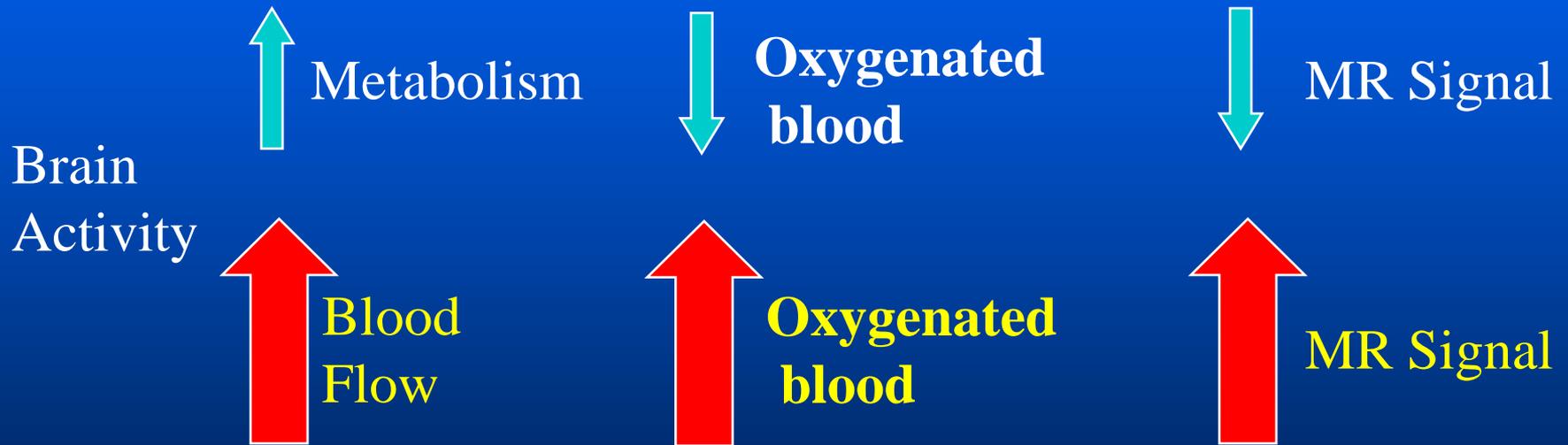
**Neural Activity  
In Response to task**



# What do we measure with fMRI?



# What do we measure with fMRI?



# BOLD fMRI

Active State - Rest State = FI

More

Oxygenated/Deoxygenated  
Blood

SO

Stronger Signal

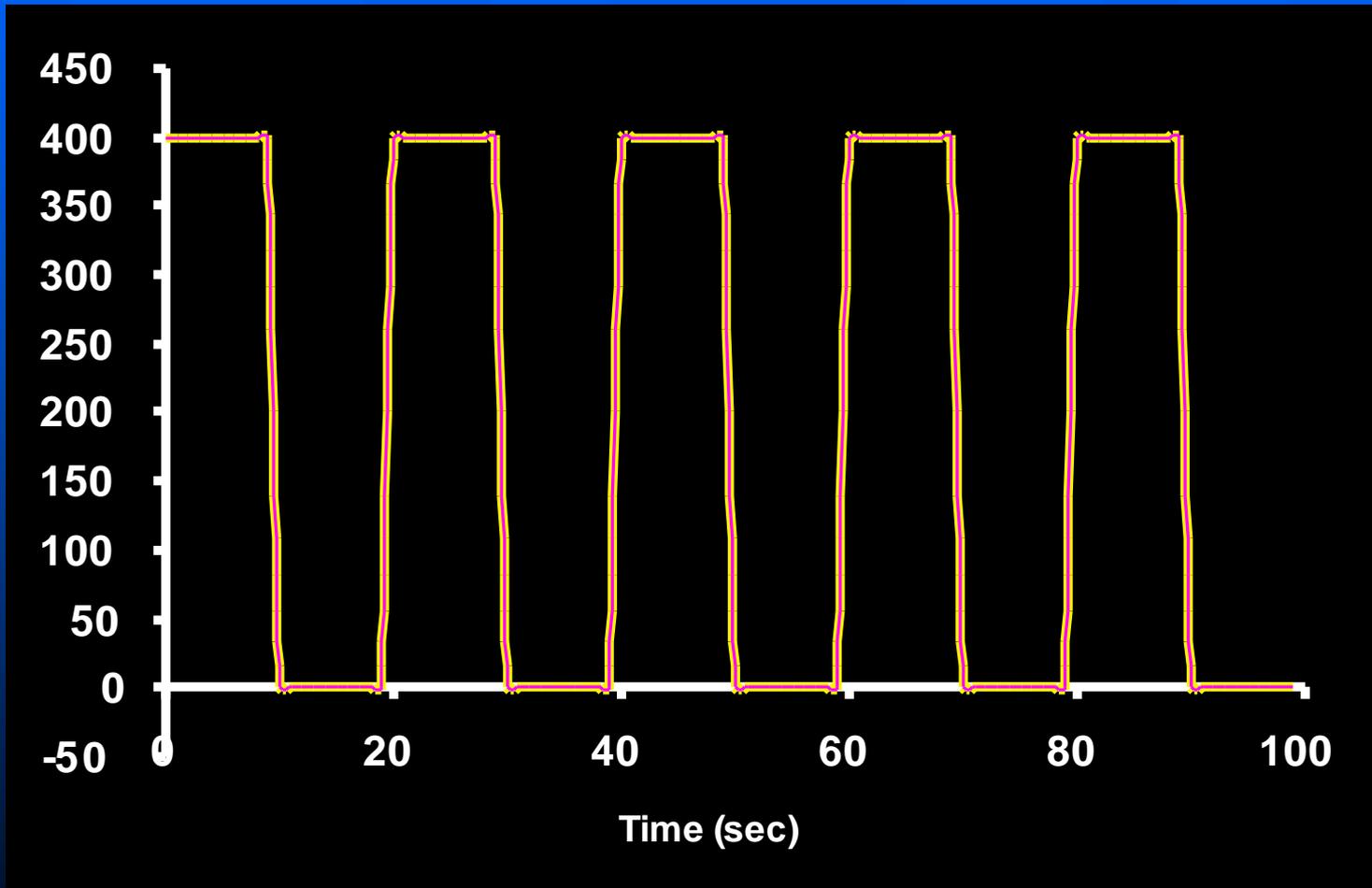
Less

Oxygenated/Deoxygenated  
Blood

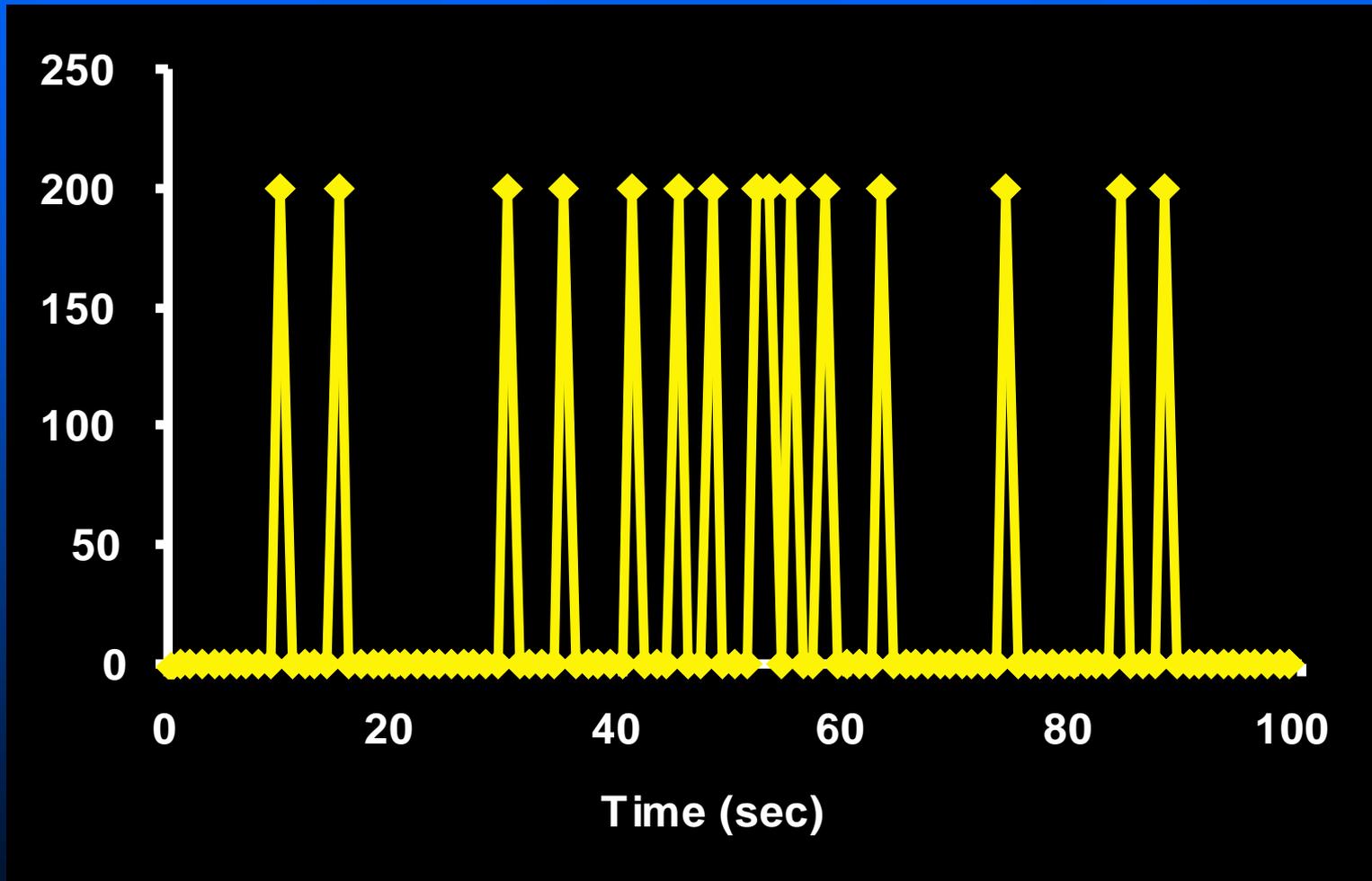
SO

Weaker Signal

# fMRI Data Acquisition Block Design



# fMRI Data Acquisition: Event Design



# Methods

## *Subjects:*

Typical Developing (TD) Controls n=21

ARND n=16

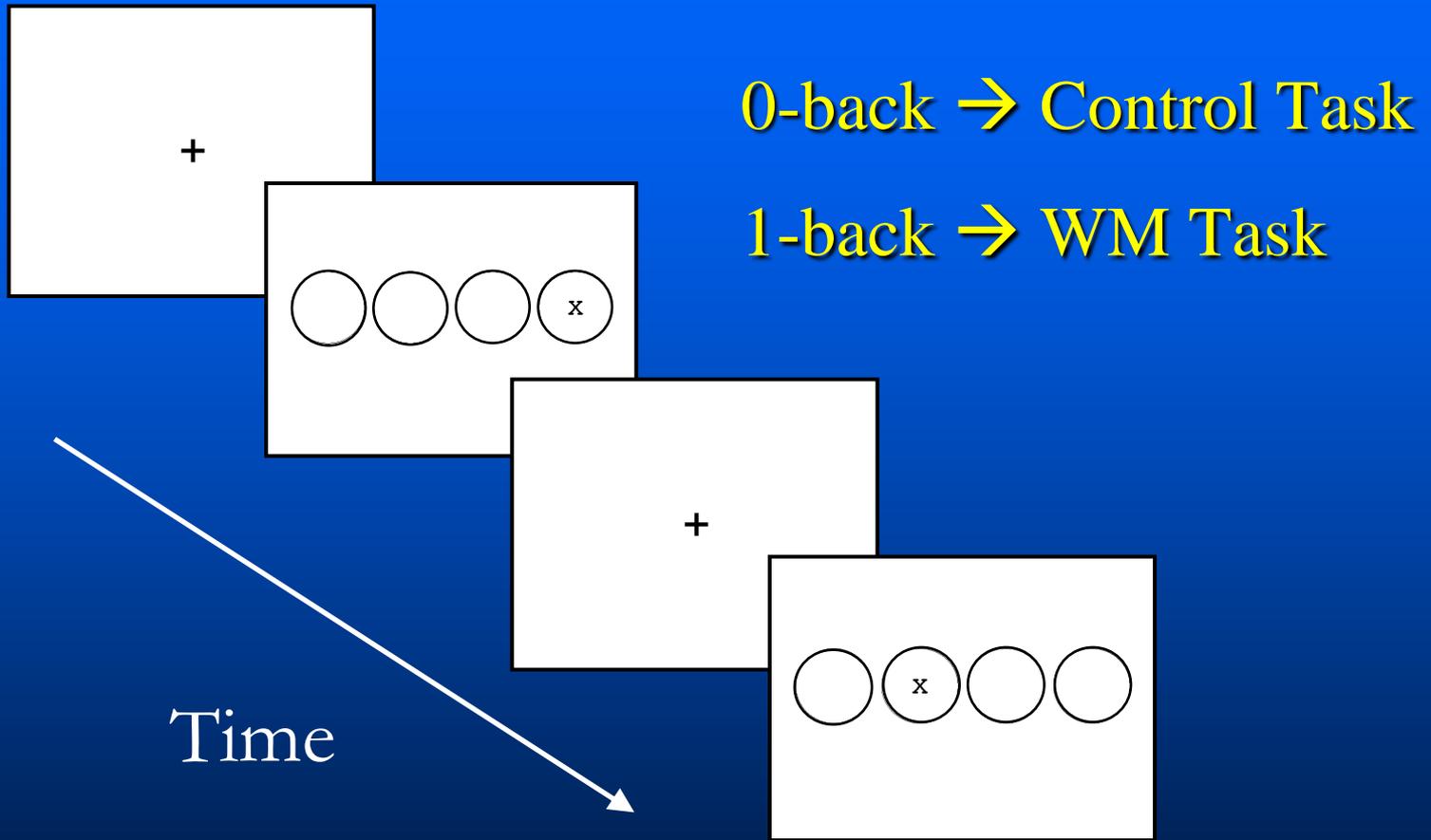
ADHD n=18

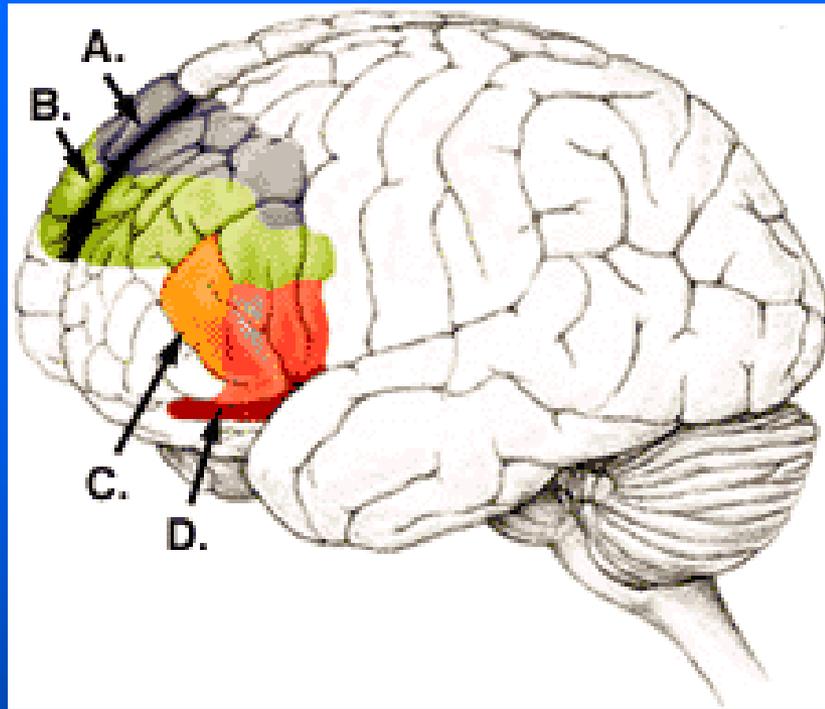
## *Event-Related fMRI*

3 Tesla Siemen's Tim Trio

- GE-EPI : TE=40 ms, TR=2 s, FOV=24cm, matrix=64x64, 28 slices, 5 mm thick parallel to anterior-posterior commissure line.
- T1-weighted images and 3D MP RAGE anatomicals

# WM Tasks

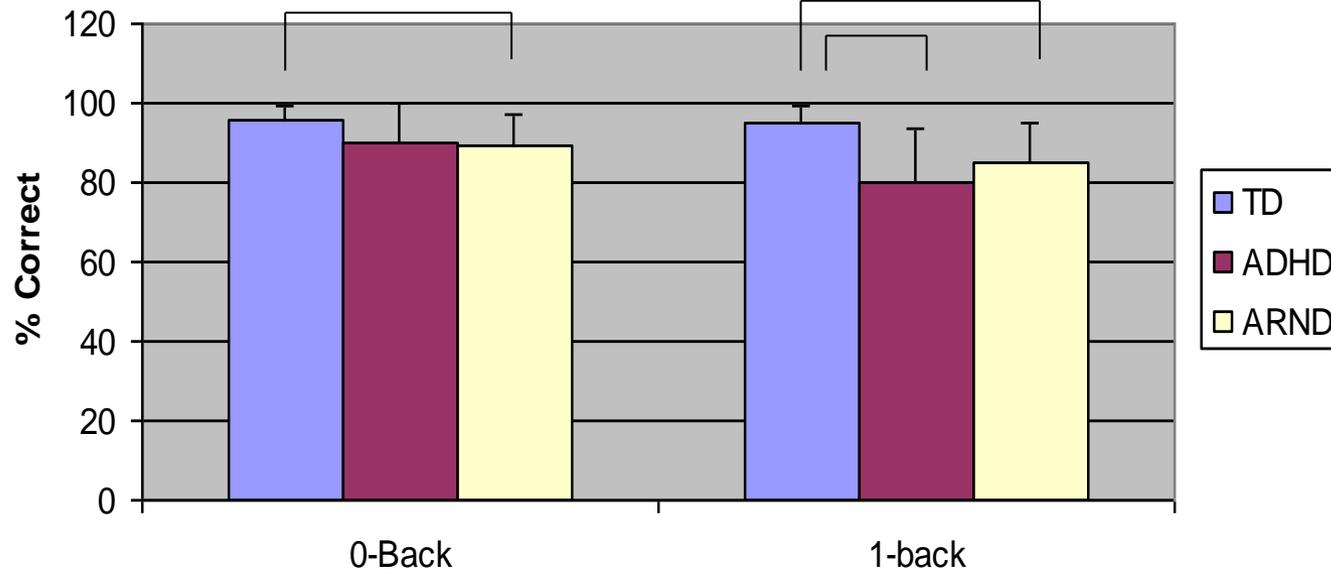




## HUMAN BRAIN: PREFRONTAL CORTEX

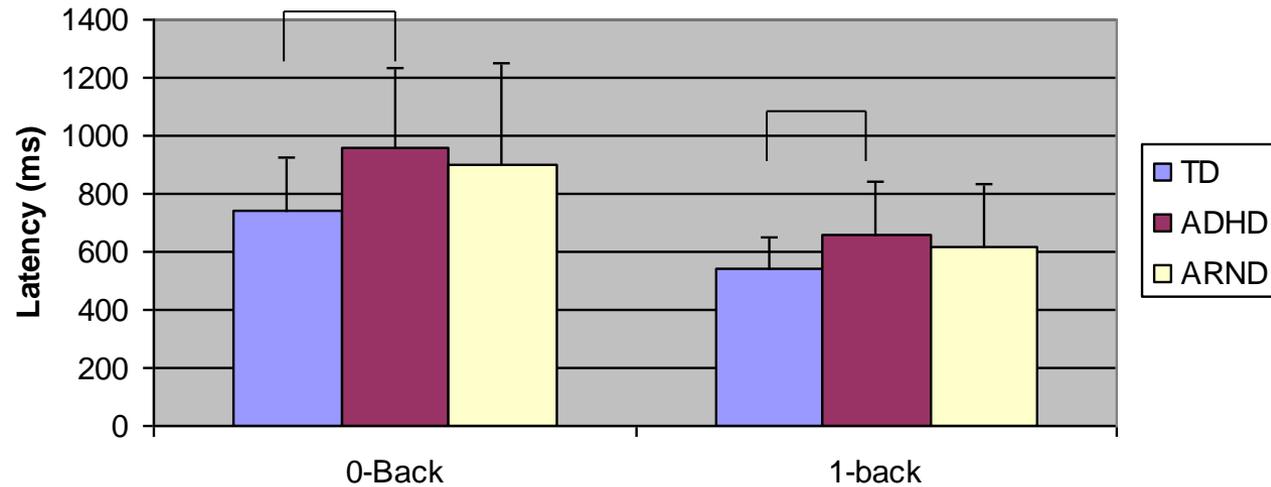
- A. Spatial working memory
- B. Spatial working memory, self-ordered tasks
- C. Spatial, object and verbal working memory, self-ordered tasks, analytic reasoning
- D. Object working memory, analytic reasoning

## 0-Back and 1-Back Tasks



$p < 0.05$   
 $p < 0.01$

## 0-Back and 1-Back Response Latency

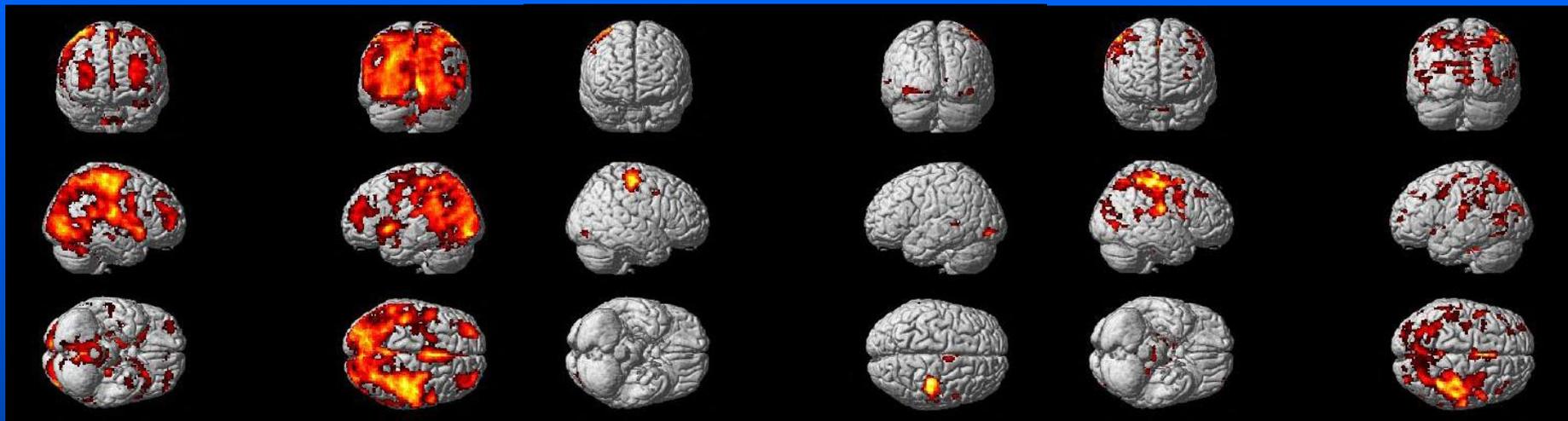


# WM task (1back and 0back)

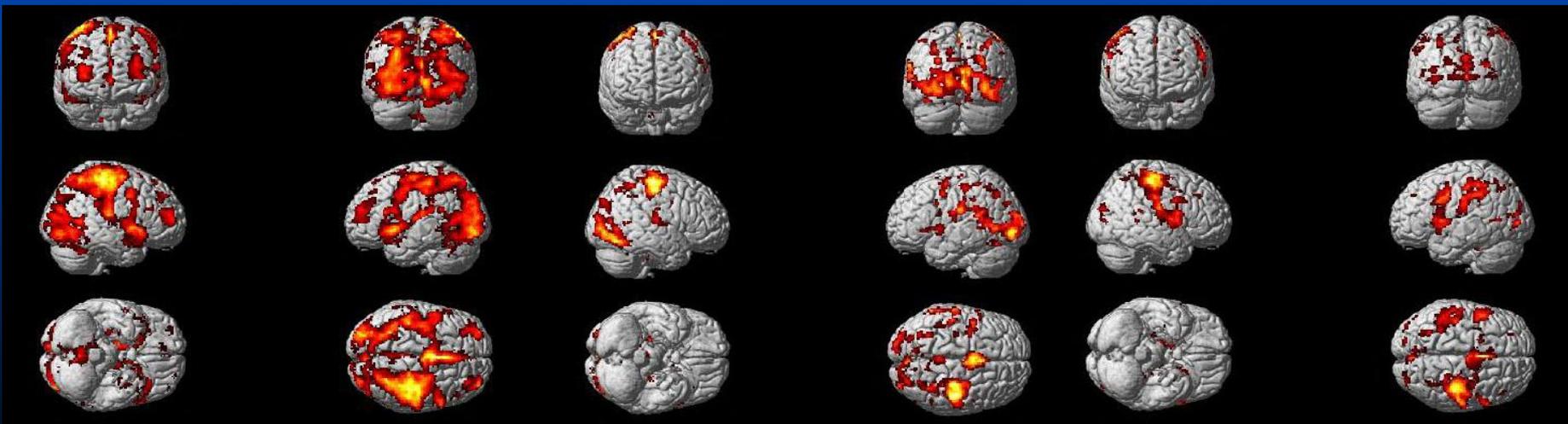
TD (N=21)

ADHD (N=18)

ARND (N=16)



Rendered images showing activity during the 1-back task at a level of  $p < 0.001$ .



Rendered images showing activity during the 0-back task at a level of  $p < 0.001$ .

# WM task (1-0 back)



TD (N=21)

ADHD (N=18)

ARND (N=16)

Parietal, Occipital,  
Cingulate

No activity

Frontal, Parietal

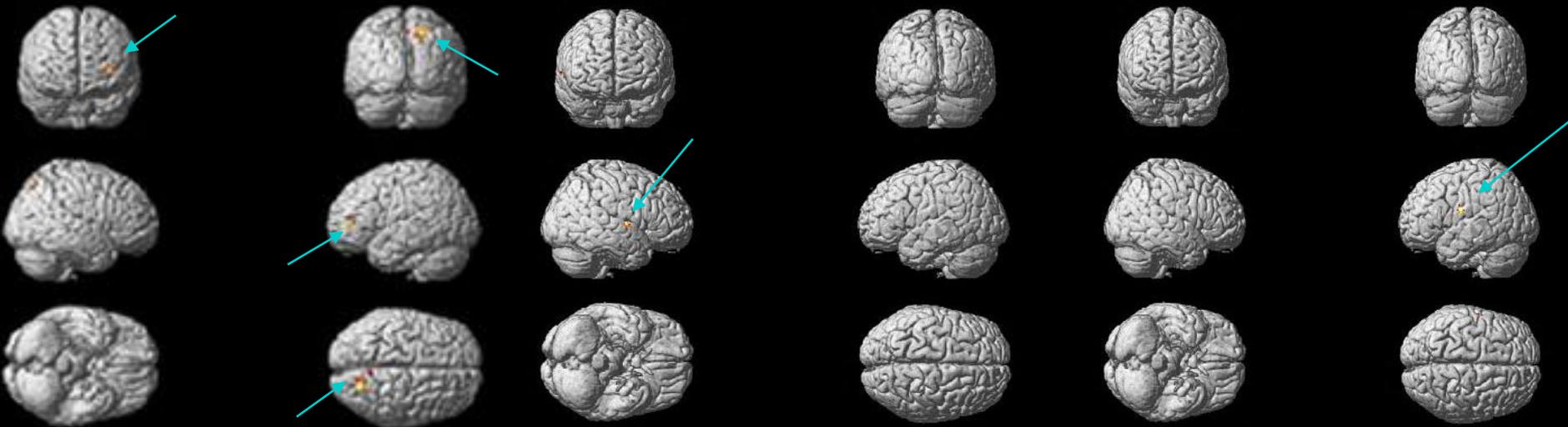
Rendered images showing activity during the subtractive contrast (1-back minus 0-back) at a level of  $p < 0.01$  cluster threshold = 10 (FWE  $< 0.035$ ).

# WM TASK

**ARND > ADHD**

**TD > ARND**

**TD > ADHD**



Frontal & Parietal

Temporal

Parietal & Occipital

t-test:  $p < 0.01$

**ANOVA – significant at  $p < 0.01$  and cluster threshold of 10; FWE $<0.035$**

# Conclusions from WM task

## 1-0 back WM task

- Frontal, parietal and occipital activity in TD consistent with performance of visual WM tasks (Malisza et al. 2005; Norman et al 2009)
- More frontal activity in children with FASD than TD consistent with previous studies (Malisza et al. 2005; Spadoni et al 2009)
- This difference extends to comparison with children with ADHD who have less frontal activity (as well as parietal activity) than ARND

Malisza, K.L. et al. 2005. *Pediatr.Res.*, 58, (6) 1150-1157.

Norman, A.L., et al. 2009. *Dev.Disabil.Res.Rev.*, 15, (3) 209-217.

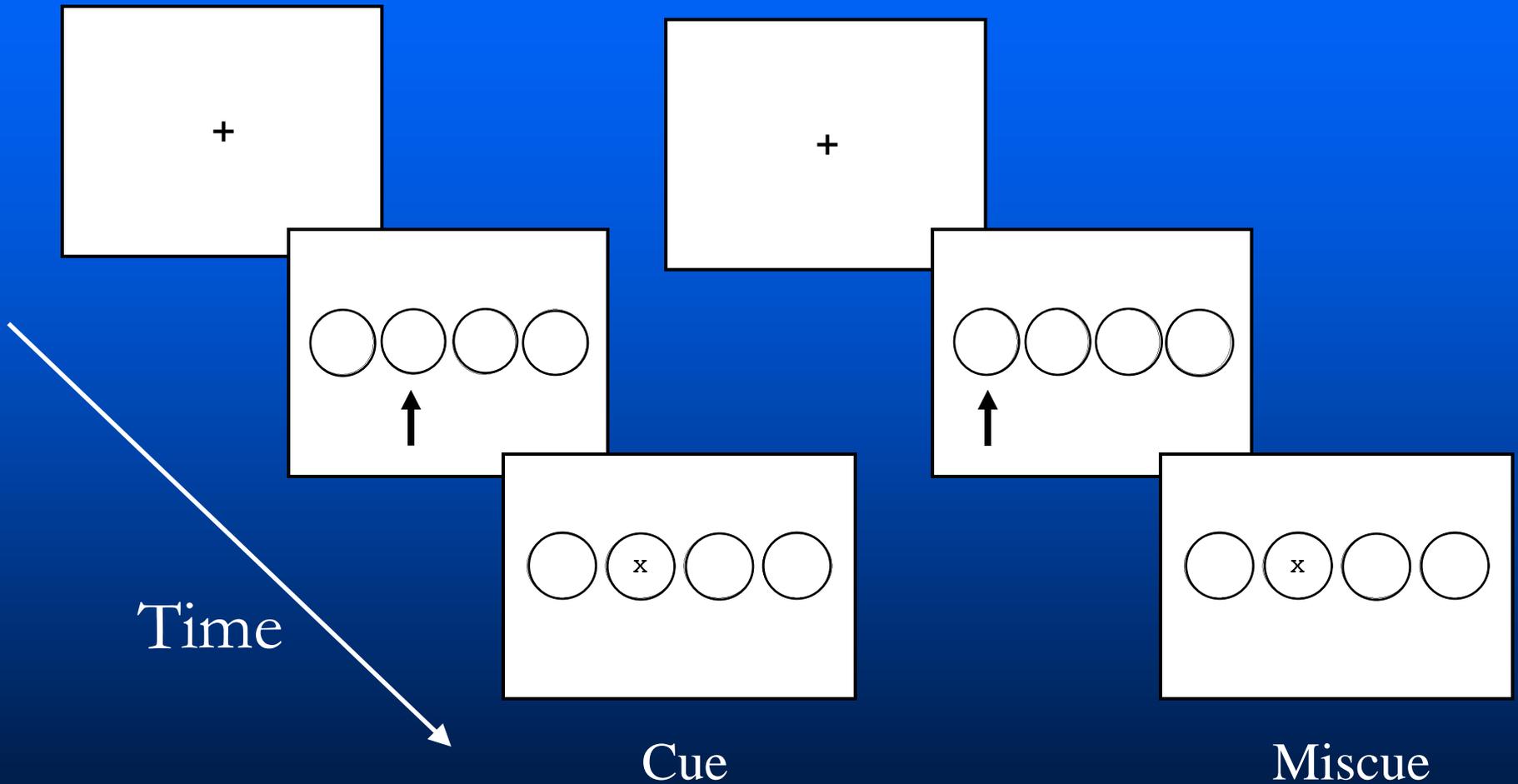
Spadoni, A.D., et al. 2009. *Alcohol Clin Exp.Res.*, 33, (12) 2067-2076.

# Conclusions from WM task

## 1-0 back WM task

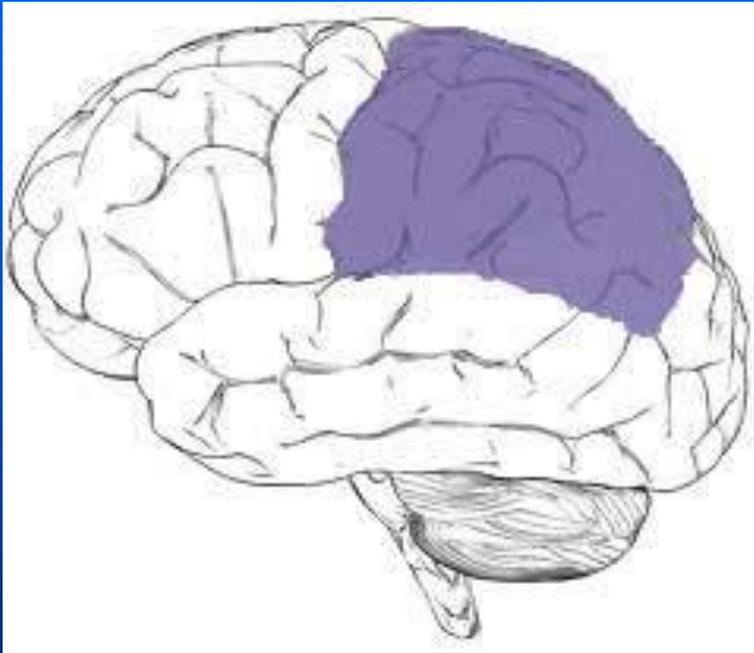
- No cingulate activity in ARND and ADHD may reflect cortical dysfunction related to effort in the control of attention
- No inferior parietal in ADHD group may reflect diminished capacity to maintain spatial location information in WM

# Attention Task – Spatial Cueing



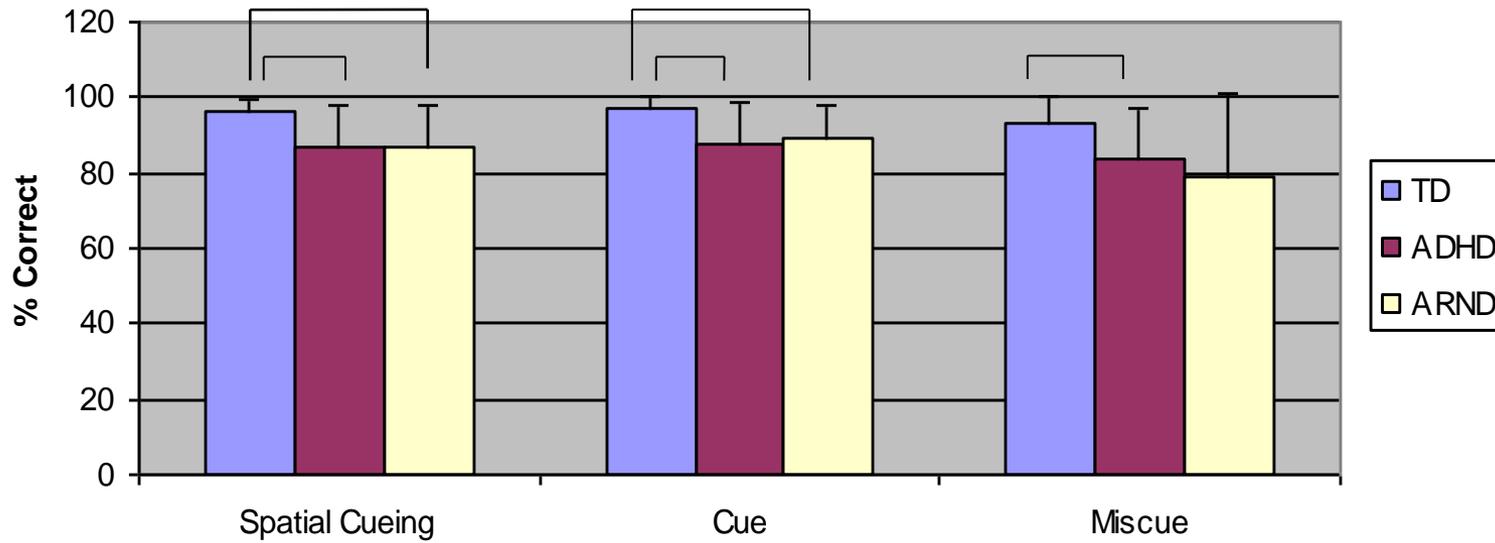
Task: Button press at the location of the “x”

# Attention Tasks

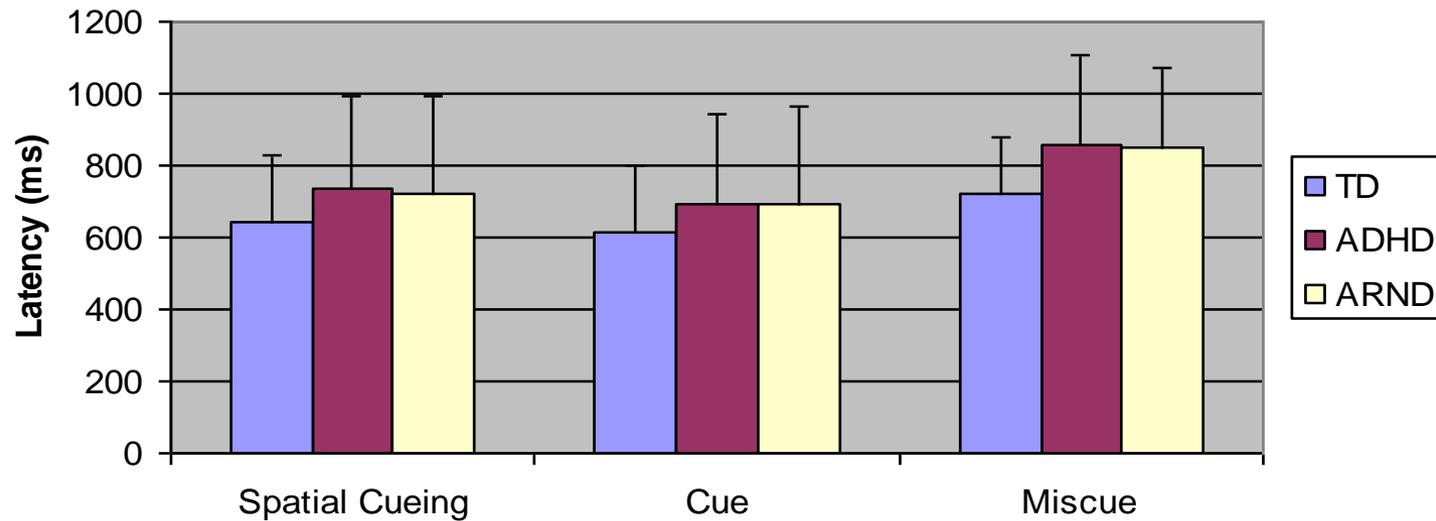


- Spatial information
- Visual perception
- Shifting attention

## Spatial Cueing



## Spatial Cueing Response Latency

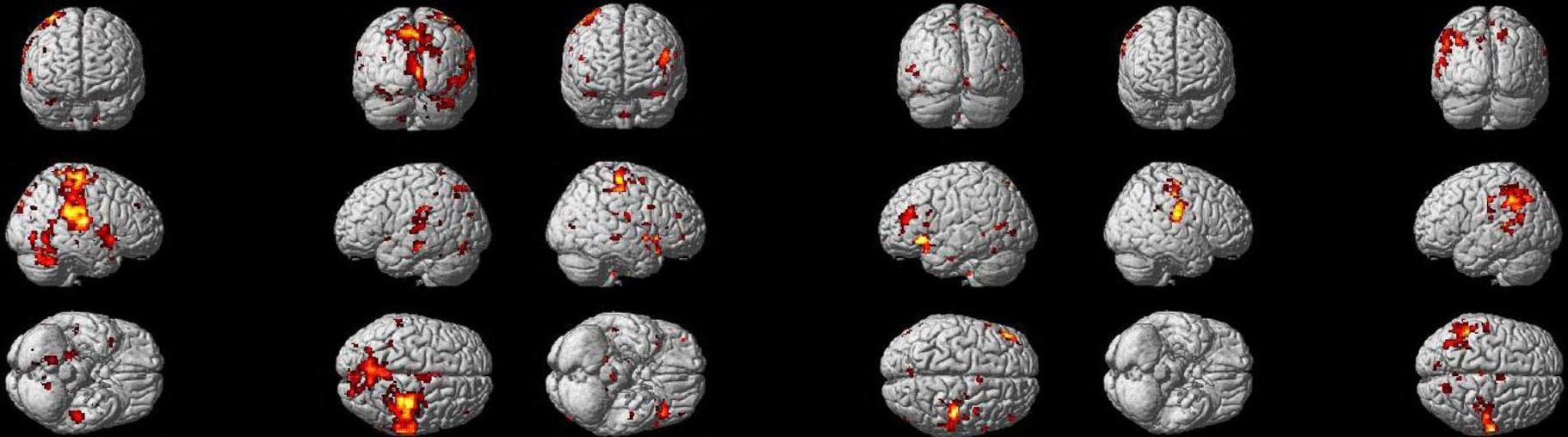


$p < 0.05$

$p < 0.01$

# Attention Task – Spatial Cueing

Cue + Miscue - 0back



TD  
(N=21)

ADHD  
(N=18)

ARND  
(N=16)

Rendered images showing activity during the cue+miscue-0back task at  $p < 0.01$  cluster threshold = 10 (FWE  $< 0.035$ ).

# Attention Task – Spatial Cueing

## Cue + Miscue - 0back

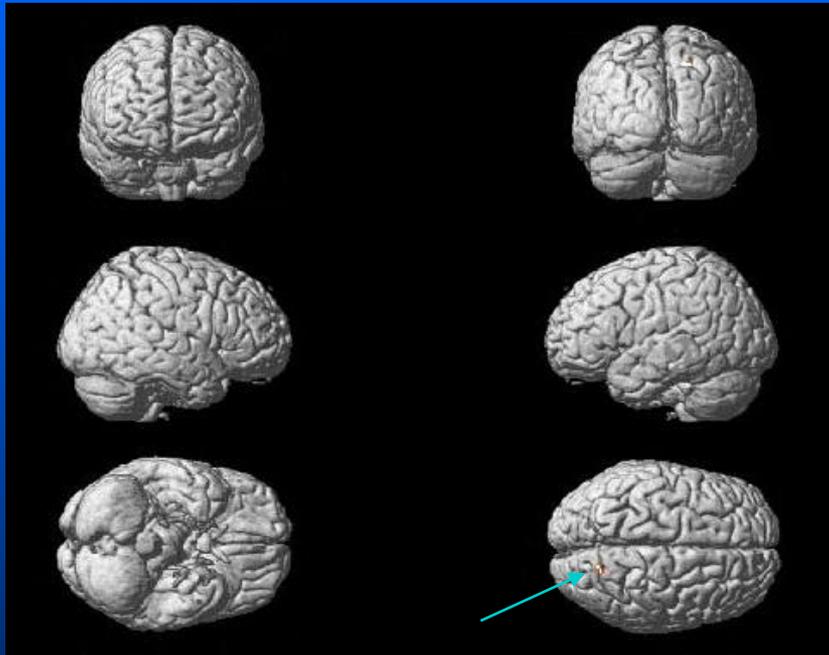
Brain Region	TD (n = 21)		ARND (n =16)		ADHD (n = 18)	
	Left	Right	Left	Right	Left	Right
Insula	13	-	40	13	13	13
Caudate	-	-	-	-	-	+
Putamen	+	-	-	-	-	+
Substantia Nigra	+	-	-	-	-	+
Globus Pallidus	+	-	-	-	-	-
Subthal. Nucl.	-	+	-	-	-	-
Amygdala	+	-	-	-	-	+
Thalamus	++	-	-	-	-	+
Parahippocampus	35	-	-	19, 27	34, 36	34, 37

**BOLD activation in Brodmann's areas for Cue + Miscue - 0back (p<0.01) cluster threshold =10 (FWE <0.035).**

# Spatial Cueing Task

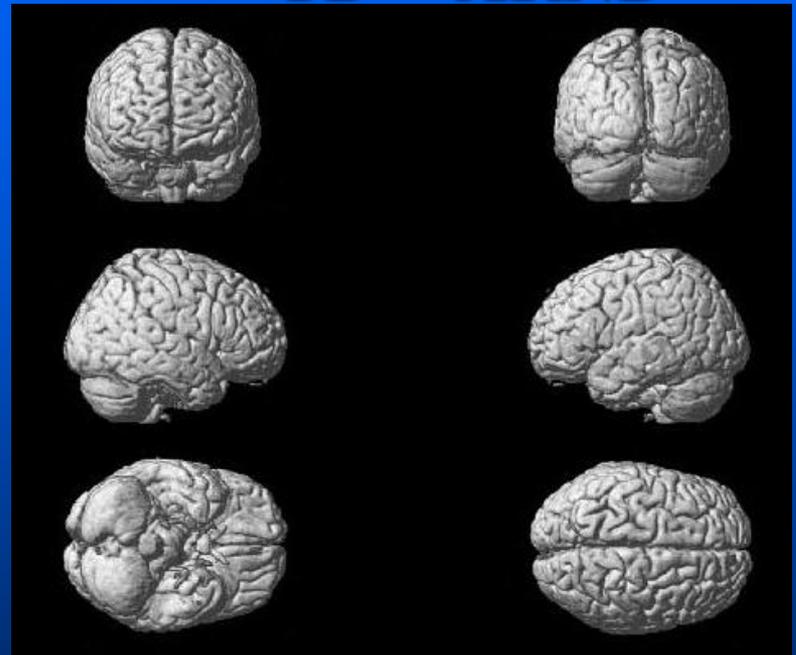
## Cue + Miscue – 0back

**ARND > ADHD**



Parietal

**TD > ARND**



Cingulate

t-test:  $p < 0.01$

**ANOVA – significant at  $p < 0.01$  and cluster threshold of 10; FWE  $< 0.035$**

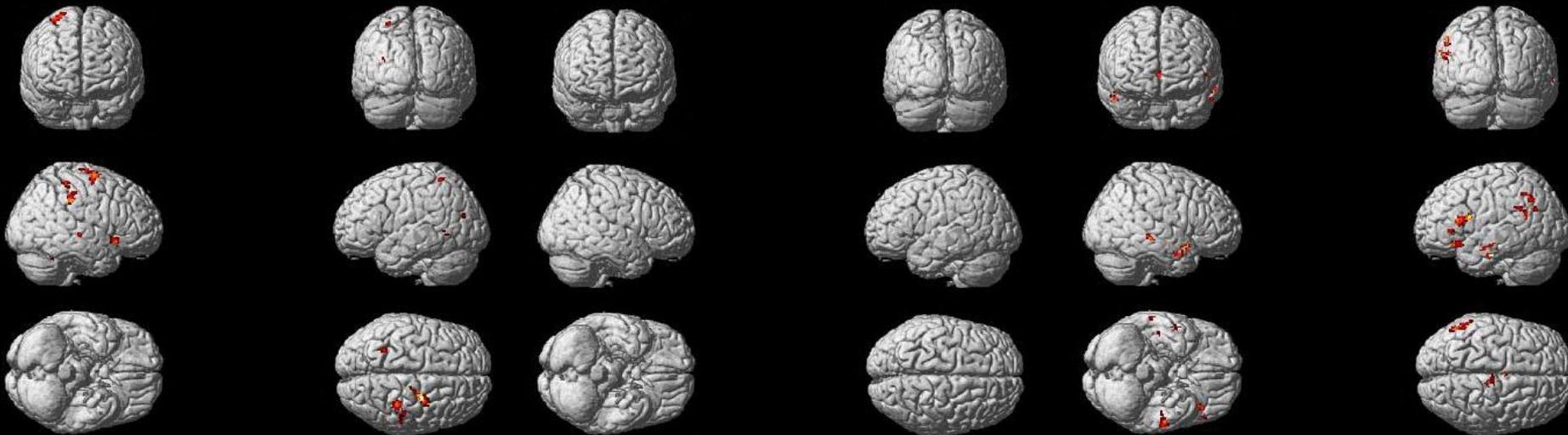
# Attention Task – Spatial Cueing

## Miscue - Cue

TD

ADHD

ARND



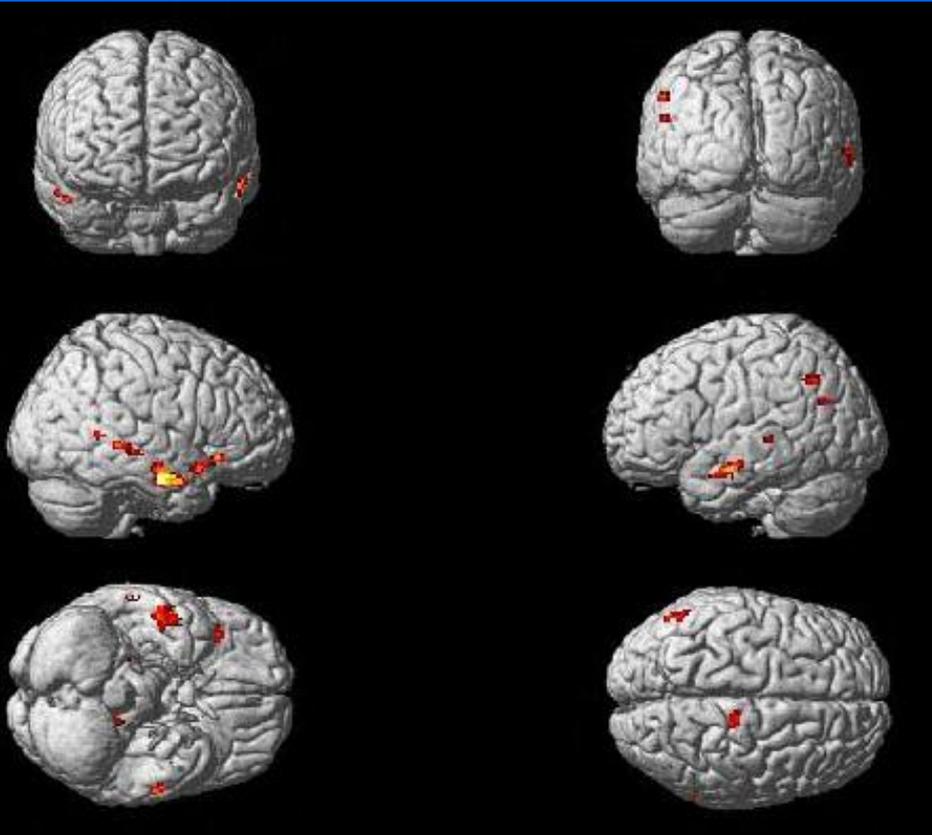
No activity

Rendered images showing activity during the cue-miscue task at  $p < 0.01$  cluster threshold = 10 (FWE  $< 0.035$ ).

# Spatial Cueing Task

Miscue - Cue

**ARND > ADHD**



Frontal, Parietal,  
Temporal, Cerebellum,  
Insula, Caudate,  
Claustrum,  
Parahippocampus

t-test:  $p < 0.01$

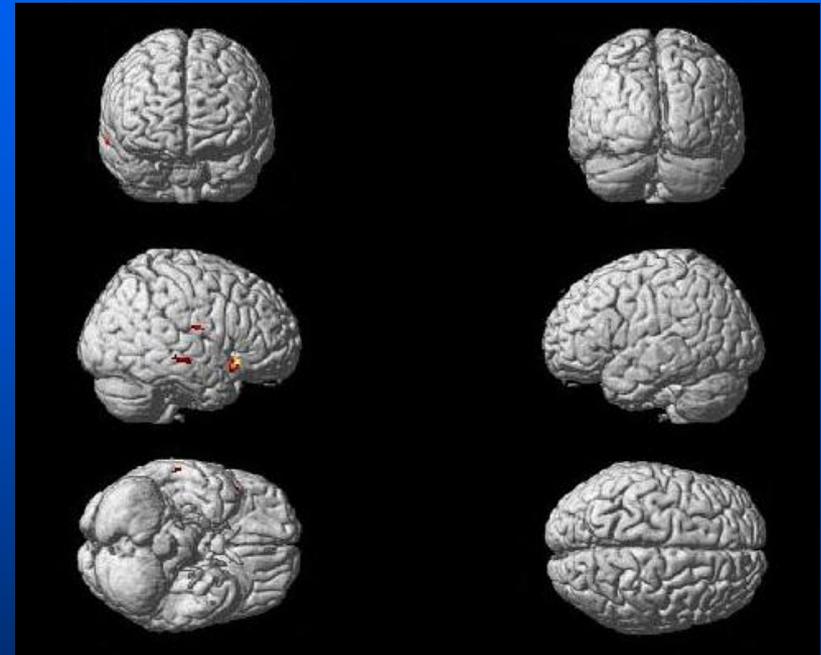
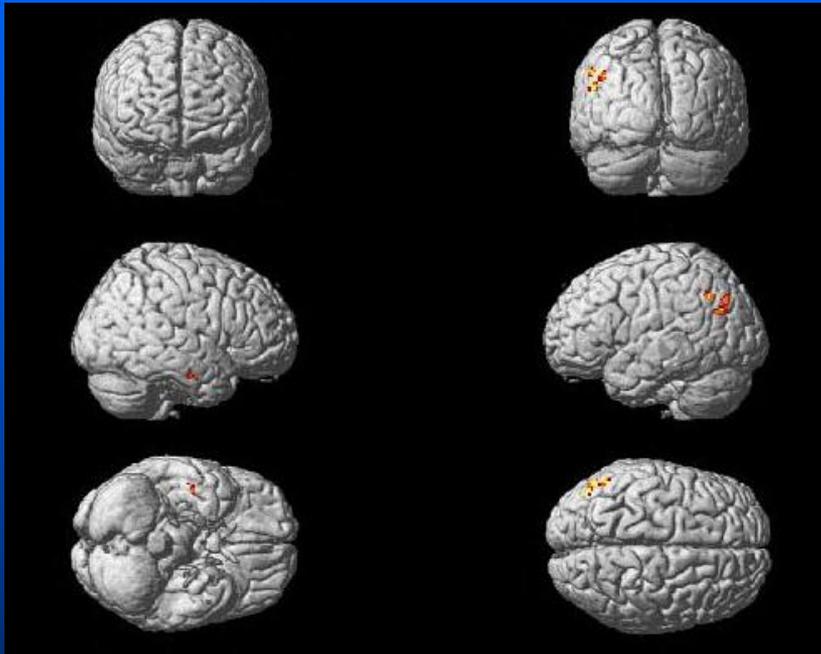
ANOVA – significant at  $p < 0.01$  and cluster threshold of 10; FWE $<0.035$

# Spatial Cueing Task

Miscue - Cue

**ARND > TD**

**TD > ADHD**



Parietal, Temporal, Caudate,  
Parahippocampus

Frontal, Parietal, Temporal,  
Cingulate, Cerebellum

t-test:  $p < 0.01$

**ANOVA – significant at  $p < 0.01$  and cluster threshold of 10; FWE $<0.035$**

# Conclusions-Attention-Spatial Cueing

Cue + Miscue - 0back  
Attention and Shifting Attention

Significant Group Differences:

ARND > ADHD in parietal region (attention)

TD > ARND in cingulate (attention)

# Conclusions-Attention-Spatial Cueing

Miscue - Cue

Shifting Attention

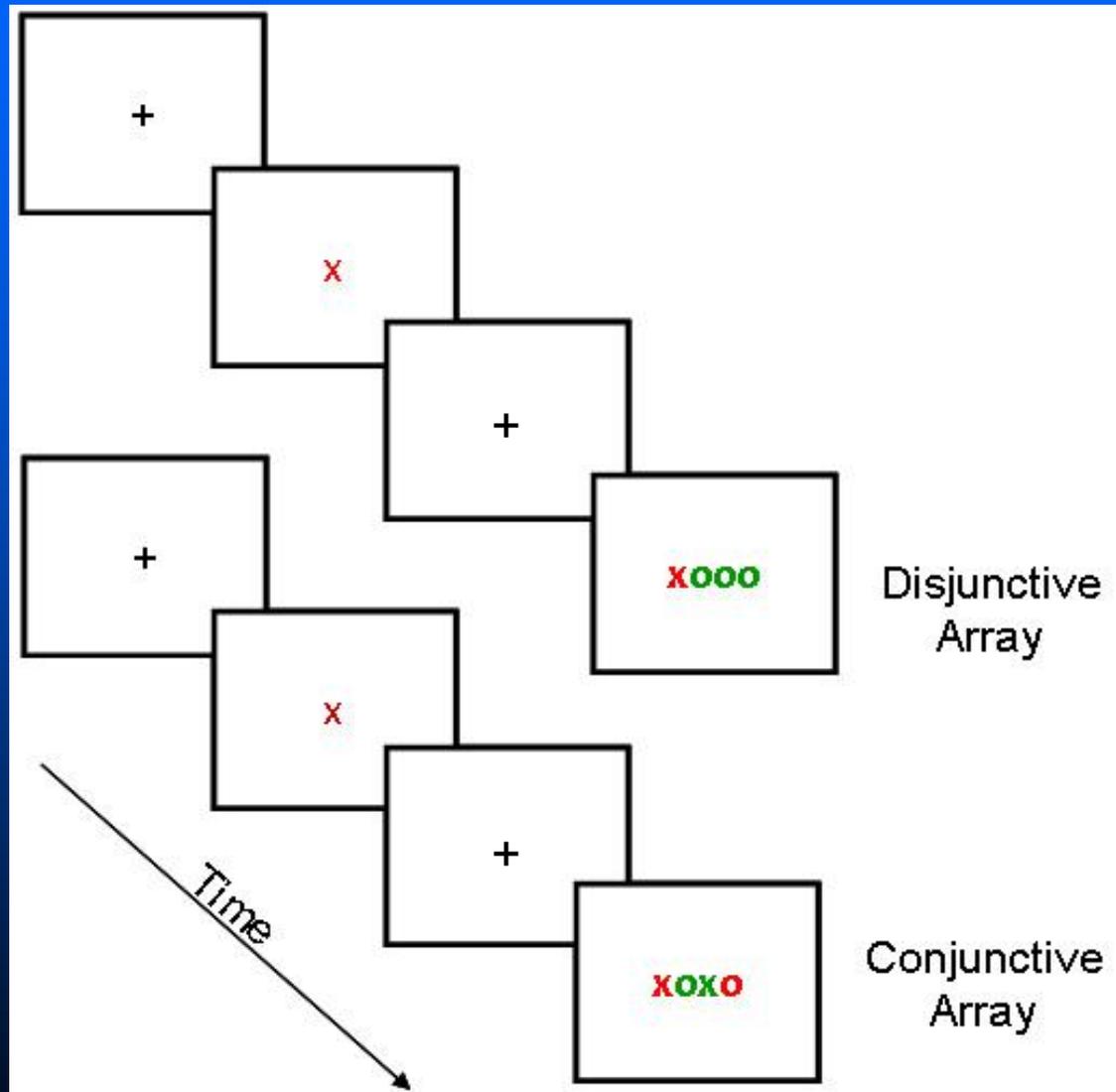
Significant Group Differences:

- ARND Greater activity than ADHD and TD in **Parietal**, Temporal, Caudate, Parahippocampal gyrus
- Greater ARND than ADHD in the Frontal (reorienting, executive control), Cerebellum, Insula, Claustrum
- TD > ADHD in Frontal, **Parietal**, Temporal, Cingulate, Cerebellum

# Attention – Spatial Cueing

- ADHD less anterior cingulate (alerting), frontal (reorienting, exec control), than TD
- Functional abnormalities in putamen in ADHD
  - less BOLD (especially in miscue) (Konrad et al. Biol Psychiatry 2006;59:643)
- FASD - lower accuracy in visual focus attention
  - For shift attention – more accurate than ADHD (i.e. no diff compared to TD and ADHD signif less accurate than TD)
  - No problems disengaging and reengaging attention (Mattson et al. 2006 Neuropsychology 20; 361)

# Attention Task – Conjunction Task



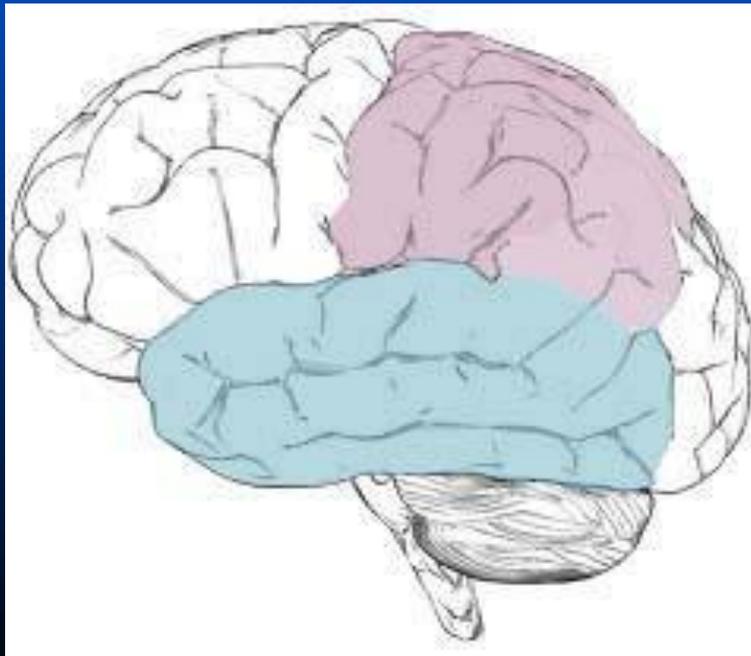
# Conjunction

## Parietal - Attention

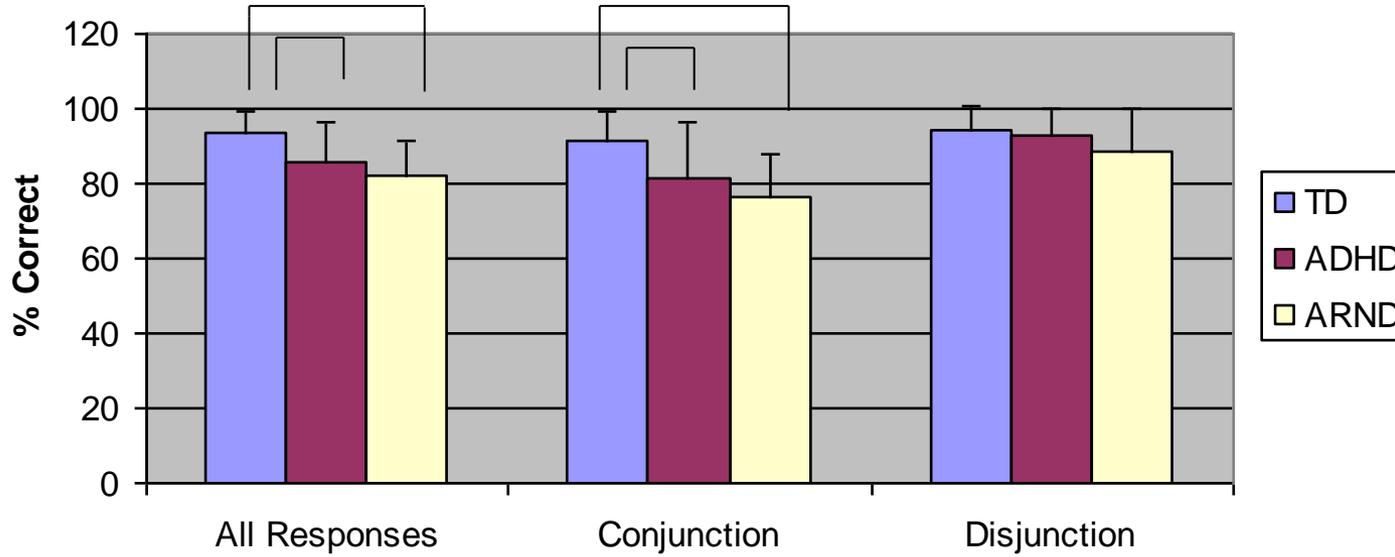
- Sensation and perception
- Integrates sensory input
- Spatial information
- Shifting attention

## Temporal - Attention

- Selective attention
- Visual perception
- Organization of sensory input
- Encoding features

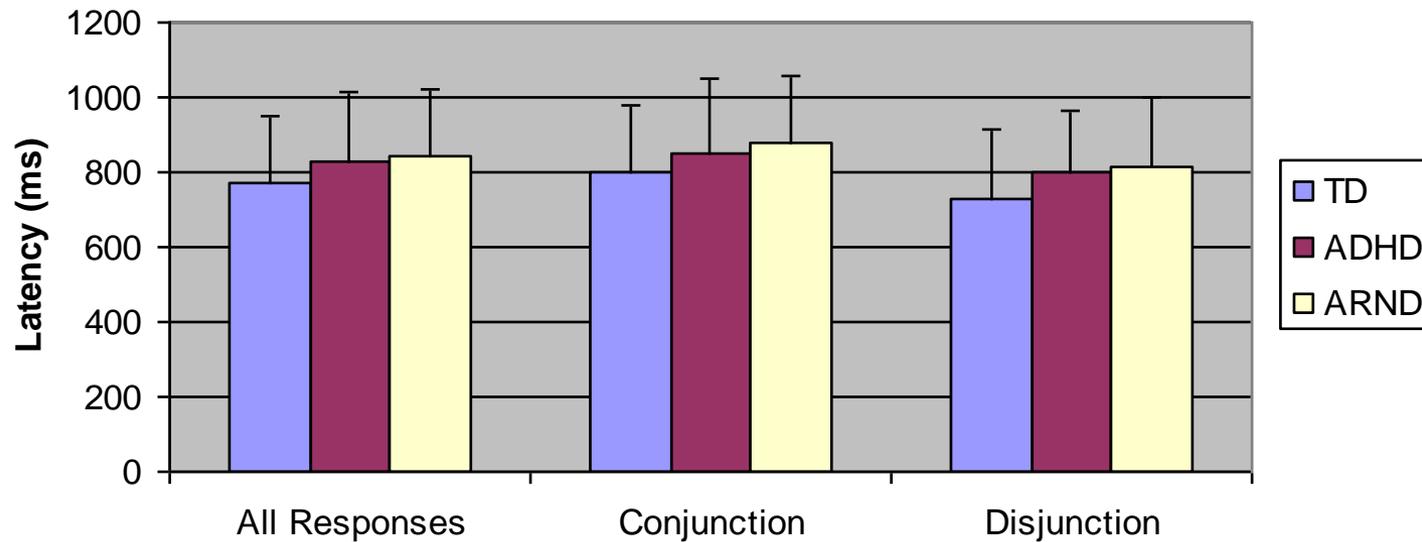


### Conjunction

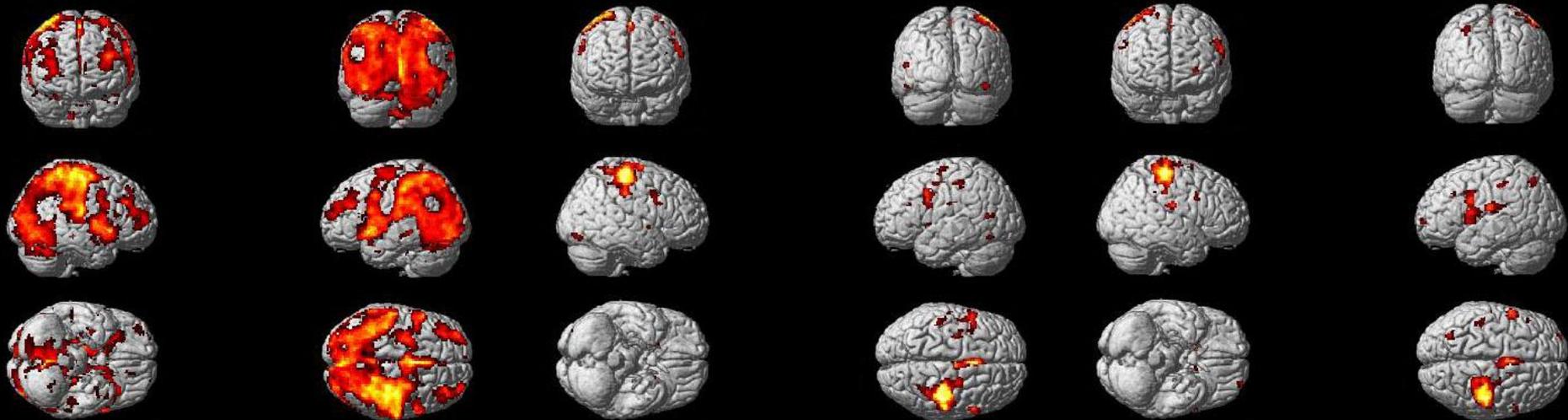


$p < 0.05$   
 $p < 0.01$

### Conjunction Response Latency



# Attention Task Conjunction



TD (N=21)

ADHD (N=17)

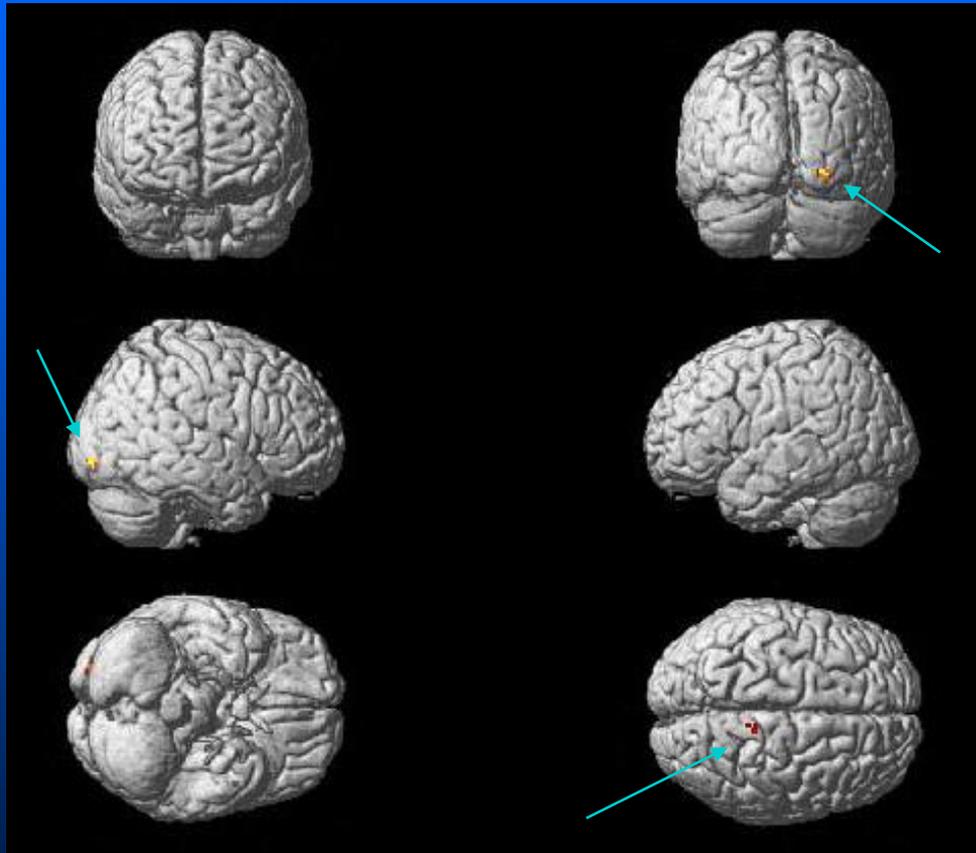
ARND (N=14)

No temporal,  
occipital

Rendered images showing activity during the conjunction task at  $p < 0.001$  and cluster threshold 10.

# Attention Task Conjunction

**ARND < ADHD**



Frontal/Parietal,  
Occipital

t-test:  $p < 0.01$

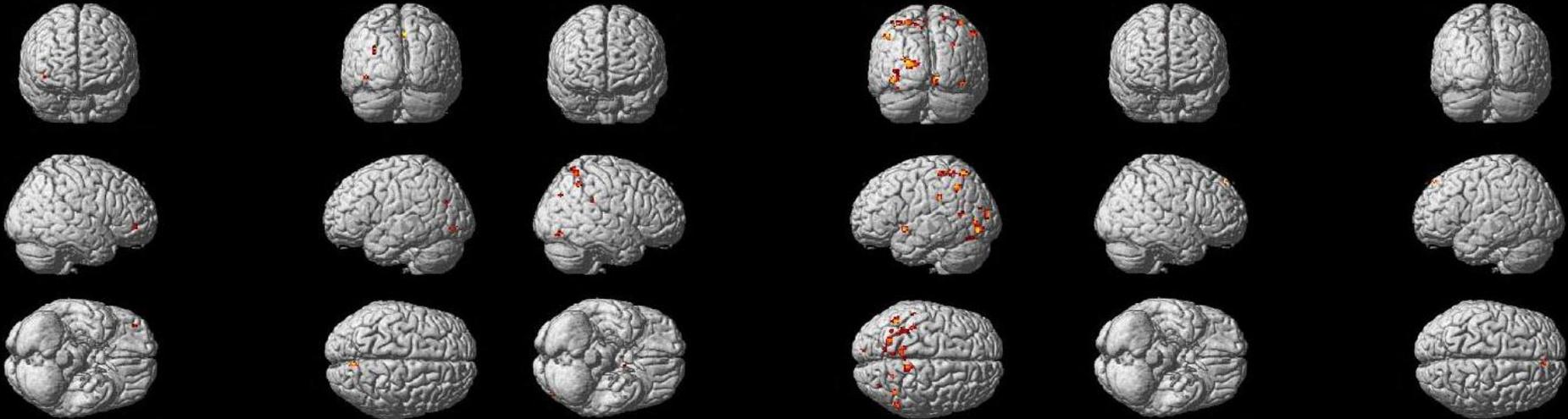
ANOVA – significant at  $p < 0.01$  cluster threshold = 10 (FWE  $< 0.035$ ).

# Attention Task Conjunction

**TD > ADHD**

**TD > ARND**

**TD < ARND**



Frontal,  
Parietal,  
Occipital

Frontal,  
Parietal, Temporal,  
Occipital, Cingulate

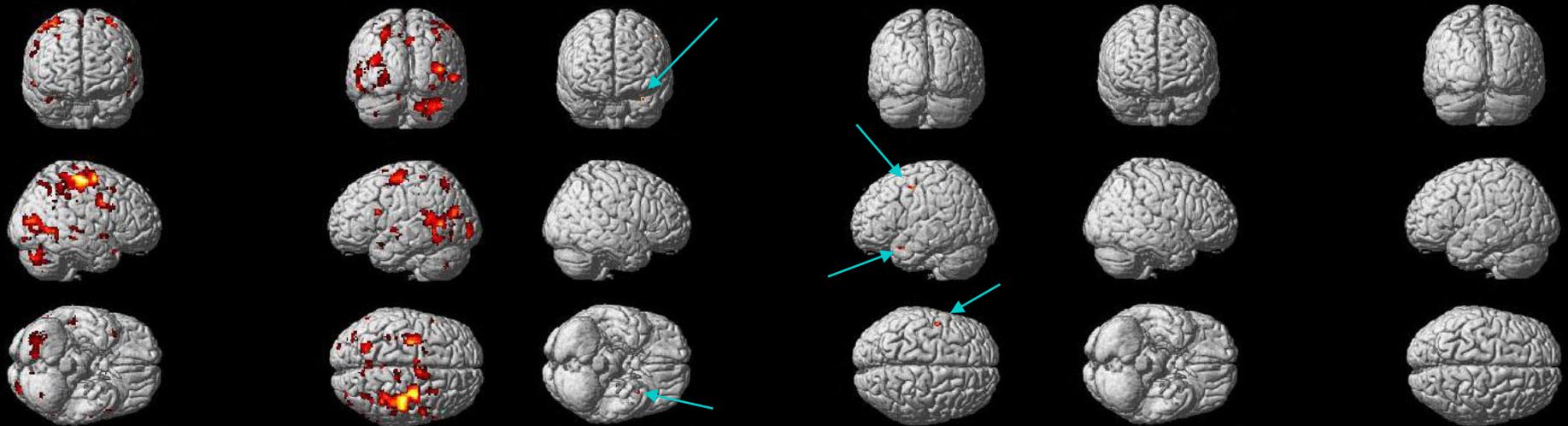
Frontal

t-test:  $p < 0.01$

ANOVA – significant at  $p < 0.01$  cluster threshold = 10 (FWE  $< 0.035$ ).

# Attention Task

## Conjunction - Disjunction



TD (N=21)

ADHD (N=17)

ARND (N=14)

Frontal, temporal

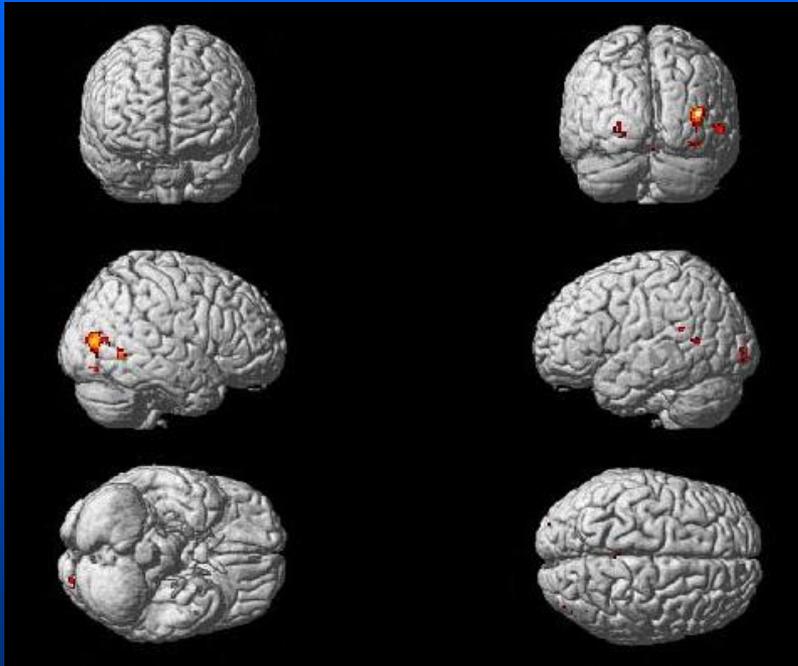
No activity

Rendered images showing activity in the subtractive contrast (conjunction minus disjunction) at  $p < 0.01$  cluster threshold = 10 (FWE  $< 0.035$ ).

# Attention Task

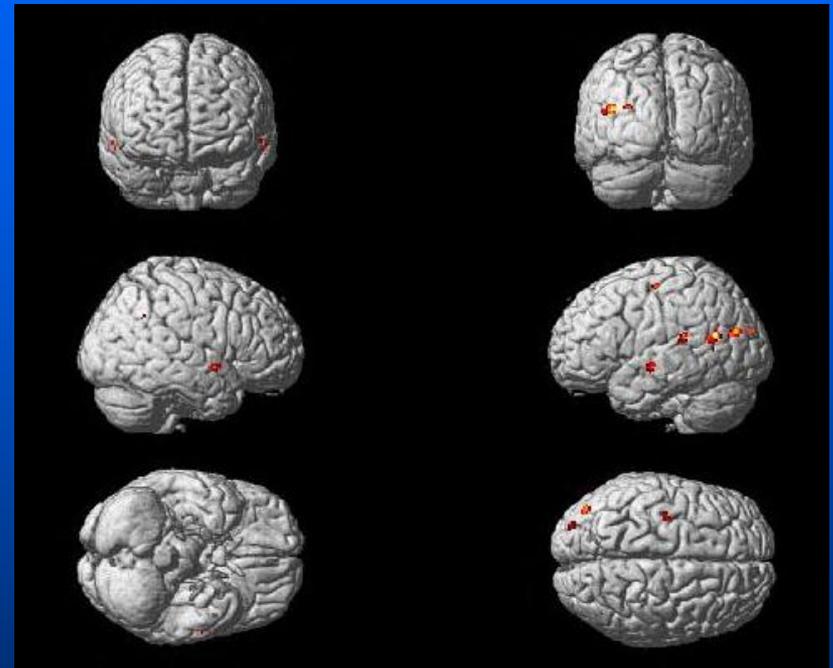
## Conjunction - Disjunction

**TD > ARND**



Parietal, Temporal,  
Occipital,  
Cingulate, Cerebellum,  
Parahypocampus

**TD > ADHD**



Frontal, Parietal, Temporal,  
Occipital, Insula, Caudate,  
Parahypocampus

t-test;  $p < 0.01$

# Conclusions – Attention tasks

## Conjunction

### Significant Group Differences:

- ARND < ADHD in Frontal/Parietal and Occipital (attention)
  - More effort in ADHD to maintain attention
- TD greater activity than both ARND and ADHD in Frontal, Parietal and Occipital
- More Temporal and Cingulate in TD than ARND
  - Temporal region involved in visual pattern recognition affected in ARND and ADHD

# Conclusions – Attention tasks

## Conjunction-Disjunction

- No activity in ARND in temporal area suggests damage to ventral extrastriate pathway (visual pattern recognition)
  - May aid in discrimination of ARND from ADHD
- Thalamus involved in posterior attention systems (Posner & Petersen 1990). **All groups show activity in the thalamus during conjunction task,** but only TD group activity in (conjunction – disjunction) contrast suggests ARND and ADHD do not differentially allocate attentional effort across low-distraction and high-distraction conditions.

# Conclusions – Attention tasks

## Significant Group Differences

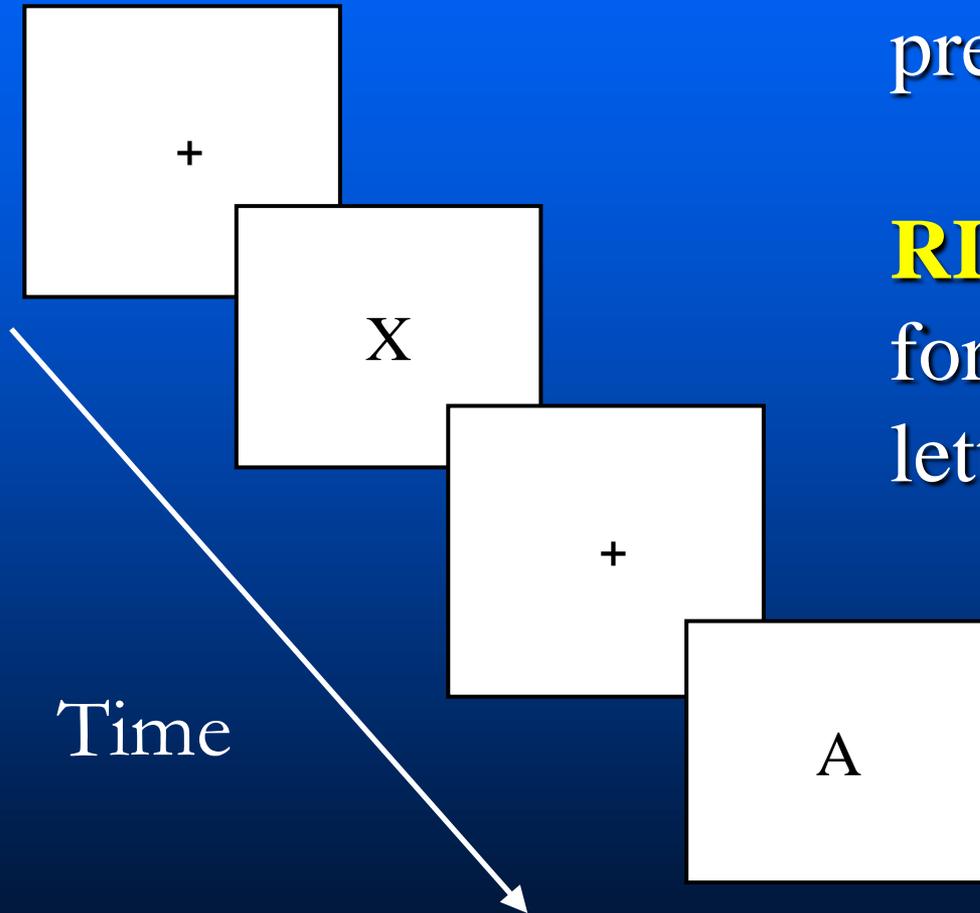
### (Conjunction-Disjunction)

- Caudate (response selection) activity in TD only following subtraction of disjunction task.
  - FASD - decreased caudate volumes (Norman et al 2009 *Dev.Disabil.Res.Rev.*, 15, (3) 209-217).
- No significant differences between ARND and ADHD
- Poorer performance in ARND on the more difficult conjunction task compared to TD
  - No difference between ARND and ADHD

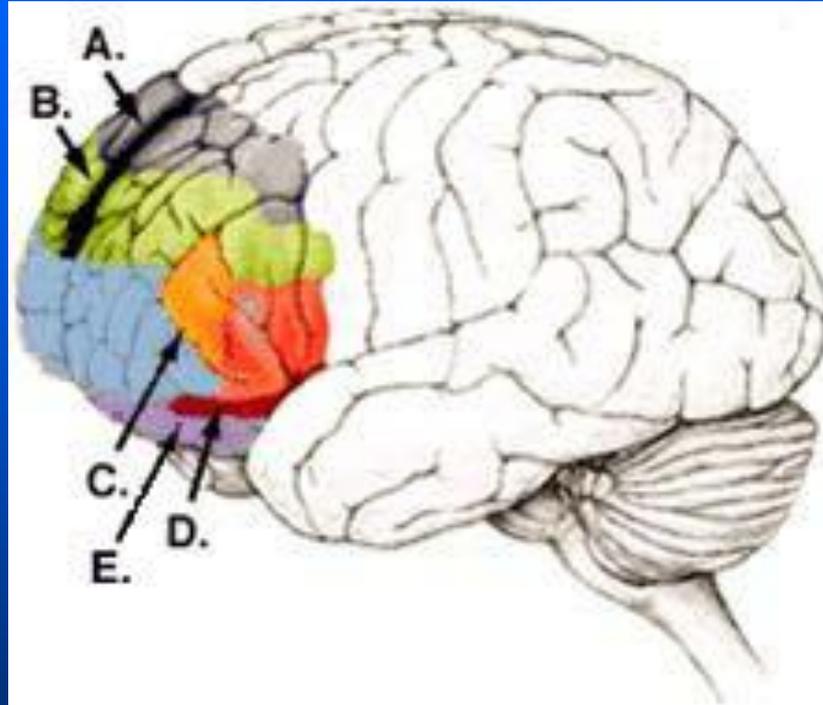
# Response Inhibition Task

**Control task** – button press for all letters

**RI task** – button press for all letters **EXCEPT** letter A (2 runs)



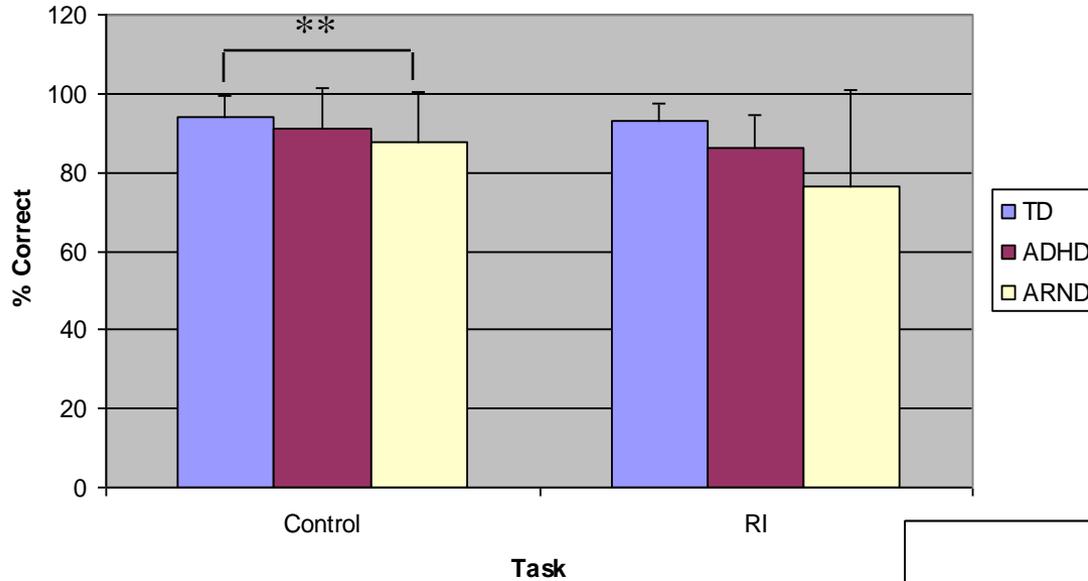
# Lobes of the Cerebral Cortex



E. **Response inhibition**, planning, decision making

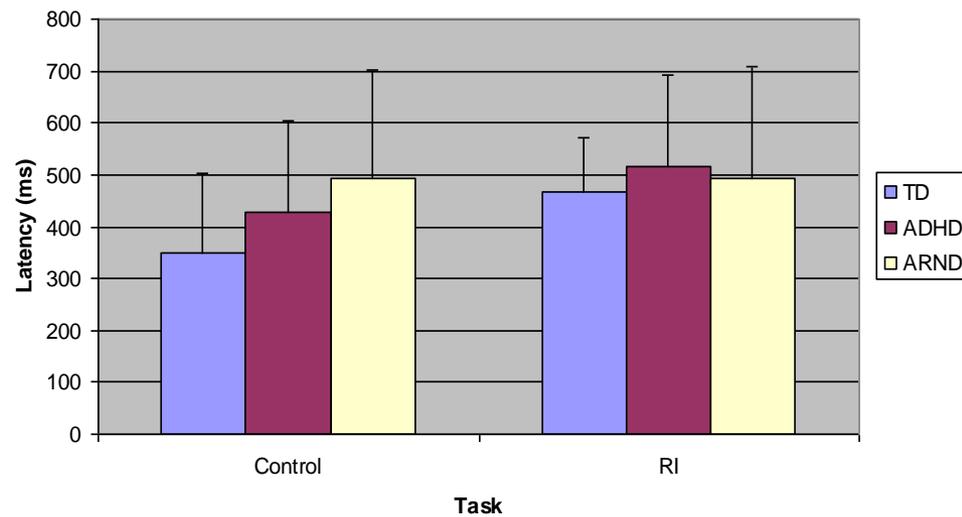
# Response Inhibition

Correct Responses RI Task

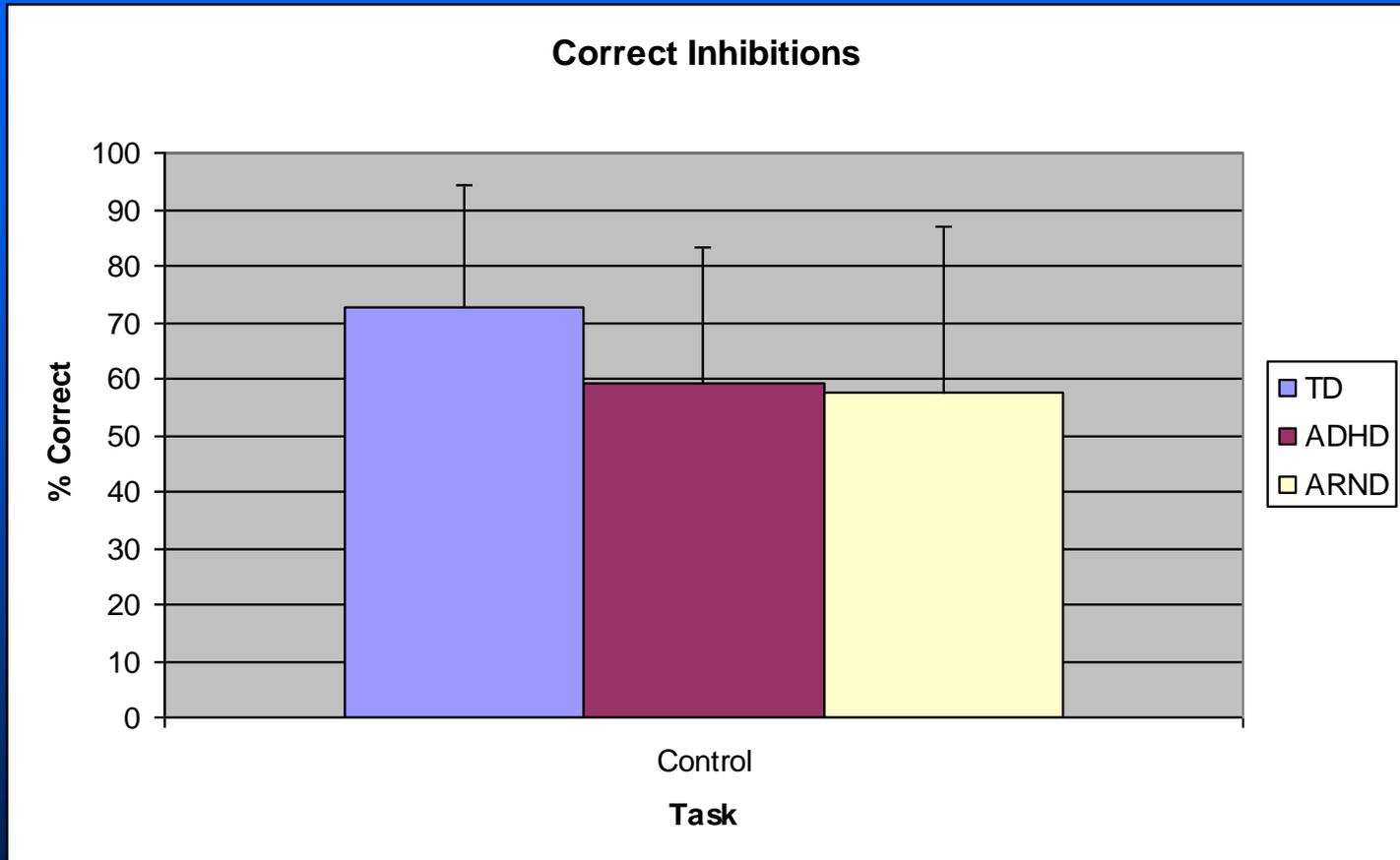


$p < 0.05$   
 $p < 0.01$

Response Latency RI task

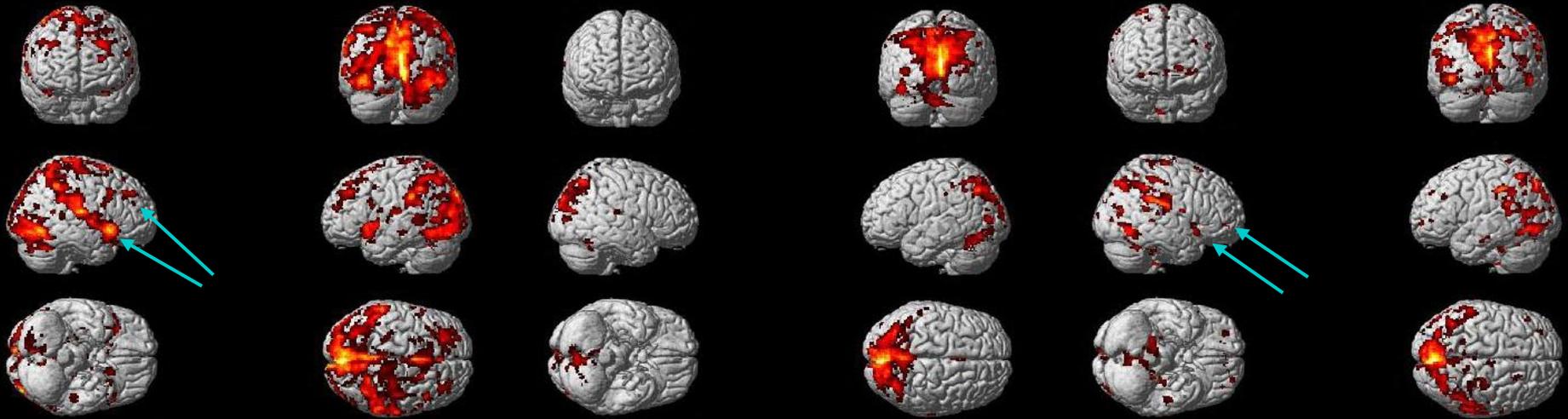


# Response Inhibition



# Response Inhibition Task

RI1+RI2 - Control



TD (N=21)

ADHD (N=17)

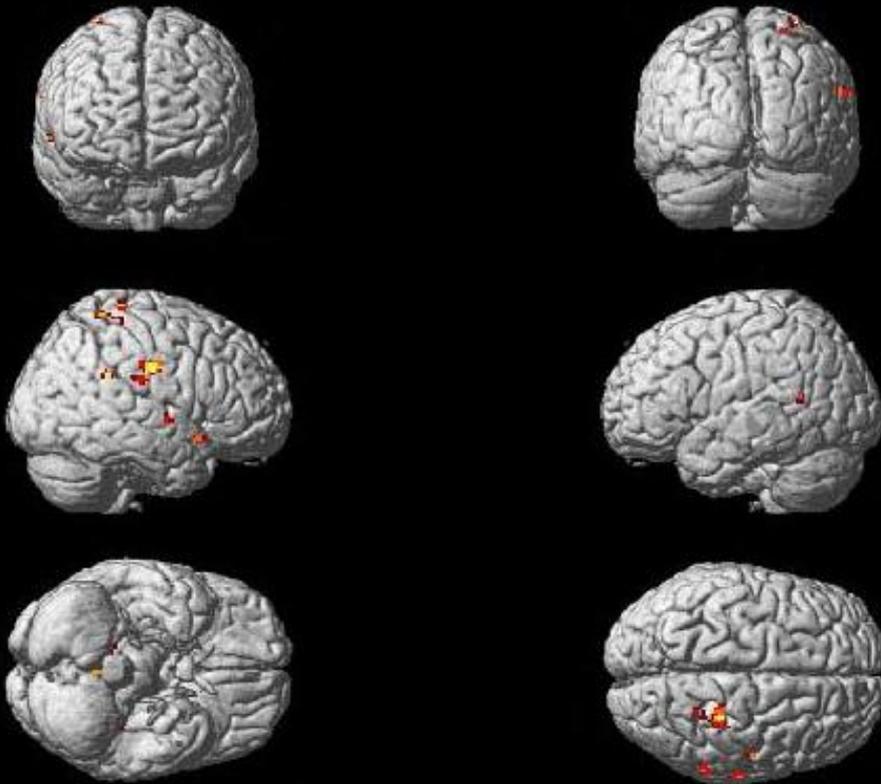
ARND (N=12)

Rendered images showing activity for subtractive contrast: RI1+RI2-control at  $p < 0.01$ .

# Response Inhibition

RI1+RI2 - Control

**ARND > ADHD**



Frontal, Parietal,  
Temporal, Occipital,  
Cerebellum, Insula,  
Clastrum,  
Thalamus,  
Hippocampus,  
Parahypocampus

t-test:  $p < 0.01$

ANOVA – significant at  $p 0.01$  and cluster threshold of 10; FWE $<0.035$

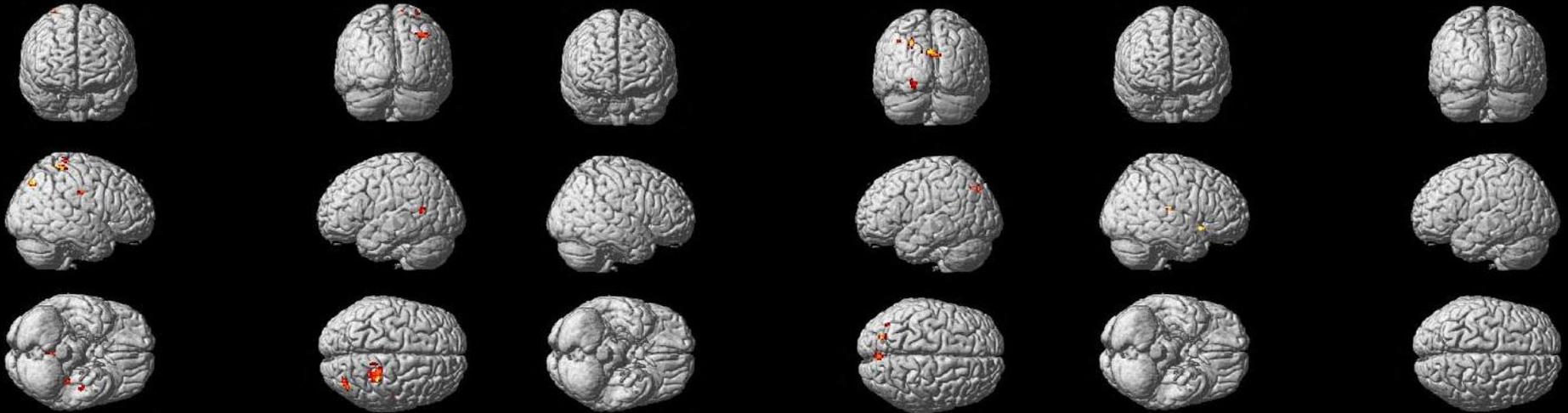
# Response Inhibition

RI1+RI2 - Control

**TD < ARND**

**TD < ADHD**

**TD > ADHD**



**Frontal**, Parietal,  
Temporal, **Cingulate**,  
Cerebellum, Insula,  
Claustrum, **Caudate**,  
Parahypocampus

Parietal, Occipital

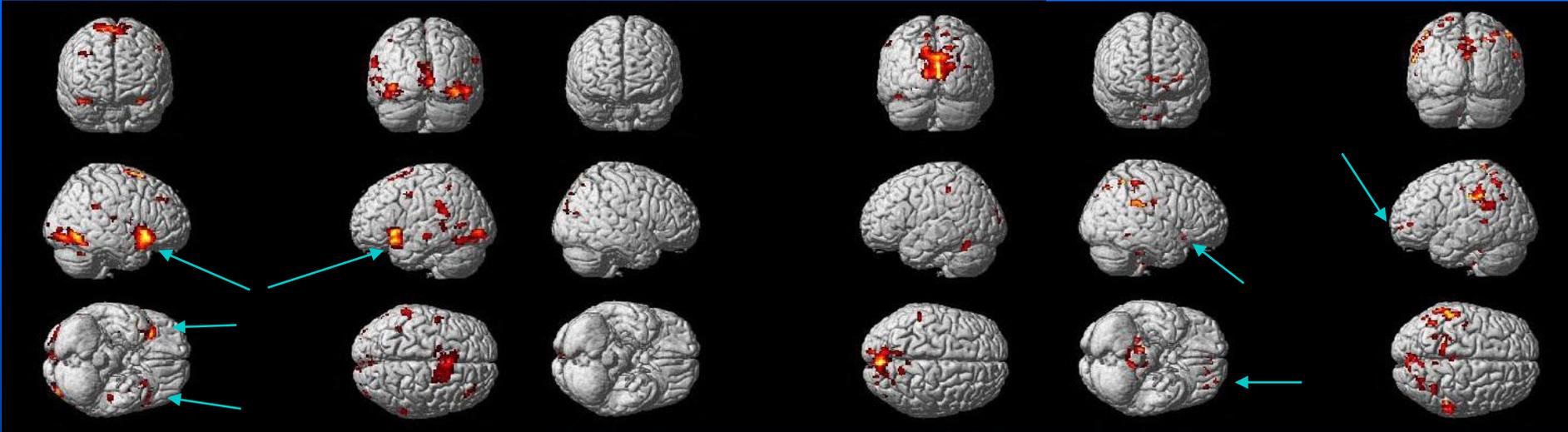
Temporal, Insula

t-test:  $p < 0.01$

**ANOVA** – significant at  $p 0.01$  and cluster threshold of 10;  $FWE < 0.035$

# Response Inhibition

Non-target A - Control



TD (N=21)

ADHD (N=17)

ARND (N=14)

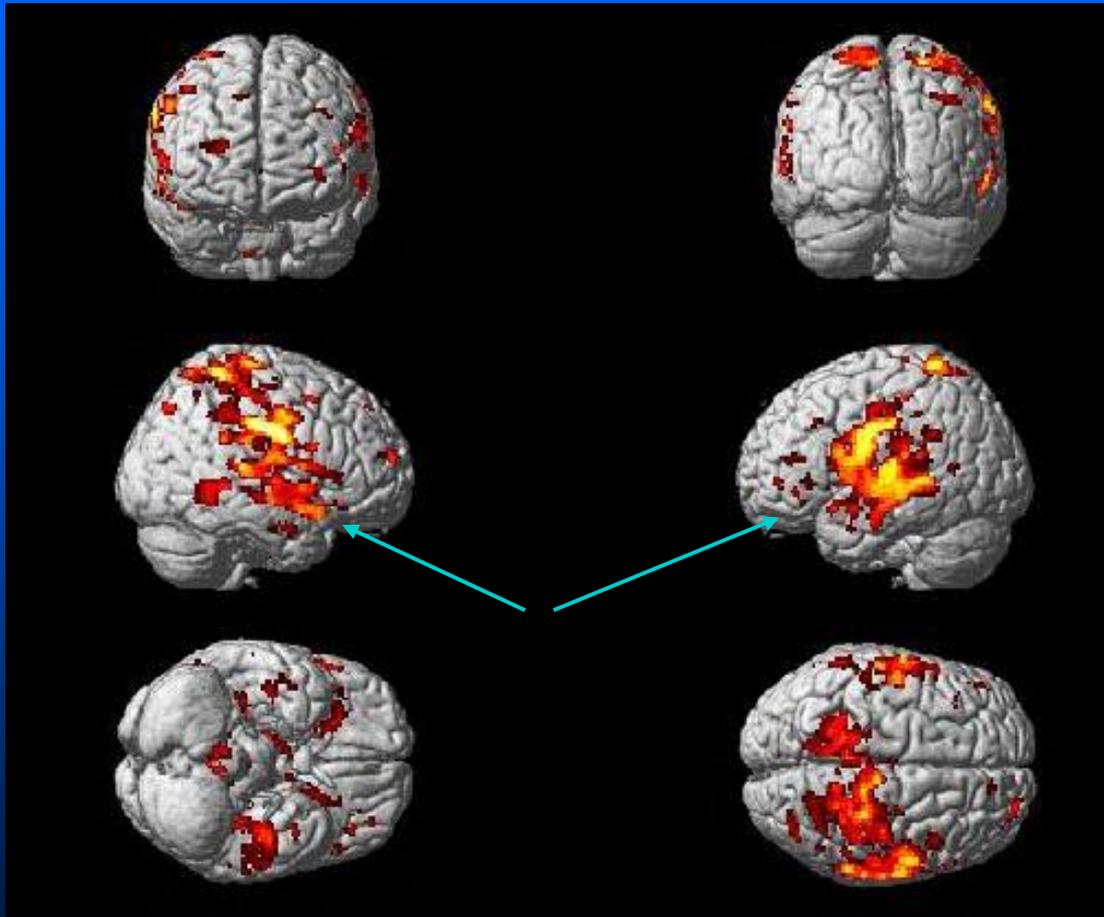
No orbito-frontal

Rendered images showing activity for subtractive contrast: Non-target “A” – control at  $p < 0.01$  cluster threshold = 10 (FWE  $< 0.035$ ).

# Response Inhibition

Non-target A - Control

**ARND > ADHD**



**Frontal**, Parietal,  
Temporal, Cingulate,  
Cerebellum, Insula,  
Hypothalamus,  
Thalamus,  
Parahippocampus

t-test;  $p < 0.01$

ANOVA – significant at  $p < 0.01$  and cluster threshold of 10; FWE $<0.035$

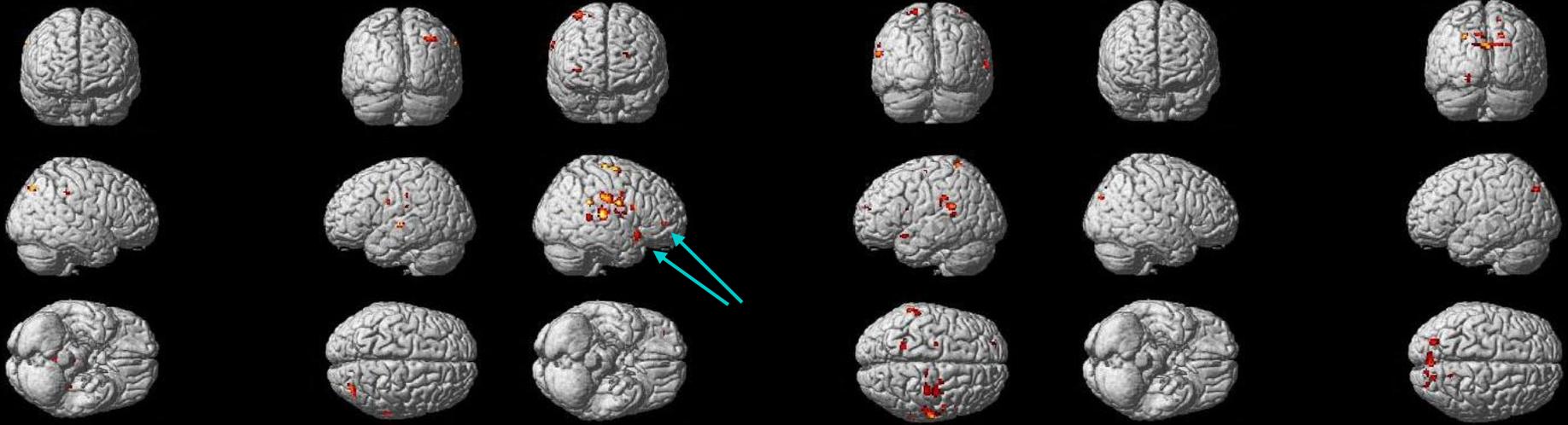
# Response Inhibition

Non-target A - Control

**TD < ARND**

**TD > ADHD**

**TD < ADHD**



Frontal, Parietal,  
Temporal,  
Cerebellum, Insula,  
Parahippocampus

Frontal, Parietal,  
Temporal, Cingulate,  
Insula, Putamen,  
Thalamus,  
Parahippocampus

Parietal,  
Occipital,  
Cingulate

t-test;  $p < 0.01$

ANOVA – significant at  $p < 0.01$  and cluster threshold of 10; FWE < 0.035

# Conclusions – Response Inhibition

## Non-target “A” inhibition – control

- Clear Temporal/Orbital-frontal activity in TD, some in ARND, **NOT in ADHD**
  - Orbitofrontal region involved in RI
- Both ARND and TC greater activity than ADHD in **Frontal (Orbitofrontal)**, Parietal, Temporal, Cingulate, Insula, Thalamus, Parahippocampus
  - Regions linked to inhibition, attention and response selection

# Response Inhibition Conclusions

- Cingulate and Prefrontal areas involved in RI
  - Cingulate activity during inhibition in all groups
  - Greater frontal and cingulate in TD compared to ADHD consistent with others (Pliska et al 2006; Tamm et al. 2004)
- Significant parietal, temporal, frontal, cingulate, thalamus and striatal activity in ARND over ADHD – linked to attention
- Can potentially use RI to distinguish ADHD from ARND

# General Conclusions

- fMRI to potentially distinguish ARND and ADHD
- WM
  - Increased frontal activity in ARND
  - Parietal activity in ARND & TD not in ADHD
- Attention
  - Spatial cueing – switching attention not a problem for ARND more parietal than ADHD
  - Conjunction – encoding attention – no activity in ARND in temporal compared to ADHD
- RI
  - Signif. greater activity in ARND over ADHD

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