

FMRI REVEALS LONG-TERM EFFECTS OF PRENATAL DRUG EXPOSURE ON VISUOSPATIAL WORKING MEMORY NETWORKS DURING ADOLESCENCE

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AIMS

To examine whether prenatal drug exposure exerts lasting effects on neural functioning by altering the activations supporting visuospatial working memory (VSWM) abilities during adolescence.

INTRODUCTION

The impact of prenatal drug exposure during early childhood

The effects of prenatal drug exposure have been examined extensively in infants and young children across a range of developmental domains (e.g., physical growth, intelligence, language, motor functioning, and attention). In these global domains, the neurobiological effects of prenatal drug exposure appear to play a more subtle role in children's development than originally thought with reported effects being no greater than other known teratogens or environmental risk factors (Frank et al., 2001). However, little is known about the long-term outcomes in specific cognitive abilities and underlying neural functioning during the school-age years.

The impact of prenatal drug exposure during the school-aged years

Research has shown that, as children develop, visual spatial working memory abilities may be altered as a result of prenatal substance exposure. For example, Schroeder et al., (2004) found decreased visuomotor speed and efficiency accessing an internal spatial map during a behavioral paradigm in a sample of school-aged children exposed to cocaine in utero.

Brain imaging studies have implicated altered structure and/or function in a number of regions required for successful working memory. Studies investigating school-aged children with a history of prenatal drug exposure using structural MRI have reported an overall reduction in cerebral cortex gray matter volume (Rivkin et al., 2008; Walhovd et al., 2007), including the caudate (Avants et al., 2007; Rao et al., 2007; Walhovd et al., 2007), and parietal regions (Singer et al., 2006). Alterations in white matter tracts in frontal callosal fibers have also been reported (Duckworth Warner et al., 2006), and have been shown to be related to behavioral measures of executive functioning. One study using MRS reported increases in creatine levels in both frontal white matter and striatum (Smith et al., 2001). Functional MRI studies report reductions in overall cerebral blood flow, with relative increases in anterior and superior brain regions (Rao et al., 2007). Reductions in left PFC activity have also reported in an fMRI investigation of non-spatial working memory (Hurt et al., 2008).

Current study

fMRI was used to examine activation patterns during a visuospatial working memory (VSWM) paradigm in adolescents (12 to 15 years of age) who were enrolled in a longitudinal investigation of the effects of prenatal drug exposure (cocaine and heroin).

HYPOTHESIS

Exposure to drugs during the prenatal period will alter brain development and result in alterations to neural activation patterns during a visuospatial working memory task in adolescence.

METHODS

Participants

Participants were part of an ongoing longitudinal research study examining long-term effects of prenatal drug exposure. Thirty-two African American adolescents between 12 and 15 years of age participated in the study. Four participants were left handed (1 exposed, 3 non-exposed). One participant (exposed group) was excluded due to excessive motion artifact. The nondrug-exposed group was drawn from a comparison group recruited from the same local community.

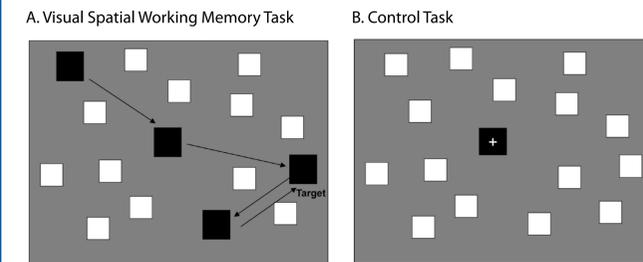
Table 1: Participant Demographics

	Prenatal drug-exposed Group (N = 17)	Non-exposed Group (N = 14)	Statistical Comparison
Age mean (s.d.)	14 years, 6 months (1 year, 6 months)	13 years, 6 months (1 year, 3 months)	$t_{(29)} = 2.54, p < .05$
Gender (Male : Female)	9 : 8	5 : 9	$\chi^2 = 0.92, df = 1, NS$
IQ (WASI) mean (s.d.)	90.88 (11.60)	92.43 (9.71)	$t_{(29)} = 0.39, NS$

PROCEDURE

Participants performed a 2-back VSWM paradigm that required dynamic storage and manipulation of spatial information and a control task (which required observation of visual stimuli, sustained attention, and a motor response). In the VSWM task, individual darkened squares were presented sequentially in 1 of 16 different spatial locations (Figure 1A). Participants were instructed to press a button whenever the darkened square returned to the immediately preceding location (i.e., "the location it just left"). In the control task, an individual darkened square was presented in the center spatial location alternated with a plus sign (Figure 1B). Subjects were instructed to press a button when the plus sign appeared. Individual stimulus duration for each condition was 1 second. Reaction times were recorded via a button press to the target stimuli.

Figure 1.



Training

- Participants practiced the task on a desktop computer and subsequently in a mock scanner.

fMRI acquisition and analysis

- Scanner = 3T Siemens Allegra; Whole Brain BOLD EPI; 39 oblique axial (30° axial to coronal), 4mm slices; TR = 2 sec; TE = 27 ms; Flip Angle = 80°; FOV = 22cm; Run time = 7 min.
- Participants completed one 7-minute run that alternated between a 30 second control task and 30 seconds of the VSWM task in a block design.
- Common activations and group differences in brain responses were analyzed in AFNI (Cox 1996).

RESULTS

Behavioral Data

A repeated-measures ANOVA was used to compare accuracy and reaction time between groups using a 2 Group (Exposed, Non-exposed) x 2 Task (Control, VSWM) design.

Table 2: Behavioral Data

	Accuracy (% correct)		Group Difference
	Control Task	VSWM Task	
Drug-exposed mean (s.d.)	89.46% (9.21%)	83.58% (12.10%)	$F_{(1,28)} = 1.19, NS$
Non-exposed mean (s.d.)	91.67% (7.61%)	84.29% (16.59%)	
	Reaction Time (ms)		Group Difference
	Control Task	VSWM Task	
Drug-exposed mean (s.d.)	472.66 (44.93)	528.00 (58.17)	$F_{(1,28)} = 0.56, NS$
Non-exposed mean (s.d.)	475.74 (68.99)	495.79 (69.91)	

- There were no significant differences in accuracy or reaction time between groups.
- There was a main effect of condition for both accuracy and reaction time.
 - Across groups, percent correct was greater for the control versus the VSWM task, $F_{(1,28)} = 5.82, p < .05$.
 - Across groups, reaction time was faster to the control versus the VSWM task, $F_{(1,28)} = 12.57, p = .001$.

fMRI Data

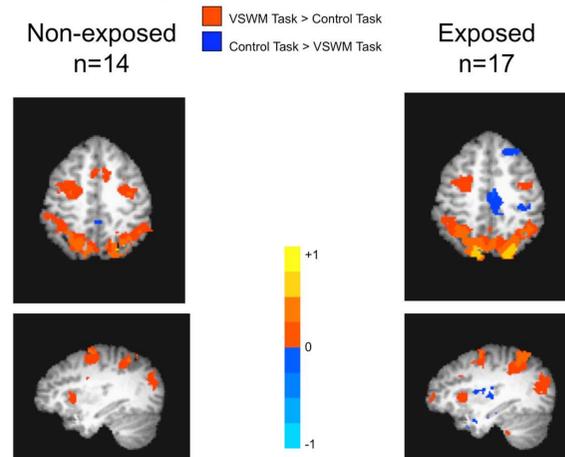
Whole-brain analyses within each group explored task-related activations. Post-hoc t-tests determined the magnitude and direction of significant changes in activation for each group ($p_{corrected} < 0.05$) as well as differences between the two groups ($p < .001$ at the individual voxel level, cluster size $> 200\mu l$).

Within Group Differences [VSWM Task Activation] - [Control Task Activation]

- In both groups, there was a significant effect of task, bilaterally (see Figure 2).
- The VSWM task produced significantly greater activation in frontal and parietal regions compared to the control task.

Figure 2.

Difference maps for each group [VSWM Task - Control Task]

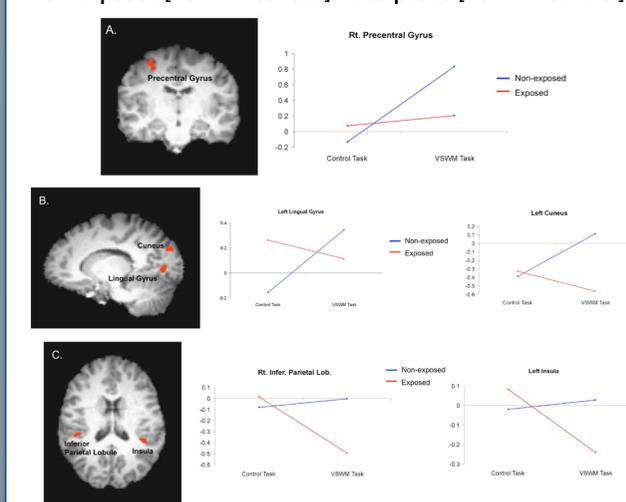


Between Group Differences [Non-exposed Difference Map] - [Exposed Difference Map]

- There was a significant difference between the difference maps in 5 regions: right precentral gyrus, left cuneus, left lingual gyrus, left insula, and right inferior parietal lobule.

Figure 3.

Between Group Difference Maps Non-exposed [VSWM - Control] vs. Exposed [VSWM - Control]



SUMMARY & DISCUSSION

- Within group difference maps indicated that participants in both groups activated frontoparietal regions during the VSWM task.
- Between group difference maps revealed that, compared to the drug-exposed group, the non-exposed group showed significantly greater activation in the precentral gyrus during the working memory task.
 - Activation in this region is most likely reflective of response preparation for the task.
- In addition, the non-exposed group showed significantly greater activation in the cuneus and lingual gyrus during the working memory task.
 - Activation in these regions may be associated with visual processing of the stimuli and attention.
- Taken together, these data suggest the group exposed to substances of abuse during the prenatal period may be less able to prepare to respond and use perceptual attention regions of the brain to process information.
- The prenatal drug-exposed group exhibited significantly greater deactivations in the right inferior parietal lobule and left insula during the working memory task.
 - These regions are not typically thought to play a role in visual spatial working memory and may reflect alterations in regions supporting successful working memory performance, as task performance did not differ between the two groups.
- Future directions include analysis of a priori ROIs, covarying age, examining pubertal effects and connectivity analyses.

CONCLUSION

Regions in the frontoparietal network commonly recruited during visuospatial working memory paradigms were activated in both drug-exposed and non-exposed groups.

Group differences emerged in the right precentral gyrus, left cuneus and left lingual gyrus suggesting that the drug-exposed group was less capable of engaging regions associated with response preparation and perceptual attention in working memory in comparison to the non-exposed group.

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