Effects of Prenatal Drug Exposure on Adolescent Brain Activation During a Visuospatial Working Memory Task

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OBJECTIVE

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

BACKGROUND

Cognitive Outcomes Associated with Prenatal Drug Exposure (PDE)

Previous research examining effects of prenatal drug exposure (PDE) has yielded mixed results regarding cognitive performance during school age years. Associations between PDE and tests of global functioning (IQ and academic achievement) tend to be minimal and are typically attenuated by environmental variables (e.g., caregiving environment). On the other hand, significant negative associations have been reported in tests of executive functioning (sustained attention, inhibitory control, and behavioral regulation), even with covariate control. For example, studies by both Schroder and colleagues (2004) and Mayes and colleagues (2006) report impaired performance on tests of visuospatial working memory in school age children as a result of prenatal cocaine exposure.

Neural Outcomes Associated with Prenatal Drug Exposure (PDE)

Findings from cognitive paradigms are consistent with animal models of PDE (Harvey, 2004) that report developmental abnormalities in brain regions associated with strong dopaminergic innervation including the striatum, anterior cingulate cortex, and prefrontal cortex. In humans, these regions are putatively involved in executive functions that coordinate the basic cognitive processes required for goal-directed action (e.g., working memory, attention, inhibitory control, and planning).

For example, studies investigating school-aged children with a history of PDE using structural MRI have reported an overall reduction in cerebral cortex gray matter volume (Rivkin et al., 2008), including the caudate (Avants et al., 2007; Rao et al., 2007) and parietal regions (Singer et al., 2006). Alterations in white matter tracts in frontal callousal 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). Finally, 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 nonspatial working memory (Hurt et al., 2008).

CURRENT STUDY

In the current study, fMRI was used to examine activation patterns during a visuospatial working memory (VSWM) paradigm in adolescents who were enrolled in a longitudinal investigation of the effects of prenatal drug exposure (cocaine and heroin). We hypothesized that exposure to drugs during the prenatal period would alter brain development and result in alterations to neural activation patterns during a VSWM task.

METHODS

Participants

Participants included 20 adolescents with a history of PDE and 15 non-exposed adolescents from a comparison group drawn from the same community. All participants were African Americans between 12 and 15 years of age, 5 were left-handed (see Table 1 below).

	Prenatal Drug-Exposed Group (N=20)	Comparison Group (N=15)	Group Difference Statistics Bold indicates significant difference
Current Characteristics:			
Age at scan (years)	**14.3, (1.0)**	**13.5, (1.1)**	**$F(1,33) = 6.20$, p = .02**
Gender	10 male, 10 female	5 male, 10 female	Chi square(1)= 0.97, p=.32
Participant's IQ (WASI)	91.25, (11.58)	94.2, (12.27)	$F(1,33) = 0.53$, p=.47
Currently in non-maternal care	**50%**	**0%**	**Chi square(1)= 10.5, p=.001**
Current caregiver IQ (WASI)	84.6, (13.60)	89.4, (13.42)	$F(1,33) = 1.11$, p=.30
Birth Characteristics:			
Birthweight (z score)	-.68 (.67)	-.17 (1.13)*	$F(1,32) = 2.73$, p=.11
Birth head circumference (z score)	-.66 (.86)	-.45 (.94)*	$F(1,32) = 0.45$, p=.51
Birth height (z score)	**-.49 (1.13)**	**.37 (.74)***	**$F(1,32) = 6.21$, p=.02**
Mothers age at birth (years)	**27.05 (4.64)**	**23.6 (4.99)**	**$F(1,33) = 4.44$, p=.04**
Maternal education at birth (years)	10.90 (1.33)	11.67 (.82)	$F(1,33) = 3.85$, p=.058
Apgar scores (1min)	range 6-9, mode = 8	range 6-9, mode = 8*	Mann-Whitney U = 113.5, p=.49
Apgar scores (5min)	range 8-10, mode = 9	range 8-10, mode = 9*	Mann-Whitney U = 120.5, p=.48
Prenatal exposure to alcohol	during pregnancy-47%, pre-pregnancy-16%, never-37%^	during pregnancy-27%, pre-pregnancy-7%, never-67%	Chi square(2)= 3.02, p=.22
Prenatal exposure to cigarettes	**during pregnancy-75%,pre-pregnancy-11%, never-11%^**	**during pregnancy-27%, pre-pregnancy-13%, never-60%**	**Chi square(2)= 10.50, p<.005**

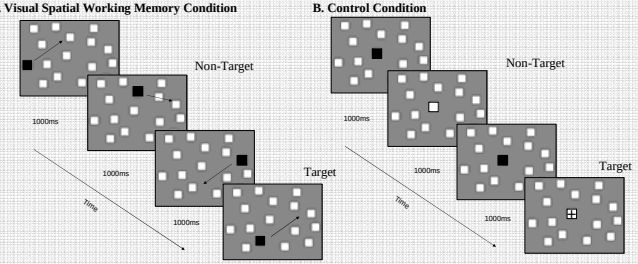
*n=13-14, ^n=19

PROCEDURE

fMRI Paradigm

Task: Participants performed a 2-back VSWM paradigm that required dynamic storage and manipulation of spatial information and a control task that 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 A). 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 B). 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.

A. Visual Spatial Working Memory Condition **B. Control Condition**



Training: Participants practiced the task on a desktop computer and in a mock scanner.

fMRI acquisition and analysis: Participants completed one 6-minute run that alternated between 30 seconds of the control task and 30 seconds of the VSWM task in a block design. Brain responses were analyzed using the AFNI software package (Cox 1996). Comparisons included VSWM vs. Control task and Non-exposed [VSWM - Control] vs. Exposed [VSWM - Control] with $p < 0.05$ corrected for multiple comparisons. 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.

RESULTS

Behavioral Performance

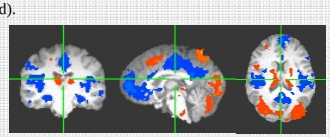
Behavioral performance on the task (i.e., accuracy and response time) did not differ between the groups (covariates: age and gender).

	Prenatal Drug Exposure Group (n=19)	Comparison Group (n=15)	Statistic
Control			
% correct	89.8%, (8.8%)	91.1%, (7.6%)	$F(1, 30) = 0.07$, p=.80
RT	475.8ms, (42.40ms)	476.5ms, (66.3ms)	$F(1, 30) = 0.006$, p=.98
VSWM			
% correct	84.2%, (11.3%)	85.1%, (16.2%)	$F(1, 30) = 0.03$, p=.87
RT	528.5ms, (60.1ms)	497.6ms, (67.5ms)	$F(1, 30) = 0.19$, p=.67

Whole Brain Analyses – Across Groups

Across all participants, the VSWM task activated the frontal-parietal attention network including: bilateral superior parietal lobules, precuneus, middle frontal gyri, superior frontal gyri, and insular cortex. Significant deactivations were observed in regions of the "default network," including the left anterior cingulate gyrus, medial frontal gyrus, posterior cingulate, and bilateral parahippocampal cortices (p<.05 corrected).

Difference Map
VSWM - Control



Red = VSWM > Control
Blue = Control > VSWM

Region (Talairach)	Peak (LPI: x, y, z)			micrL	Region (Talairach)	Peak (LPI: x, y, z)			micrL
Left Precuneus - BA31	0	-68	+24	177195	Left Insula - BA13	-32	+20	+6	2494
Left Cingulate (near)	-16	-32	+22	59082	Right Middle Occipital Gyrus - BA18	+26	-96	+4	2438
Right Middle Frontal Gyrus - BA6	+30	+6	+46	34664	Right Superior Frontal Gyrus - BA10	+26	+48	+2	2433
Left Medial Frontal Gyrus - BA10	-6	+46	+12	30853	Right Angular Gyrus - BA39	+50	-70	+38	2115
Right Insula - BA13	+42	-14	+4	25499	Left Middle Temporal Gyrus - BA21	-60	-16	-8	1638
Left Middle Frontal Gyrus - BA6	-38	0	+46	18812	Left Inferior Frontal Gyrus - BA46	-54	+28	+12	1143
Right Thalamus/ Lat. Post. Nucleus	+14	-18	+14	5994	Right Inferior Frontal Gyrus - BA47	+34	+30	-6	1097
Left Precentral Gyrus - BA4	-36	-28	+62	5845	Right Precentral Gyrus - BA4	+56	-16	+40	1005
Left Thalamus/ Lat. Post. Nucleus	-18	-22	+14	3608	Left Cerebellar Tonsil	-38	-56	-48	945
Right Cerebellar Tonsil	+22	-38	-42	3529	Left Middle Frontal Gyrus - BA10	-38	+52	+10	877
Right Insula - BA13	+34	+20	+6	3255	Right Cerebellum	+28	-66	-48	584
Left Inferior Frontal Gyrus - BA47	-34	+32	-8	3253	Left Middle Temporal Gyrus - BA21	-42	+4	-28	546
Left Angular Gyrus/ IPL - BA39	-48	-68	+38	3105	Left Red Nucleus (near)	0	-28	-2	474
Right Superior Frontal Gyrus - BA8	+16	+40	+48	2581					

Whole Brain Analyses – Between Groups

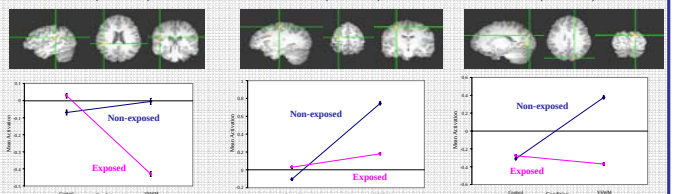
Whole brain between group comparisons revealed 3 regions that were differentially activated in the drug-exposed compared to the non-exposed group (covariates: age and gender, p<.05 corrected). These regions were the right inferior parietal lobule, right precentral gyrus, and left cuneus. Significant differences in these regions remained after statistically controlling environmental variables that differed between the groups, including placement in nonmaternal care, maternal age at time of birth and prenatal exposure to cigarettes.

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

Right Inferior Parietal Lobule
LPI: +48 -32 +22
(459 microL)

Right Precentral Gyrus
LPI: +32 -14 +56
(405 microL)

Left Cuneus
LPI: -14 -86 +32
(351 microL)



DISCUSSION

The VSWM task activated a common network in both the exposed and non-exposed groups. Although no significant differences were found between groups in behavioral performance, there were significant differences in neural activation between the groups suggesting differences in the underlying neural circuitry used in during the task.

The drug-exposed group showed deactivation of the right inferior parietal lobule compared to no change in the non-exposed group. This region has been previously associated with visuospatial processing. The non-exposed group showed activations in both the right precentral gyrus and left cuneus compared to no significant change in the drug-exposed group. These regions have previously been associated with response preparation and perceptual attention respectively.

Group differences in activation were not related to differences in birth characteristics such as placement in nonmaternal care, maternal age at time of birth and prenatal exposure to cigarettes, nor were they correlated with performance on the task.

Future directions include analysis of *a priori* ROIs and connectivity analyses to ascertain network use differences.

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 inferior parietal lobule, right precentral gyrus, and left cuneus suggesting that the drug-exposed group was less capable of engaging regions associated with visuospatial processing, response preparation, and perceptual attention during this working memory task.

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