Frontostriatal Connectivity in Children during Working Memory and the Effects of Prenatal Methamphetamine, Alcohol, and Polydrug Exposure

Florence F. Roussotte[a, b]   Jeffrey D. Rudie[c]   Lynne Smith[d]   Mary J. O'Connor[c]
Susan Y. Bookheimer[c]   Katherine L. Narr[e]   Elizabeth R. Sowell[a, b]

[a]Developmental Cognitive Neuroimaging Laboratory, Children's Hospital Los Angeles and Department of Pediatrics, University of Southern California, [b]University of California, Los Angeles (UCLA), Department of Neurology, and [c]UCLA Department of Psychiatry and Biobehavioral Sciences, Los Angeles, Calif., [d]Harbor-UCLA Medical Center, Department of Pediatrics, Torrance, Calif., and [e]Laboratory of NeuroImaging, Department of Neurology, University of California, Los Angeles, Calif., USA

Abstract
Various abnormalities in frontal and striatal regions have been reported in children with prenatal alcohol and/or methamphetamine exposure. In a recent fMRI study, we observed a correlation between accuracy on a working-memory task and functional activation in the putamen in children with prenatal methamphetamine and polydrug exposure. Because the putamen is part of the corticostriatal motor loop whereas the caudate is involved in the executive loop, we hypothesized that a loss of segregation between distinct corticostriatal networks may occur in these participants. The current study was designed to test this hypothesis using functional connectivity MRI. We examined 50 children ranging in age from 7 to 15, including 19 with prenatal methamphetamine exposure (15 of whom had concomitant prenatal alcohol exposure), 13 with prenatal exposure to alcohol but not methamphetamine, and 18 unexposed controls. We measured the coupling between blood oxygenation level dependent (BOLD) fluctuations during a working-memory task in four striatal seed regions and those in the rest of the brain. We found that the putamen seeds showed increased connectivity with frontal brain regions involved in executive functions while the caudate seeds showed decreased connectivity with some of these regions in both groups of exposed subjects compared to controls. These findings suggest that localized brain abnormalities resulting from prenatal exposure to alcohol and/or methamphetamine lead to a partial rewiring of corticostriatal networks. These results represent important progress in the field, and could have substantial clinical significance in helping devise more targeted treatments and remediation strategies designed to better serve the needs of this population.

Copyright © 2012 S. Karger AG, Basel

Dr. Elizabeth R. Sowell
Developmental Cognitive Neuroimaging Laboratory, Keck School of Medicine
University of Southern California, Children's Hospital Los Angeles
4650 Sunset Blvd., Mailstop #130, Los Angeles, CA 90027 (USA)
Tel. +1 323 361 7347, E-Mail esowell@chla.usc.edu

Introduction

Prenatal exposure to drugs of abuse is a significant public health concern. In particular, methamphetamine abuse is an important medical and social problem as up to 17 million Americans have reportedly used it, including approximately 19,000 pregnant women [1]. While animal studies show that exposure to a single drug can cause lasting effects on the developing brain, human studies which attempt to parse specific effects of exposure to any one of many drugs of abuse are much more complicated. The issue of polydrug exposure is inherent to most human retrospective studies, as most women who use methamphetamine also drink alcohol and smoke.

Fetal Alcohol Spectrum Disorders (FASDs) represent a variety of neurological, behavioral and growth abnormalities that result from the damaging effects of prenatal alcohol exposure on the brain. FASDs are a serious public health issue in the USA and in many other countries, in particular South-Africa [2] and Italy [3]. In the USA, it occurs in around 2–5% of births [4], affecting about 40,000 newborns every year and is the leading preventable cause of intellectual disability. The estimated lifetime costs reach about 5 billion USD annually in the USA alone [5].

Alcohol is a central nervous system depressant, which decreases cortical and subcortical activity through its interactions with membrane receptors. It crosses the placenta and the blood-brain barrier and can exert teratogenic effects on the developing fetus through various mechanisms, including alcohol-induced hypoxia [6], increased embryonic oxidative stress [7, 8] and disruption of growth factor signaling [9, 10]. Animal models have demonstrated that prenatal alcohol exposure results in a variety of structural and metabolic brain abnormalities [11], including reductions in spinal and cranial motor neuron production and size [12]; disturbance of neurogenesis and/or gliogenesis in the neocortex [13], cerebellum [14] and hippocampus [15]; increased neuronal cell death [16]; abnormal neuronal migration, and decreased myelination [17].

The negative effects of prenatal alcohol exposure in humans have been extensively documented since the 1970s. The cognitive and behavioral deficits associated with FASDs are wide-ranging and potentially very severe [18, 19]. Human neuroimaging studies have reported widespread structural, functional and metabolic brain abnormalities associated with prenatal alcohol exposure in many cortical and subcortical structures. Abnormalities in the frontal lobe have been documented [20], and among subcortical regions, the published literature suggests that the basal ganglia and diencephalon are particularly affected. Specifically, decreased volumes of the basal ganglia have been reported, and remain significant, even after controlling for reductions in total brain volume [21].

Though not as prevalent as alcoholism, methamphetamine abuse is also a significant public health concern. This psychostimulant with well-documented neurotoxic effects on mature monamine neurons [22, 23] accumulates in the placenta in high concentrations [24]. According to rodent models, most of its teratogenic effects also involve disruptions of monoamine systems, including synaptic remodeling of axonal terminals [25] and disruptions in monoamine transmitter levels, in particular frontal [26] and striatal [27–29] dopamine depletion.

In humans, prenatal exposure to methamphetamine leads to signs of motor abnormalities [30–32], restricted fetal growth [33, 34], underarousal and increased stress [30, 32], impaired visual motor integration [35, 36], reduced attention and decreased verbal and spatial memory [36], and pronounced deficits in parentally rated executive functioning [37]. Consistent with rodent models, the neuroimaging literature shows prominent effects on dopamine-rich frontostriatal circuits, including volume reductions in the globus pallidus and putamen [36] and in two subregions of the caudate [38], volume increases in the anterior cingulate and inferior frontal gyrus [38], and lower diffusion in frontal white matter [39]. Metabolic abnormalities have also been reported in the striatum [40] and the frontal white matter [35].

In a recent fMRI investigation, we observed a correlation between working-memory performance and functional activation in the putamen in children with prenatal methamphetamine and polydrug exposure [41]. This finding was intriguing because the putamen is part of the frontostriatal motor loop [42, 43] whereas the caudate is involved in the executive loop [43, 44]. The basal ganglia have long been implicated in motor behavior and recent animal studies have thoroughly characterized the role of the putamen in the visuospatial and temporal organization of movements [45]. In the last decade, it became clear that the basal ganglia also played an important role in various aspects of cognitive function [46]. Human studies of Parkinson's [47] and Huntington's [48, 49] diseases have strongly suggested that frontostriatal circuits involving the caudate nucleus were involved in various executive functions, including visual and/or spatial working memory. In addition, rigorous studies in primates

have demonstrated that basal ganglia outputs to the prefrontal cortex were extensive and widespread, suggesting a strong influence of the basal ganglia on the cognitive processes associated with the frontal lobes [50].

Given that the animal literature suggests that striatal dopamine depletion occurs as a result of prenatal methamphetamine exposure [28] and that human studies have shown that striatal dopamine depletion (for instance in Parkinson's disease) leads to reduced spatial segregation between different corticostriatal loops [51], we hypothesized that a similar mechanism may take place in this population [41]. In the present study, we aimed to test this hypothesis by comparing corticostriatal connectivity patterns during an N-Back working-memory task in children with prenatal methamphetamine exposure with those in unexposed controls. Though our fMRI study provided no evidence for a change in corticostriatal connectivity in the alcohol-only group, these participants were included in the present investigation in order to determine whether connectivity differences similar to those predicted in the methamphetamine-exposed group were present in these children. Based on our recent findings, our specific hypothesis was that the putamen would show increased connectivity with frontal brain regions involved in executive functions while the caudate would show decreased connectivity with some of these frontal regions, in subjects with methamphetamine and polydrug exposure, compared to controls.

Materials and Methods

Participants

Participants in this study were the same subjects who were previously examined in a recent fMRI study by our group [41] and the same imaging data were also used in the present study. As detailed in our previous report and summarized below, prospective participants were screened for various types of exclusion criteria. Fifty subjects ranging from 7 to 15 years of age were included in the analyses presented here. Each participant was classified into one of three groups based on prenatal exposure histories: a methamphetamine-exposed group (MAA, n = 19, 15 with concomitant alcohol exposure, age range 7–13), an alcohol-exposed group (ALC, n = 13, age range 7–15), and a nonexposed control group (CON, n = 18, age range 7–15). Exposure status was established by extensive interviews administered to the parents or adult guardians of participants. Additionally, social, medical and/or legal records were used when available to confirm exposure histories.

Participants were included in the MAA group if prenatal exposure to methamphetamine was confirmed by parental or guardian report, or by maternal or infant medical records. Fifteen of the 19 children in the MAA group were also exposed to alcohol prenatally. Children in the MAA group were recruited from three sources: (1) older children of mothers who were in a methamphet-

Table 1. Alcohol exposure clinical severity by group

	MAA (n = 19)	ALC (n = 13)	CON (n = 18)
No alcohol	4	0	18
Exposed (least severe)	1	0	0
ARND	9	4	0
Sentinel	2	2	0
PFAS	2	3	0
FAS (most severe)	1	4	0

Sentinel = Shows mild facial dysmorphology.

amine rehabilitation program and had infants born positive for methamphetamine; (2) a social skills training group for children with FASDs at UCLA, and (3) self-referral in response to advertisements and word-of-mouth. ALC participants were exposed to 4 or more drinks per occasion at least once per week or 14 drinks or more per week and were not exposed to methamphetamine during gestation (n = 13). Most ALC subjects were recruited from the same social skills training group as the MAA subjects. Typically developing controls (CON) were excluded from the study if they had been exposed to illicit drugs or to more than 2 alcoholic drinks on any occasion or an average of 1 drink or more per week during gestation. CON subjects (n = 18) were recruited from the same Los Angeles communities as the exposed groups via advertisement, and effort was made to recruit from similar socioeconomic strata.

Details of diagnostic procedures for FASDs used to classify ALC and MAA subjects are described in another report [52]. Briefly, an experienced clinician examined alcohol-exposed children using the Diagnostic Guide for Fetal Alcohol Syndrome (FAS) and Related Conditions [53]. This system uses a 4-digit diagnostic code reflecting the magnitude of expression of four key diagnostic features of FAS: (1) growth deficiency, (2) the FAS facial phenotype, including short palpebral fissures, flat philtrum, and thin upper lip, (3) central nervous system dysfunction, and (4) gestational alcohol exposure. This classification method has been shown to correlate with brain function and structure [54]. Using these criteria, children with alcohol exposure (with or without concomitant methamphetamine exposure) were diagnosed with FAS, partial FAS, sentinel features, or alcohol-related neurodevelopmental disorder (ARND). Table 1 illustrates the clinical severity of alcohol exposure in each group.

Other exclusion criteria precluding participation in the study for subjects in all three groups included: (1) prenatal exposure to opiates, (2) age younger than 7 years, (3) IQ less than 70, (4) head injury with loss of consciousness for more than 20 min, (5) a physical (e.g. hemiparesis), psychiatric, or developmental (e.g. autism) disability that would preclude participation, (6) other potential known causes of mental deficiency (e.g. chromosomal disorders), (7) significant maternal illness with increased risk for fetal hypoxia (e.g. sickle cell disease), (8) presence of metallic implants in the body which posed a risk for MRI. Additionally, subjects were excluded from the study if they performed below 1.5 standard deviations from the mean performance of their group on the N-Back
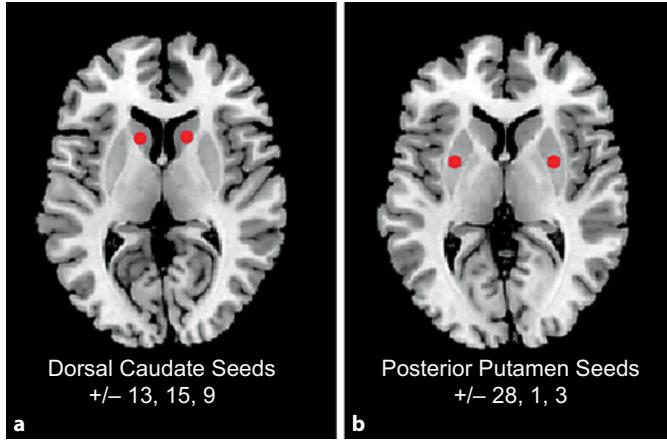
Fig. 1. Bilateral striatal seeds. The numbers represent MNI coordinates (x, y, z).

task (n = 7), or due poor fMRI data quality (n = 8). After the exclusion of all unsuitable subjects, the 50 remaining participants were included in the analyses described below. Data about precise timing and dosage of exposure to methamphetamine and/or alcohol were not available. However, in the MAA group, examination of parents' reports revealed that, out of the 19 mothers, at least 11 also used tobacco during pregnancy, at least 5 used marijuana, and 1 admitted to cocaine and tranquilizer use.

Procedures

Following a complete description of the study protocol, all participants and their parents gave informed assent/consent according to procedures approved by the UCLA Institutional Review Board.

Image Acquisition

fMRI data were collected on a 3-tesla Siemens Allegra head-only magnet. Multislice echo-planar imaging was used with a gradient echo echo-planar imaging sequence. We used TR = 3 s, TE = 25 ms, 3 mm slice thickness with 1 mm skip, 36 slices, 64 × 64 pixels yielding 3.1 mm in-plane resolution with whole-brain acquisition. A high-resolution T_2-weighted echo-planar imaging volume was collected in the anterior commissure-posterior commissure plane, coplanar with the functional scan to facilitate the subsequent spatial registration of each subject's data into the Montreal Neurological Institute (MNI)-152 standard coordinate space (TR = 5 s, TE = 33 ms, flip angle = 90°, 3 mm slice thickness with 1 mm skip, 36 axial slices covering the entire brain, matrix size = 128 × 128 with 1.6 × 1.6 mm in-plane resolution).

Functional Imaging Task: Visuospatial N-Back

The visuospatial N-Back task consisted of rest and experimental blocks, with 3 rest blocks (30 s each, during which subjects stared at a blank screen) and 12 experimental blocks with 4 each of 0, 1 and 2-Back blocked trials randomly interspersed. The 0, 1 and 2-back blocks started with a display of the instructions 'Push for Center', 'Push for 1-Back', and 'Push for 2-Back', respectively [for a visual depiction of the task, see ref. 41]. Each experimental block consisted of 16 stimuli presented for 500 ms each, with a 1,500-ms

interstimulus interval. The stimulus 'O' was presented in one of 9 distinct visuospatial locations. In the 1-back task, participants were asked to respond if the stimulus was in the same location as the previous stimulus, and in the 2-back task they were asked to respond if the stimulus was in the same location 2 steps back. The entire task lasted 8.2 min. Prior to scanning, each subject was administered two practice blocks of the N-Back task on a laptop. Only subjects who were able to perform the task during the prescan training session were administered the task in the scanner.

Image Analysis
Preprocessing

fMRI data processing was carried out using FEAT (fMRI Expert Analysis Tool) Version 5.98, part of FSL [FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl, ref. 55]. Unless otherwise noted, all of the individual tools drew from that library. Prior to analysis, each image was partially processed and assessed for image quality using the following preprocessing methods: they were motion corrected using MCFLIRT [Motion Correction FMRIB's Linear Image Registration Tool, ref. 56] but not smoothed, and visually inspected for artifact. In the parent study [41], 5 subjects had been excluded due to visible slice dropout on more than 10 volumes and 3 participants had been excluded because of excessive field distortion, caused by movement outside of the field of view over the course of the scanning session. In the remaining participants included in the present study (total n = 50, with 18 CON, 13 ALC, and 19 MAA subjects), the following prestatistics processing was applied: non-brain removal on structural- and motion-corrected functional images using FSL's Brain Extraction Tool [37, 55], spatial smoothing using a Gaussian kernel of FWHM 6.0 mm, grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with Σ = 30.0 s). Registration to both high-resolution, T_2-weighted structural and the MNI-152 standard space template images was carried out with FLIRT [FMRIB's Linear Image Registration Tool, ref. 56, 57], using 6 and 12 degrees of freedom, respectively.

Functional Connectivity MRI Data Analysis

Time series statistical analysis was carried out using FMRIB's fMRI Expert Analysis Tool (FEAT version 5.98). In order to examine whole-brain connectivity with nodes of interest, we used anatomically based regions of interest (ROIs): 4-mm diameter spheres centered in the left and right dorsal caudate (±13, 15, 9) (fig. 1a) and the left and right posterior putamen (±28, 1, 3) (fig. 1b). The choice of particular MNI coordinates for our striatal ROIs was based on a recent fMRI study of the functional connectivity of the human striatum in healthy subjects [58], which demonstrated differential patterns of connectivity among striatal subregions, and used a rigorous procedure for selecting seed coordinates based on the Talairach atlas space [59] and transforming them into MNI space using the algorithm implemented by Brett [60].

We extracted time series from our ROIs and correlated them with every voxel in the brain to generate connectivity maps for each subject for each ROI. Individual correlational maps were converted into z-statistic maps using Fischer's *r*-to-*z* transformation and then combined at the group level using the ordinary least-squares method. All within- and between-group connectivity maps were thresholded at z > 1.7 (i.e. p < 0.05) and corrected for multiple comparisons at the cluster level (p < 0.05) using

Roussotte/Rudie/Smith/O'Connor/
Bookheimer/Narr/Sowell

Table 2. Demographics and performance for each group

	MAA (n = 19)	ALC (n = 13)	CON (n = 18)	Group differences
Age	9.16 ± 1.83	11.46 ± 2.44	10.28 ± 2.61	ALC>MAA $F_{(2, 49)} = 3.93$, $p = 0.023$
Female/male	8/11	4/9	9/9	None
Accuracy (total)	0.84 ± 0.08	0.88 ± 0.07	0.92 ± 0.04	CON>MAA $F_{(2, 49)} = 6.47$, $p = 0.002$
Accuracy (2-Back)	0.71 ± 0.11	0.78 ± 0.10	0.80 ± 0.09	CON>MAA $F_{(2, 49)} = 4.50$, $p = 0.019$
FSIQ	97.47 ± 14.08	86.67 ± 16.49	111.67 ± 14.61	CON>ALC $F_{(2, 48)} = 10.62$, $p < 0.001$; CON>MAA $F_{(2, 48)} = 10.62$, $p = 0.017$

Values expressed as means ± SD.

Gaussian random-field theory. In order to explore the specific effects of prenatal methamphetamine exposure, we conducted whole-brain pair-wise group analyses (i.e. MAA vs. CON, ALC vs. CON, and MAA vs. ALC) and included alcohol exposure clinical severity as a parameterized between-group covariate (with a score of 0 indicating no prenatal alcohol exposure, 1 indicating some alcohol exposure or a diagnosis of ARND, 2 indicating a sentinel diagnosis, 3 representing a diagnosis of partial FAS and 4 representing an FAS diagnosis, table 1).

Follow-Up Analyses

Additional analyses were performed in order to address the methodological concern related to using global signal regression as a preprocessing step [61]. All analyses were also conducted without global signal regression. Each of the major patterns of between-group differences was also present when global signal regression was not used (data not shown). Therefore, given that the signal-to-noise ratio was higher when global signal regression was used and that anticorrelations were not the focus of our hypotheses, we have opted to present all results with global signal regression.

In addition, we attempted to address the possible confounding effects of two variables that differed between groups, namely task performance and age (table 2). We performed additional analyses, with accuracy on the 2-Back (most difficult) condition of the N-Back working-memory task added as a between-group covariate, and with the age of participants included as a between-group covariate in separate analyses. This allowed us to model variance in functional connectivity due to group differences in age and in task performance.

Statistical Analysis of Demographic Data

Statistical analyses were conducted using SYSTAT 12.0. Group differences in age, Full Scale Intelligence Quotient (FSIQ), and performance on the N-Back task were evaluated using two-sample independent t tests. Group differences in gender were assessed with a Fisher's exact test of significance.

Results

Demographics

Demographic descriptors and behavioral performance on the N-Back task and on FSIQ measures were described in our previous report [41] and are reproduced in table 2. Groups did not differ from each other in gender distribution. The groups differed in FSIQ [$F_{(2, 48)} = 10.62$], with the CON group scoring significantly higher than both the ALC ($p < 0.001$) and MAA groups ($p = 0.017$), but the MAA and ALC groups did not differ from each other.

The groups also differed in age [$F_{(2, 49)} = 3.93$], with the ALC group being significantly older than the MAA group ($p = 0.023$) but not the CON group; the CON and MAA groups did not differ from each other. The groups differed in overall accuracy on the N-Back task [$F_{(2, 49)} = 6.47$, $p = 0.002$] and in accuracy on the 2-Back condition of the task [$F_{(2, 49)} = 4.50$, $p = 0.019$]. In both cases, the CON group scored significantly higher than the MAA group but not the ALC group; the two exposed groups did not differ from each other. The within-group positive and negative connectivity patterns as well as the between-group differences in connectivity were very similar for all 4 seeds when task performance or age was regressed out (data not shown), suggest that the findings described below were not explained by group differences for either variable. According to the Edinburgh Handedness Inventory, 26 of the 50 subjects were strong right-handers, 18 were mixed right-handers, 2 were neutral (both in the ALC group), 2 were mixed left-handers (1 from the MAA

group and 1 from the CON group), and 2 were pure left-handers (1 from the MAA group and 1 from the ALC group).

Within-Group Connectivity: Positive Relationships
Dorsal Caudate Seeds

Consistent with the involvement of the dorsal caudate in executive functions [43, 58], in the CON group, the caudate seeds were positively correlated with prefrontal regions involved in cognitive control (fig. 2). Qualitative comparisons of results suggest some discrepancies between groups, primarily in frontal areas involved in dopaminergically mediated executive processing. Positive correlations of the caudate seeds with these regions were more apparent in the CON group than in both exposed groups. However, MAA subjects seemed to show weaker connections of the seeds primarily with medial prefrontal regions while ALC participants showed a similar pattern but more pronounced in lateral prefrontal regions.

Posterior Putamen Seeds

Consistent with the involvement of the posterior putamen in motor functions [43, 58], in the CON group, the putamen seeds were positively correlated with sensorimotor areas, most prominently the primary and supplementary motor cortex. In the exposed groups, the putamen seeds showed a similar pattern of connectivity with sensorimotor areas, but qualitative comparisons suggest some discrepancies between groups. In both exposed groups, the putamen seeds were *also* positively correlated with more anterior brain regions, including areas involved in executive tasks (fig. 3). However, in MAA subjects, this effect appeared more pronounced in the left than in the right putamen, while in ALC participants, these functional connections between the putamen and prefrontal regions were more apparent in the right putamen than in the left.

Within-Group Connectivity: Negative Relationships
Dorsal Caudate Seeds

Consistent with the negative connectivity patterns of the dorsal caudate documented in healthy subjects [58], in the CON group, the caudate seeds were negatively correlated with the cerebellum, occipital cortex, and primary motor cortex bilaterally. They also showed a negative correlation with the precuneus and superior parietal lobule, in both hemispheres (fig. 2). Qualitative comparisons suggest some discrepancies between groups. In both exposed groups, the caudate seeds appear to be negatively correlated with fewer regions. In particular, the negative

correlations with occipital regions seem to be absent in exposed subjects (fig. 2).

Posterior Putamen Seeds

Consistent with the negative connectivity patterns of the posterior putamen reported in healthy subjects [58], in the CON group, the putamen seeds were negatively correlated with the dorsolateral prefrontal cortex (superior frontal gyrus), the posterior cingulate, the precuneus, and the angular gyrus in both hemispheres. Negative correlations with the cerebellum and inferior occipital cortices were also observed (fig. 3). Qualitative comparisons suggest some discrepancies between groups. In the exposed groups, the putamen seeds appear to be negatively correlated with fewer regions. In particular, the negative correlations with superior frontal regions seem much reduced in exposed subjects (fig. 3).

Group Differences in Corticostriatal Connectivity

Consistent with our predictions, functional connectivity between the dorsal caudate and the frontal executive network was reduced in MAA subjects compared to CON subjects. Decreased functional connectivity between caudate seeds and frontal areas was also observed in the ALC group relative to the CON group, though there were minor differences between the two exposed groups (fig. 4). In the MAA group, the right caudate showed decreased functional connectivity with most prefrontal areas, and the left caudate seed showed such reduced connectivity primarily with medial prefrontal regions (paracingulate, anterior cingulate cortex, frontal poles, fig. 3). However, in ALC subjects, the caudate seeds showed decreased functional connectivity with prefrontal areas only in lateral subregions (such as the inferior frontal gyrus, especially in the right hemisphere). The ALC group also showed reduced connectivity between the caudate seeds and the right medial temporal lobe (fig. 4). These differences between the two exposed groups, however, were marginally significant, as illustrated in figure 6.

Consistent with our hypotheses, functional connectivity between the posterior putamen and the frontal executive network was increased in MAA subjects compared to CON subjects. Greater functional connectivity between putamen seeds and frontal areas was also observed in the ALC group relative to the CON group, but there were small differences in laterality between the two exposed groups. In the MAA group, the left putamen seed showed increased connectivity with most prefrontal areas relative to the CON group while the right putamen seeds seemed to have increased functional connections

Roussotte/Rudie/Smith/O'Connor/
Bookheimer/Narr/Sowell
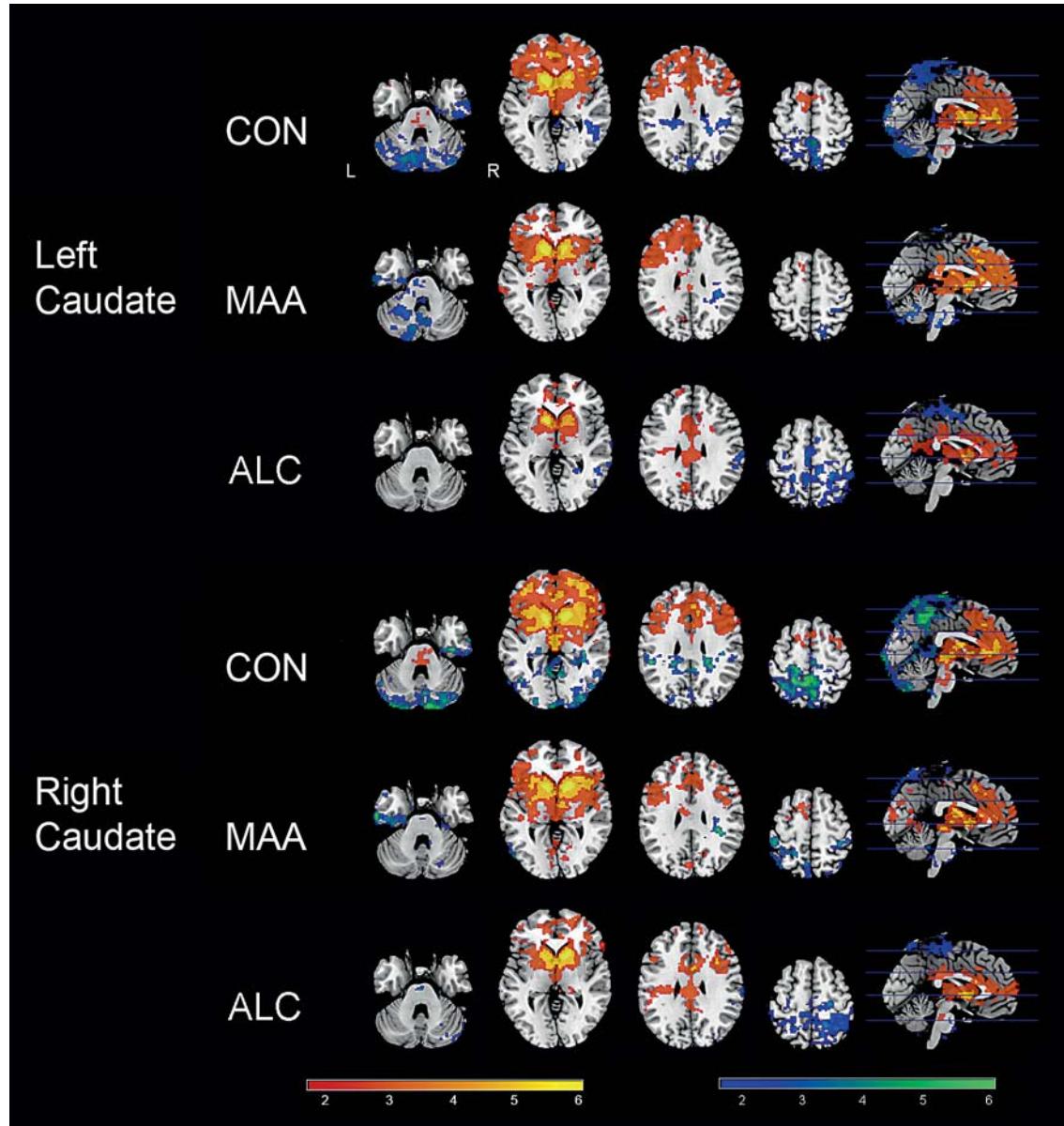
Fig. 2. Caudate seeds: within-groups connectivity maps. Axial and sagittal sections displaying group average connectivity maps for the left and right caudate seeds. Maps are thresholded at z > 1.7 (p < 0.05) and corrected for multiple comparisons at the cluster level (p < 0.05). Colors on the maps correspond to the color bars at the bottom. Warm colors represent regions of positive connectivity with the seed region. Cool colors represent regions of negative connectivity with the seed region.

with the most superior frontal regions only. In the ALC group, however, both putamen seeds increased their functional coupling with superior and inferior subregions, though the effect appeared less pronounced than for the left putamen in the MAA group. These differences are illustrated in figure 6.

Discussion

The current investigation constitutes the first report of loss of segregation between distinct corticostriatal loops in children with prenatal exposure to methamphetamine and/or alcohol. While previous studies had reported
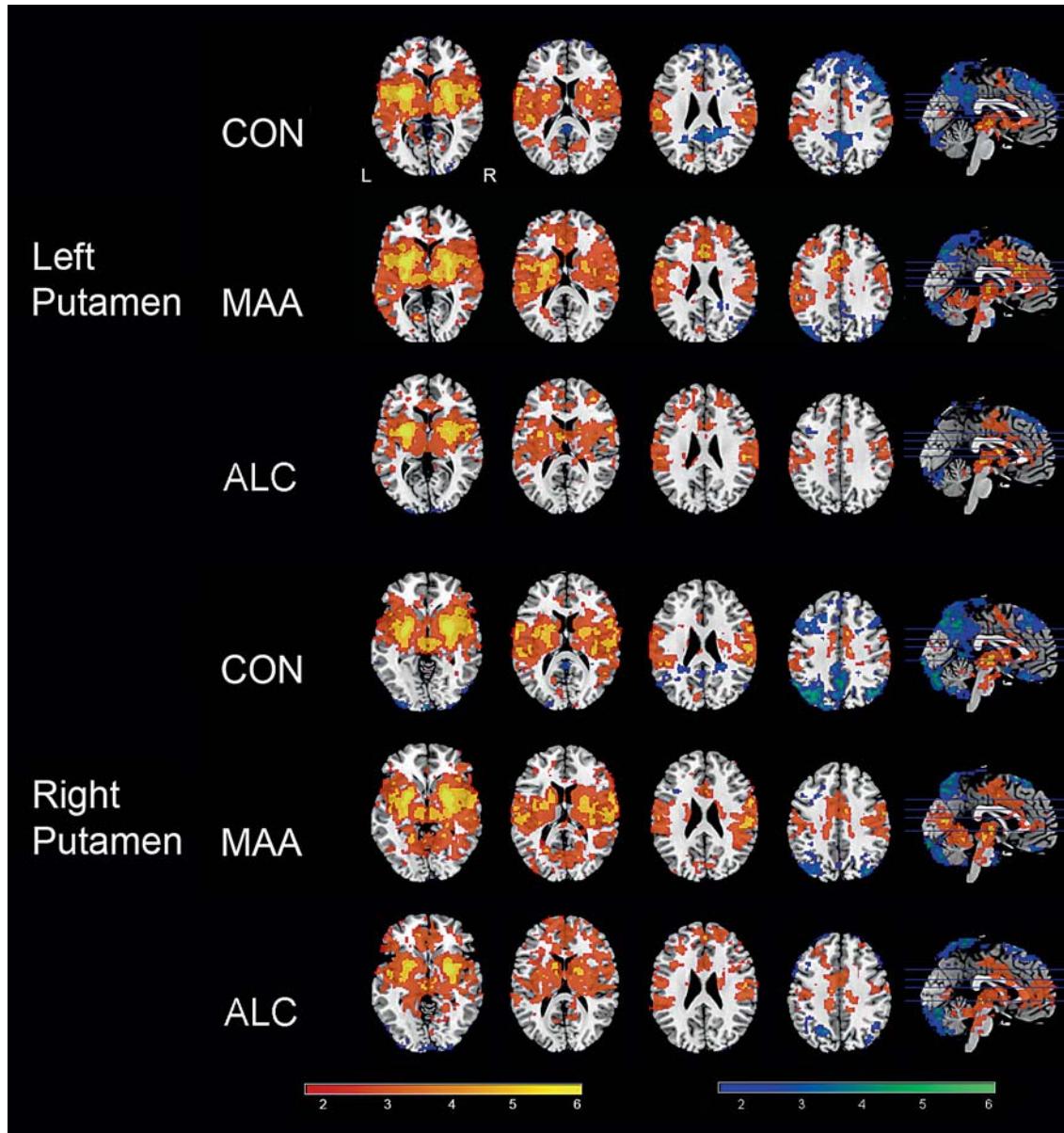
Fig. 3. Putamen seeds: within-groups connectivity maps. Axial and sagittal sections displaying group average connectivity maps for the left and right putamen seeds. Maps are thresholded at z > 1.7 (p < 0.05) and corrected for multiple comparisons at the cluster level (p < 0.05). Colors on the maps correspond to the color bars at the bottom. Warm colors represent regions of positive connectivity with the seed region. Cool colors represent regions of negative connectivity with the seed region.

structural and metabolic abnormalities in the striatum, frontal lobe and frontal white matter of subjects prenatally exposed to alcohol or stimulants [as reviewed in ref. 62], the current study describes a possible higher-order effect of these localized abnormalities at the network level of brain function. This finding represents an important

step toward a deeper and broader understanding of the neurological impact of prenatal methamphetamine and/or alcohol exposure on the developing human brain, and could have important clinical relevance. Describing and characterizing the overall reorganization of neural networks that occurs in this population may ultimately help
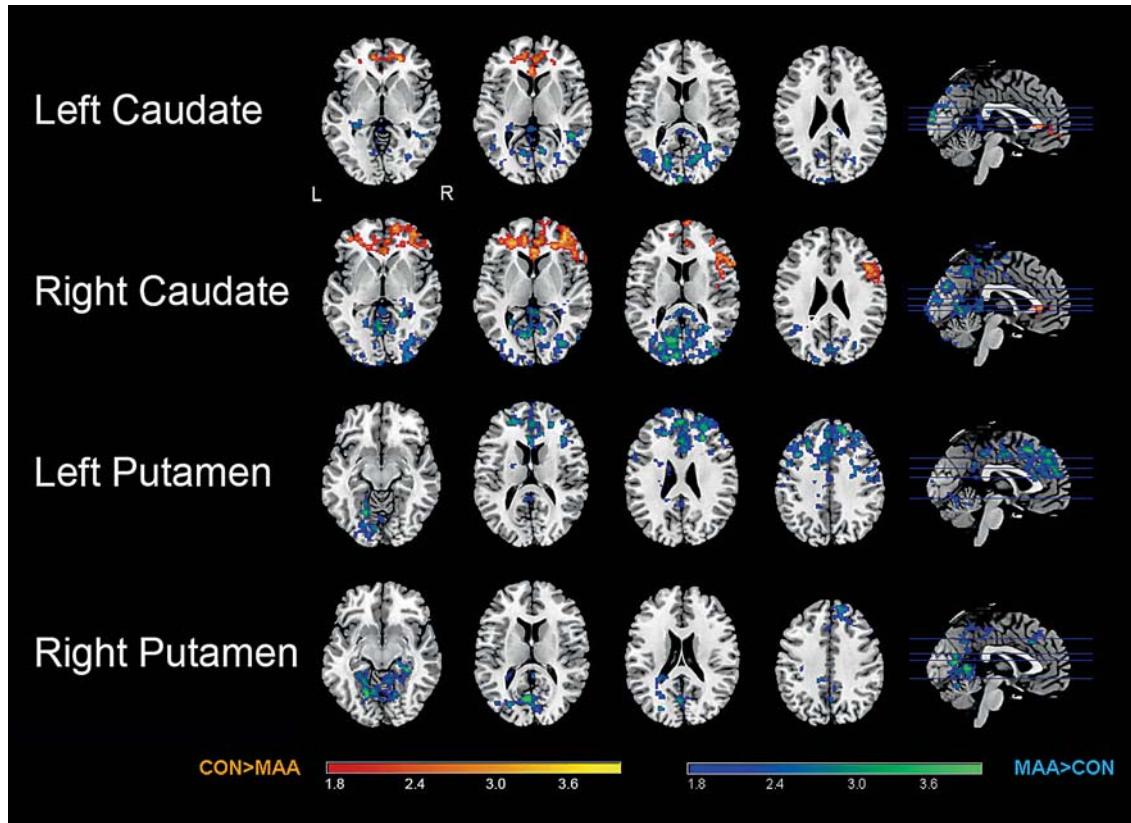
Fig. 4. Between-groups contrast maps: CON versus MAA. Axial and sagittal sections displaying between-groups contrast maps for all 4 striatal seeds. Maps are thresholded at z > 1.7 (p < 0.05) and corrected for multiple comparisons at the cluster level (p < 0.05). Colors on the maps correspond to the color bars at the bottom. Warm colors represent areas where connectivity with the seed region is lower in the MAA group than in the CON group. Cool colors represent areas where connectivity with the seed region is higher in the MAA group than in the CON group.

bridge the gap between our awareness of specific localized brain abnormalities and the application of this knowledge toward improved treatments and remediation approaches.

In the CON group, most of our findings of positive and negative connectivity patterns for the dorsal caudate and posterior putamen replicated the results of a recent resting-state functional connectivity study of the human striatum in healthy adults [58] and the conclusions of a recent meta-analysis of 126 functional connectivity studies of the basal ganglia [63]. Here we describe very similar findings in children, suggesting these networks are formed during childhood. Specifically, the dorsal caudate seed was primarily positively correlated with the dorsolateral prefrontal cortex and other cognitive control regions, while the posterior putamen seed was primarily associated with the primary and supplementary motor cortices.

The negative relationships of striatal seeds in the CON group were also consistent with the documented negative connectivity patterns of the caudate and putamen in healthy adults [58]. Finally, most of our findings in the CON group seemed to be bilateral; that is, the positive and negative coactivation patterns were similar for the right and left striatal seeds, consistent with other reports in healthy subjects [58, 63].

There were striking differences in the connectivity patterns of striatal seeds in both exposed groups, indicative of a shift in corticostriatal connections in individuals with prenatal methamphetamine and/or alcohol exposure. Consistent with our predictions, in the MAA group, both caudate seeds showed reduced positive connectivity with frontal regions compared to CON subjects, while the left putamen seed showed increased connectivity with prefrontal areas involved in executive functioning. Al-
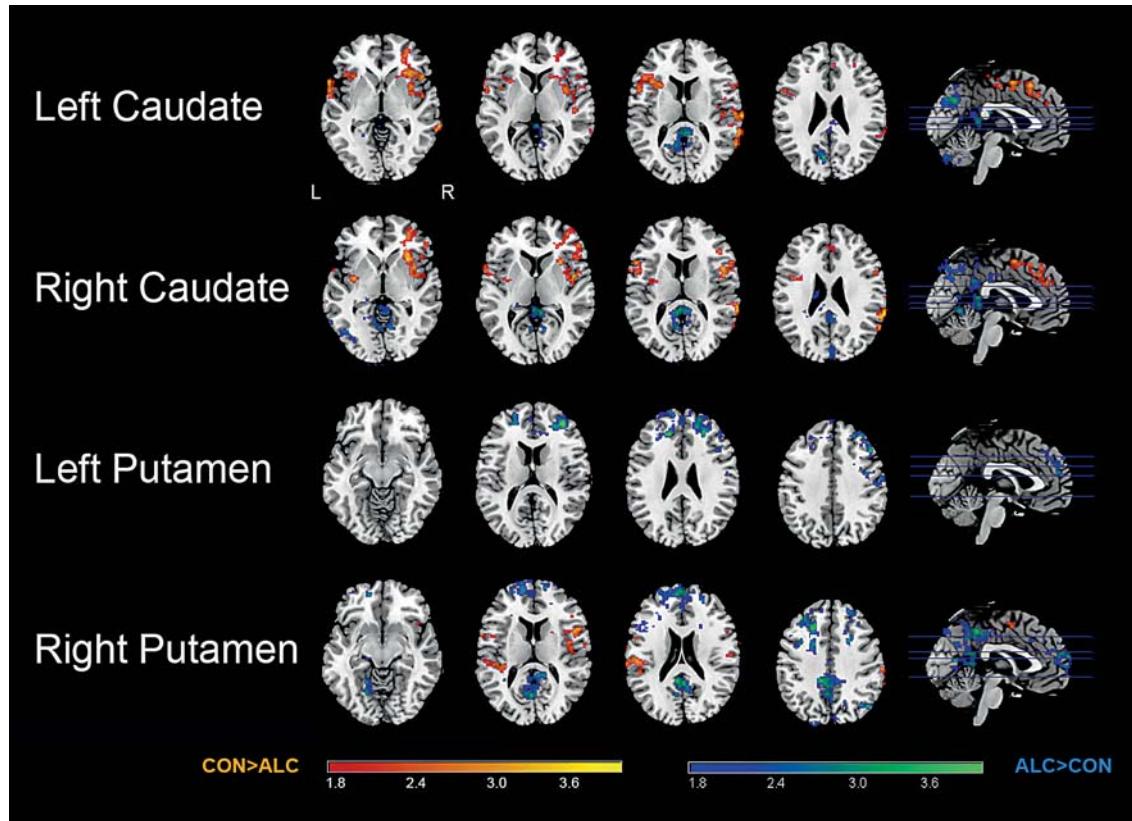
Fig. 5. Between-groups contrast maps: CON versus ALC. Axial and sagittal sections displaying between-groups contrast maps for all 4 striatal seeds. Maps are thresholded at z > 1.7 (p < 0.05) and corrected for multiple comparisons at the cluster level (p < 0.05). Colors on the maps correspond to the color bars at the bottom. Warm colors represent areas where connectivity with the seed region is lower in the ALC group than in the CON group. Cool colors represent areas where connectivity with the seed region is higher in the ALC group than in the CON group.

though our earlier study did not provide evidence for such changes in functional connectivity in the alcohol-only group, in this connectivity study, the ALC group showed very similar alterations. In both exposed groups, functional connectivity between the dorsal caudate and the frontal executive network decreased while a portion of this network increased its coupling with the posterior putamen. Taken together, these findings suggest that in exposed subjects, the prefrontal executive loop may become partitioned into two different corticostriatal loops, with some frontal regions being connected to the dorsal caudate, and others to the posterior putamen.

These increased functional interactions between corticostriatal circuits that are normally segregated could represent a compensatory mechanism in response to damage to specific parts of the network. In FASDs, the caudate appears to be more affected than other basal gan-

glia regions [64, 65]. In addition, postmortem studies have established that methamphetamine users show a reduction in dopamine levels that is much stronger in the caudate than in the putamen [66]. Given that high concentrations of methamphetamine can be detected in the placenta [24] and that individuals with prenatal exposure show the same types of frontostriatal abnormalities as adult abusers [as reviewed in ref. 62], it is reasonable to assume that individuals exposed during gestation are likely to show a regional pattern of striatal dopamine depletion similar to the one reported in methamphetamine users. Thus, in both groups of prenatally exposed subjects, it is possible that parts of the prefrontal executive loop may be redirected away from the more damaged caudate and towards the less affected putamen.

It is ambiguous whether such compensatory mechanisms represent mostly beneficial or maladaptive conse-
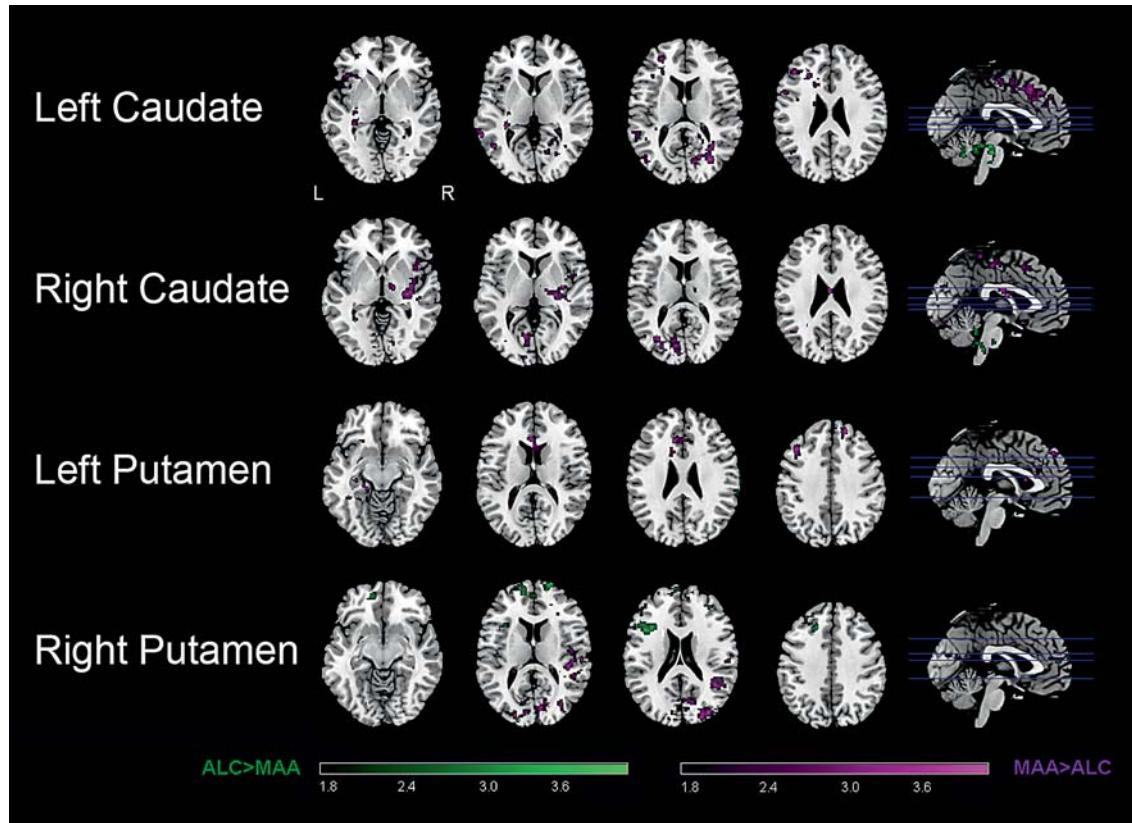
Fig. 6. Between-groups contrast maps: MAA versus ALC. Axial and sagittal sections displaying between-groups contrast maps for all 4 striatal seeds. Maps are thresholded at $z > 1.7$ ($p < 0.05$) and corrected for multiple comparisons at the cluster level ($p < 0.05$). Colors on the maps correspond to the color bars at the bottom. Green colors represent areas where connectivity with the seed region is lower in the MAA group than in the ALC group. Violet colors represent areas where connectivity with the seed region is higher in the MAA group than in the ALC group.

quences of structural damage to striatal structures in our exposed participants. Although some evidence suggests that the collateral sprouting from spared dopaminergic fibers may be involved in behavioral recovery following lesions to dopaminergic neurons [67], it is possible that these increased interactions between different corticostriatal networks lead to a detrimental loss of specificity, resulting in a maladaptive overlap between the executive and motor loops. In healthy individuals, the center-surround inhibitory pattern of the corticostriatal system leads to specific enhancement of activity in the loop involved in the task being performed, coupled with suppression of competing cortical networks [68]. The loss of functional segregation between corticostriatal loops reported here may lead to a disruption of this center-surround inhibitory pattern, resulting in impaired suppression of competing networks while performing a task. In

this study, it is plausible that such a loss of network specificity may have led MAA subjects to process the motor and executive components of the N-Back task in a less distinct, thus less efficient manner, which could underlie their decreased performance on the task compared to the CON group. This hypothesis is intriguing, and future studies should aim at elucidating the particular positive and negative behavioral correlates of such remapping of corticostriatal connectivity.

The etiology of the differences observed between the two exposed groups remains largely unclear. Nevertheless, one can postulate that the left-right asymmetry of the observed changes in putamen connectivity (which appeared to be left-lateralized in the MAA group but right-lateralized in ALC participants), may be related to emerging evidence suggesting that striatal structures may be more damaged in the right hemisphere in persons

prenatally exposed to alcohol, but more pronounced in the left hemisphere in subjects with prenatal methamphetamine exposure. As discussed in our recent fMRI study [41], it appears that the only human report of physiological abnormalities in the striatum of subjects with FASDs showed decreases in relative regional metabolic rates in the caudate head bilaterally, but only in the right caudate body and right putamen [69]. In addition, an fMRI study of prenatal alcohol exposure reported decreased activation in the right caudate in alcohol-exposed children and adolescents during a response-inhibition task, suggesting functional abnormalities in this region [70]. In contrast, our group reported white-matter abnormalities in corticostriate projections restricted to the left hemisphere in an overlapping sample of subjects with prenatal methamphetamine exposure [71], partially replicating a previous report [39]. Although speculative, this proposition raises the possibility that alcohol and methamphetamine exposure during gestation may have distinct effects on brain structure and function. The differences we observed between the two exposed groups may be due to distinct mechanisms of teratogenic action for the two drugs, or to interactions between them which may have differentially affected the two hemispheres during ontogeny.

There are two major limitations to this study. The first one is related to the design of the analyses. The changes in functional connectivity in the exposed groups were observed during a working-memory task, as opposed to resting-state data, which is free of task-induced coactivation. Thus, we cannot exclude the possibility that these group differences may represent a pattern of altered connectivity driven by this particular task. Further, although we found nearly identical results in our follow-up analyses which included subjects' age or task accuracy as between-group covariates, it is not clear that this design accounted for all the variance due to possible age or performance differences between the groups. Therefore, in order to increase our confidence that the altered network properties reported here represent a general consequence of prenatal exposure to methamphetamine and/or alcohol, rather than a task-specific occurrence, it is crucial that future studies replicate these findings in the context of intrinsic blood oxygenation level dependent (BOLD) fluctuations. Nevertheless, the fact that our findings in the CON group replicated most of the results of a recent resting-state fMRI study of functional connectivity of the striatum in healthy adults [58] and that these results were consistent with the conclusions of a recent meta-analysis of 126 studies of basal ganglia functional connectivity

[63], strongly suggest that the findings reported here in children are not task-specific.

The second major limitation is related to the participants in this study and to the issue of polydrug exposure. The majority of our subjects with prenatal methamphetamine exposure also had concomitant alcohol exposure. We included alcohol exposure clinical severity as a parameterized between-group covariate in our analyses in an attempt to obtain enhanced specificity for detecting methamphetamine effects; however, it is possible that higher-order interaction effects between alcohol and methamphetamine may account for some of our observations. Therefore, we must use caution in interpreting the results reported here, and in attributing our findings solely to the effects of methamphetamine exposure in the MAA group. Nonetheless, we did detect group differences supporting our a priori hypotheses; we developed these hypotheses based on specific patterns of brain activation that we observed in subjects exposed to methamphetamine and alcohol which were not significant in subjects exposed to alcohol only [41] in the same subjects studied here, and our hypotheses were consistent with animal studies with well-controlled single-drug exposure. Therefore, it is possible that the results we report in the MAA group have more to do with methamphetamine exposure, or perhaps with the combination of methamphetamine and alcohol exposure, than with alcohol exposure alone.

In addition, maternal smoking records were unavailable for many participants; thus, we were unable to add prenatal exposure to tobacco as a covariate in our analyses. This limitation is particularly concerning because the majority of mothers in the MAA group were smokers, and nicotine exposure has been shown to result in lasting abnormalities in neurogenesis in animal models [72]. We cannot exclude the possibility that nicotine exposure could contribute partly to the observed differences between exposed groups and CON subjects. However, well-controlled animal studies of prenatal exposure to alcohol and methamphetamine have shown that each of these substances is sufficient to induce lasting structural, metabolic, and behavioral changes, in the absence of any concurrent exposure to nicotine or other drugs of abuse [as reviewed in ref. 73]. Nevertheless, it is crucial that future studies examine the possibility of second-order nicotine-methamphetamine or nicotine-alcohol interactive effects.

Precise exposure histories and dosages were generally unavailable given that many of the subjects in our exposed groups had been adopted. This is true of most ret-

Roussotte/Rudie/Smith/O'Connor/
Bookheimer/Narr/Sowell

rospective human studies of prenatal drug exposure given that quantities and frequencies of drug exposure are difficult to accurately recall years after the drug use, and may be compounded by the stigma of admitting to drug use during pregnancy. Further, women who receive methamphetamine from their partners may not actually know the dosage they ingest. Potential underreporting by biological mothers is of sufficient concern that reports from adoptive mothers (based on observation of biological mothers' behavior or from social services reports) may have similar levels of validity to that of biological mothers.

It is important that future studies with larger samples investigate the possibility of interactive effects between various drugs of abuse, in particular between methamphetamine and alcohol. However, unlike animal studies which allow for much more control over experimental conditions, retrospective human studies of prenatal drug exposure are not the ideal design for isolating the effects of a particular drug on the brain. In fact, given that polydrug exposure seems to be the norm, at least in Southern California where our subjects were recruited, it is not clear that samples with 'pure' single-drug exposures would be as relevant to the populations we ultimately hope to serve.

Conclusions

Despite some significant limitations, this investigation offers important contributions to the study of prenatal exposure to drugs of abuse in humans. For the first time, we report evidence for altered functional connectivity in the striatum in children and adolescents with prenatal methamphetamine and/or alcohol exposure. Further, this study raises the possibility that such a re-wiring of corticostriatal networks may lead to unique patterns of connectivity resulting in a maladaptive overlap between the executive and motor loop, which could underlie some of the cognitive and putative motor deficits documented in this population. Future studies should aim at replicating these findings in larger samples, and with resting-state scans. Other topics for future research include determining whether these functional correlations are supported by direct anatomical white matter connections (which could be achieved, for instance, by combining resting-state functional connectivity MRI and DTI), and examining the cognitive correlates of this reorganization of corticostriatal circuits. Findings from such studies will be instrumental in helping clinicians develop appropriate pharmacologic, behavioral, educational, and occupational strategies for prevention and remediation aimed at addressing the specific needs of this population in a more targeted and efficient manner.

Disclosure Statement

Dr. Roussotte, Mr. Rudie, Dr. Smith, Dr. O'Connor, Dr. Bookheimer, Dr. Narr and Dr. Sowell report no competing interests.

References

1 Colliver JD, Kroutil LA, Dai L, Gfroerer JC: Misuse of prescription drugs: data from the 2002, 2003, and 2004 National Surveys on Drug Use and Health Substance Abuse and Mental Health Services Administration, Office of Applied Studies, Rockville, 2006.

2 May PA, et al: The epidemiology of fetal alcohol syndrome and partial FAS in a South African community. Drug Alcohol Depend 2007;88:259–271.

3 May PA, et al: Epidemiology of FASD in a province in Italy: prevalence and characteristics of children in a random sample of schools. Alcohol Clin Exp Res 2006;30:1562–1575.

4 May PA, et al: Prevalence and epidemiologic characteristics of FASD from various research methods with an emphasis on recent in-school studies. Dev Disabil Res Rev 2009;15:176–192.

5 Substance Abuse and Mental Health Administration, CfDCaP, 2006, 2007.

6 Mitchell JJ, et al: A comparative study of ethanol, hypoglycemia, hypoxia and neurotrophic factor interactions with fetal rat hippocampal neurons: a multi-factor in vitro model developmental ethanol effects. Brain Res Dev Brain Res 1998;105:241–250.

7 Pollard I: Neuropharmacology of drugs and alcohol in mother and fetus. Semin Fetal Neonatal Med 2007;12:106–113.

8 Ornoy A: Embryonic oxidative stress as a mechanism of teratogenesis with special emphasis on diabetic embryopathy. Reprod Toxicol 2007;24:31–41.

9 Feng MJ, Yan SE, Yan QS: Effects of prenatal alcohol exposure on brain-derived neurotrophic factor and its receptor tyrosine kinase B in offspring. Brain Res 2005;1042:125–132.

10 Miller MW: Expression of transforming growth factor-β in developing rat cerebral cortex: effects of prenatal exposure to ethanol. J Comp Neurol 2003;460: 410–424.

11 Miller MW, Dow-Edwards DL: Structural and metabolic alterations in rat cerebral cortex induced by prenatal exposure to ethanol. Brain Res 1988;474:316–326.

12 Barrow Heaton MB, et al: Prenatal ethanol exposure reduces spinal cord motoneuron number in the fetal rat but does not affect GDNF target tissue protein. Dev Neurosci 1999;21:444–452.

13 Miller MW, Robertson S: Prenatal exposure to ethanol alters the postnatal development and transformation of radial glia to astrocytes in the cortex. J Comp Neurol 1993;337: 253–266.

14 Shetty AK, Phillips DE: Effects of prenatal ethanol exposure on the development of Bergmann glia and astrocytes in the rat cerebellum: an immunohistochemical study. J Comp Neurol 1992;321:19–32.

15 Redila VA, et al: Hippocampal cell proliferation is reduced following prenatal ethanol exposure but can be rescued with voluntary exercise. Hippocampus 2006;16:305–311.

16 Olney JW, et al: Ethanol-induced apoptotic neurodegeneration in the developing brain. Apoptosis 2000;5:515–521.

17 Ozer E, Sarioglu S, Gure A: Effects of prenatal ethanol exposure on neuronal migration, neuronogenesis and brain myelination in the mice brain. Clin Neuropathol 2000;19:21–25.

18 Mattson SN, Riley EP: A review of the neurobehavioral deficits in children with fetal alcohol syndrome or prenatal exposure to alcohol. Alcohol Clin Exp Res 1998;22:279–294.

19 Kodituwakku PW: Neurocognitive profile in children with fetal alcohol spectrum disorders. Dev Disabil Res Rev 2009;15:218–224.

20 Sowell ER, et al: Abnormal cortical thickness and brain-behavior correlation patterns in individuals with heavy prenatal alcohol exposure. Cereb Cortex 2008;18:136–144.

21 Mattson SN, et al: A decrease in the size of the basal ganglia in children with fetal alcohol syndrome. Alcohol Clin Exp Res 1996; 20:1088–1093.

22 McCann UD, Ricaurte GA: Amphetamine neurotoxicity: accomplishments and remaining challenges. Neurosci Biobehav Rev 2004;27:821–826.

23 Yamamoto BK, Moszczynska A, Gudelsky GA: Amphetamine toxicities: classical and emerging mechanisms. Ann NY Acad Sci 2010;1187:101–121.

24 Joya X, et al: Gas chromatography-mass spectrometry assay for the simultaneous quantification of drugs of abuse in human placenta at 12th week of gestation. Forensic Sci Int 2010;196:38–42.

25 Weissman AD, Caldecott-Hazard S: Developmental neurotoxicity to methamphetamines. Clin Exp Pharmacol Physiol 1995; 22:372–374.

26 Sato M, Fujiwara Y: Behavioral and neurochemical changes in pups prenatally exposed to methamphetamine. Brain Dev 1986;8: 390–396.

27 Weissman AD, Caldecott-Hazard S: In utero methamphetamine effects. I. Behavior and monoamine uptake sites in adult offspring. Synapse 1993;13:241–250.

28 Acuff-Smith KD, et al: Stage-specific effects of prenatal D-methamphetamine exposure on behavioral and eye development in rats. Neurotoxicol Teratol 1996;18:199–215.

29 Gomes-da-Silva J, et al: Prenatal exposure to methamphetamine in the rat: ontogeny of tyrosine hydroxylase mRNA expression in mesencephalic dopaminergic neurons. Ann NY Acad Sci 2002;965:68–77.

30 Smith LM, et al: Prenatal methamphetamine use and neonatal neurobehavioral outcome. Neurotoxicol Teratol 2008;30:20–28.

31 Smith LM, et al: Motor and cognitive outcomes through three years of age in children exposed to prenatal methamphetamine. Neurotoxicol Teratol 2011;33:176–184.

32 LaGasse LL, et al: Prenatal methamphetamine exposure and neonatal neurobehavioral outcome in the USA and New Zealand. Neurotoxicol Teratol 2011;33:166–175.

33 Smith LM, et al: The Infant Development, Environment, and Lifestyle Study: effects of prenatal methamphetamine exposure, polydrug exposure, and poverty on intrauterine growth. Pediatrics 2006;118:1149–1156.

34 Nguyen D, et al: Intrauterine growth of infants exposed to prenatal methamphetamine: results from the Infant Development, Environment, and Lifestyle Study. J Pediatr 2010;157:337–339.

35 Chang L, et al: Altered neurometabolites and motor integration in children exposed to methamphetamine in utero. Neuroimage 2009;48:391–397.

36 Chang L, et al: Smaller subcortical volumes and cognitive deficits in children with prenatal methamphetamine exposure. Psychiatry Res 2004;132:95–106.

37 Piper BJ, et al: Abnormalities in parentally rated executive function in methamphetamine/polysubstance exposed children. Pharmacol Biochem Behav 2011;98:432–439.

38 Sowell ER, et al: Differentiating prenatal exposure to methamphetamine and alcohol versus alcohol and not methamphetamine using tensor-based brain morphometry and discriminant analysis. J Neurosci 2010;30: 3876–3885.

39 Cloak CC, et al: Lower diffusion in white matter of children with prenatal methamphetamine exposure. Neurology 2009;72: 2068–2075.

40 Smith LM, et al: Brain proton magnetic resonance spectroscopy in children exposed to methamphetamine in utero. Neurology 2001;57:255–260.

41 Roussotte FF, et al: Abnormal brain activation during working memory in children with prenatal exposure to drugs of abuse: the effects of methamphetamine, alcohol, and polydrug exposure. Neuroimage 2011;54: 3067–3075.

42 Alexander GE, DeLong MR, Strick PL: Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986;9:357–381.

43 Cummings JL: Frontal-subcortical circuits and human behavior. Arch Neurol 1993;50: 873–880.

44 Lewis SJ, et al: Striatal contributions to working memory: a functional magnetic resonance imaging study in humans. Eur J Neurosci 2004;19:755–760.

45 Ueda Y, Kimura M: Encoding of direction and combination of movements by primate putamen neurons. Eur J Neurosci 2003;18: 980–994.

46 Yin HH, Knowlton BJ: The role of the basal ganglia in habit formation. Nat Rev Neurosci 2006;7:464–476.

47 Thiel A, et al: Activation of basal ganglia loops in idiopathic Parkinson's disease: a PET study. J Neural Transm 2003;110:1289–1301.

48 Lawrence AD, Sahakian BJ, Robbins TW: Cognitive functions and corticostriatal circuits: insights from Huntington's disease. Trends Cogn Sci 1998;2:379–388.

49 Lawrence AD, et al: Visual object and visuospatial cognition in Huntington's disease: implications for information processing in corticostriatal circuits. Brain, 2000;123(pt 7):1349–1364.

50 Middleton FA, Strick PL: Basal-ganglia 'projections' to the prefrontal cortex of the primate. Cereb Cortex 2002;12:926–935.

51 Helmich RC, et al: Spatial remapping of cortico-striatal connectivity in Parkinson's disease. Cereb Cortex 2010;20:1175–1186.

52 O'Connor MJ, et al: A controlled social skills training for children with fetal alcohol spectrum disorders. J Consult Clin Psychol 2006; 74:639–648.

53 Astley SJ: Diagnostic guide for fetal alcohol spectrum disorders: the 4-digit diagnostic code. Seattle, University of Washington, 2004.

54 Astley SJ, Clarren SK: Measuring the facial phenotype of individuals with prenatal alcohol exposure: correlations with brain dysfunction. Alcohol Alcohol 2001;36: 147–159.

55 Smith SM: Fast robust automated brain extraction. Hum Brain Mapp 2002;17:143–155.

56 Jenkinson M, et al: Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 2002;17:825–841.

57 Jenkinson M, Smith S: A global optimisation method for robust affine registration of brain images. Med Image Anal 2001;5:143–156.

58 Di Martino A, et al: Functional connectivity of human striatum: a resting state fMRI study. Cereb Cortex 2008;18:2735–2747.

59 Talairach J, Tournoux P: Co-planar stereotaxic atlas of the human brain: 3-dimensional proportional system: an approach to cerebral imaging. Stuttgart, Thieme, 1988.

60 Brett M: The MNI brain and the Talaraich Atlas. Medical Research Council, Cognition and Brain Science Technical Report, 1999. Available at: http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml.

61 Murphy K, et al: The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? Neuroimage 2009;44:893–905.

62 Roussotte F, Soderberg L, Sowell E: Structural, metabolic, and functional brain abnormalities as a result of prenatal exposure to drugs of abuse: evidence from neuroimaging. Neuropsychol Rev 2010;20:376–397.

63 Postuma RB, Dagher A: Basal ganglia functional connectivity based on a meta-analysis of 126 positron emission tomography and functional magnetic resonance imaging publications. Cereb Cortex 2006;16:1508–1521.

64 Archibald SL, et al: Brain dysmorphology in individuals with severe prenatal alcohol exposure. Dev Med Child Neurol 2001;43:148–154.

65 Cortese BM, et al: Magnetic resonance and spectroscopic imaging in prenatal alcohol-exposed children: preliminary findings in the caudate nucleus. Neurotoxicol Teratol 2006;28:597–606.

66 Moszczynska A, et al: Why is parkinsonism not a feature of human methamphetamine users? Brain 2004;127(pt 2):363–370.

67 Mounayar S, et al: A new model to study compensatory mechanisms in MPTP-treated monkeys exhibiting recovery. Brain 2007;130(pt 11):2898–2914.

68 Parent A, Hazrati LN: Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. Brain Res Brain Res Rev 1995;20:91–127.

69 Clark CM, et al: Structural and functional brain integrity of fetal alcohol syndrome in nonretarded cases. Pediatrics 2000;105:1096–1099.

70 Fryer SL, et al: Prenatal alcohol exposure affects frontal-striatal BOLD response during inhibitory control. Alcohol Clin Exp Res 2007;31:1415–1424.

71 Colby JB, Smith L, O'Connor MJ, Bookheimer SY, Van Horn JD, Sowell ER: The effects of prenatal methamphetamine/polydrug exposure on white matter microstructure: a tract-based diffusion imaging study. Psychiatry Res, in press.

72 Slotkin TA: Fetal nicotine or cocaine exposure: which one is worse? J Pharmacol Exp Ther 1998;285:931–945.

73 Thompson BL, Levitt P, Stanwood GD: Prenatal exposure to drugs: effects on brain development and implications for policy and education. Nat Rev Neurosci 2009;10:303–312.