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Prenatal methamphetamine exposure is associated with reduced subcortical volumes in neonates

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Abstract

Objectives—Prenatal exposure to methamphetamine is associated with a range of neuropsychological, behavioural and cognitive deficits. A small number of imaging studies suggests that these may be mediated by neurostructural changes, including reduced volumes of specific brain regions. This study investigated potential volumetric changes in the brains of neonates with prenatal methamphetamine exposure. To our knowledge no previous studies have examined methamphetamine effects on regional brain volumes at this age.

Study Design—Mothers were recruited antenatally and interviewed regarding methamphetamine use during pregnancy. Mothers in the exposure group reported using methamphetamine twice/month during pregnancy; control infants had no exposure to methamphetamine or other drugs and minimal exposure to alcohol. MRI scans were performed in the first postnatal month, following which anatomical images were processed using FreeSurfer. Subcortical and cerebellar regions were manually segmented and their volumes determined using FreeView. Pearson correlations were used to analyse potential associations between methamphetamine exposure and regional volumes. The association between methamphetamine exposure and regional volumes were then examined adjusting for potential confounding variables.

Results—Methamphetamine exposure was associated with reduced left and right caudate and thalamus volumes. The association in the right caudate remained significant following adjustment for potential confounding variables.

Conclusions—Our findings showing reduced caudate and thalamus volumes in neonates with prenatal methamphetamine exposure are consistent with previous findings in older exposed children, and demonstrate that these changes are already detectable in neonates. Continuing research is warranted to examine whether reduced subcortical volumes are predictive of cognitive, behavioural and affective impairment in older children.

Keywords

Magnetic resonance imaging; prenatal methamphetamine exposure; neonate; caudate nucleus; thalamus; regional brain volumes

1. Introduction

Methamphetamine is one of the most widely used recreational drugs globally (Nguyen et al., 2010) and there is considerable evidence that exposure during pregnancy has marked effects on the infant (Carter et al., 2016; Good et al., 2010; Gorman et al., 2014; Ladhani et al., 2011; Smith et al., 2003). Given the dopaminergic activity of methamphetamine and its documented neurotoxicity in adult users (Chang et al., 2009; Sowell et al., 2010), it was expected that prenatal exposure would induce similar damaging effects on the infants concerned, considering the rapid development and growth of the central nervous system that occurs during this period (Salisbury et al., 2009). Neuropsychological and behavioural alterations have been observed in studies of children with prenatal methamphetamine

exposure, including low arousal and lethargy (LaGasse et al., 2011; Paz et al., 2009), poor fine motor skills (Smith et al., 2011), poor psychomotor and emotional adjustment (Billing et al., 1988) and aggressive behaviour (Billing et al., 1994). Deficits in visuomotor integration (Chang et al., 2009), inhibitory control (Derauf et al., 2012a), and executive function and working memory (Piper et al., 2011) have also been observed in children with *in utero* methamphetamine exposure. In view of these findings, it is of interest to determine whether these deficits reflect structural alterations in the brain related to prenatal methamphetamine exposure, and whether these alterations can already be detected in the newborn.

Magnetic resonance spectroscopy, diffusion tensor imaging and functional MRI have shown a range of metabolic, microstructural and functional alterations as a consequence of prenatal methamphetamine exposure (Buchthal et al., 2009; Chang et al., 2016, 2009; Cloak et al., 2009; Colby et al., 2012; Lu et al., 2009; Roos et al., 2015; Roussotte et al., 2011; Smith et al., 2001). In children with prenatal methamphetamine and alcohol exposure, reductions in volume in the thalamus, striatum, and left parieto-occipital and right anterior prefrontal cortices, and increased volumes of several cortical regions, were observed compared to controls and to children with alcohol exposure only (Sowell et al., 2010). Similarly, reduced caudate volumes were observed in children aged 6-7 years with prenatal methamphetamine exposure (Derauf et al., 2012b). Putamen and globus pallidus volumes were reduced in methamphetamine exposed children, with a trend towards volume reductions of the caudate, thalamus, hippocampus and cerebellum (Chang et al., 2004). A number of these reductions were related to poorer cognitive function (Chang et al., 2004).

Prenatal methamphetamine exposure has been shown to have considerable, persistent effects on dopaminergic regions of the brain such as the fronto-striatal circuits, as well as certain non-dopaminergic regions. The neuroimaging literature, however, is sparse. To our knowledge, no volumetric studies have been conducted with neonates. Such an investigation in neonates is highly warranted, not least because of the sub-optimal postnatal environment into which these children are often born (Good et al., 2010; Nguyen et al., 2010; Piper et al., 2011; Smith et al., 2003). A more complete understanding of the structural abnormalities associated with prenatal methamphetamine exposure may assist in the development of more effective interventions for concomitant cognitive and behavioural deficits. The aim of this study was thus to investigate the volumetric changes in subcortical areas and cerebellum of the brains of neonates with prenatal methamphetamine exposure. We hypothesized that increased exposure to methamphetamine would be associated with reduced volume of the striatal structures.

2. Methods

2.1 Study sample

The cohort consisted of 39 infants born to women in a Cape Coloured (mixed ancestry) community of Cape Town, South Africa, who are participating in a larger prospective longitudinal study of prenatal alcohol and drug exposure on infant development (Carter et al., 2016; Jacobson et al., 2017; Taylor et al., 2015). The rate of methamphetamine ('tik') abuse in this community is the highest in South Africa (Peltzer et al., 2010), with 35-43% of

drug treatment patients reporting it as their primary drug (Meade et al., 2015; Plüddemann et al., 2013). Rates of use among women in this community have been reported to be as high as 58% (Wechsberg et al., 2010). Methamphetamine use in this community has been strongly linked with the pervasive and unique gang culture of the area (Pasche and Myers, 2012), and is associated with increased interpersonal violence, mental health issues and sexual risk behaviours (Meade et al., 2012; Plüddemann et al., 2010; Wechsberg et al., 2008).

Pregnant mothers were recruited following initial antenatal care visits at midwife obstetric care units serving the community. The mothers were interviewed, once at recruitment and twice more before delivery, regarding their alcohol consumption using a time-line follow-back approach (Jacobson et al., 2008, 2002), and about the frequency of use (days per month) of methamphetamine, cigarettes and other drugs (marijuana ('dagga'), methaqualone ('mandrax'), and cocaine) during pregnancy. The present study consists of infants born to women in the cohort who reported using methamphetamine at least twice per month during pregnancy. The control group, recruited from the same community, comprises infants whose mothers abstained from alcohol and other drugs of abuse or who consumed no more than 2 drinks on 2 or fewer occasions during pregnancy. Exclusion criteria for pregnant women were as follows: < 18 years of age, HIV positive, treatment for medical conditions such as hypertension, epilepsy, diabetes or heart disease, and multiple pregnancy. Infant exclusion criteria were neural tube defects, major chromosomal anomalies, very low birth weight (<1200g), gestational age <30 weeks, and seizures (Carter et al., 2016).

Informed consent was obtained from each mother at recruitment and at the University of Cape Town (UCT) Child Development Research Laboratory and neuroimaging visits. Approval for this study was obtained from the ethics committees at Wayne State University and the Faculty of Health Sciences at UCT. Mothers were given breakfast and a snack during the morning at each visit. At the end of each visit, the mother received a small monetary compensation.

2.2 Interview Procedure

A staff driver and research staff nurse transported the mothers to our UCT Child Development Research Laboratory, where they were interviewed regarding their alcohol and drug use, and sociodemographic background information was obtained. They were also administered the 18-item Family Food Security interview (Bickel et al., 2000), which has been widely used to assess adequacy of food availability (e.g. (Health Canada, 2007)). Based on the mothers' responses, families were classified as food insecure if the mother reported moderate to severe hunger (Jacobson et al., 2017). Because no measure of weight prior to conception was available, we measured gestational weight gain (kg/wk) by subtracting the mother's weight at the first interview from her weight at the last one and dividing by number of weeks between the two interviews.

Urine samples were collected to examine the validity of maternal reports of drug use (Carter et al., 2016). Sample collection only began in the latter part of the larger cohort study (Jacobson et al., 2017). Urine samples from 105 women in the cohort were tested by the research nurse using the AccuTest™ 6+2 drugs of abuse panel (DTA Pty Ltd, Cape Town, South Africa), an immunochemical assay that detects metabolites of drugs commonly used

in this community (amphetamines, cocaine, methaqualone, methamphetamine, opiates and marijuana (THC)), as well as pH and creatinine to test for sample adulteration. These samples were only available for 9 of the women in the current study. However, the urine assays from the larger cohort validated the maternal reports of drug use (Carter et al., in press). None of the women refused drug testing.

2.3 Scanning

Nonsedated infants were scanned between 1 and 4 weeks after birth, with the exception of two infants born prior to 34 weeks who were scanned at 7 and 9 weeks of age, respectively (Jacobson et al., 2017).

Infants and their mothers were transported to the Cape Universities Brain Imaging Centre (CUBIC) a minimum of 1 hour prior to scanning. During this period the infants were weighed and head circumference and crown-to-heel length were measured. Neonatal behavioural characteristics (Brazelton, 1984) were assessed by a trained developmental paediatrician (CDM). Following this, the infant was swaddled firmly and placed in a VacFix® vacuum cushion (S&S Par Scientific, Houston, TX) for later use in immobilising the infant's head in the coil, in accordance with an adapted protocol for neuroimaging assessment of nonsedated newborns (Laswad et al., 2009). Earplugs were used to protect the infant from the noise of the scanner. The infant was then fed by the mother and allowed to fall asleep.

MRI scanning was performed using a Siemens 3 T Allegra scanner. A custom-built circularly polarised birdcage coil, designed for use with neonates, was used for transmission and reception of the signal. Several sequences were acquired during the protocol. For this study a motion navigated multiecho gradient echo sequence was used, with the following protocol parameters: FOV 114 mm, 128 slices, TR 20 ms, TE 1.46/ 3.14/ 4.82/ 6.5/ 8.18/ 9.86/ 11.54/ 13.22 ms, 1 mm³ isotropic resolution. The sequence was acquired twice, with flip angles of 5° and 20°, respectively.

The sleeping infant was positioned in the scanner and immobilised by means of the VacFix® cushion. An oxygen saturation and pulse monitor probe was secured to the infant's foot, and this was monitored during the scanning period.

2.4 Data synthesis

The individual echoes from the two flip angle acquisitions were split, tissue parameters estimated and an image volume synthesised using FreeSurfer (Fischl et al., 2004). A flip angle of 24° was chosen as that which produced optimal contrast.

2.5 Manual Segmentation

Regions of interest (ROIs) were viewed and manually delineated using Freeview software (FreeSurfer image analysis suite <http://surfer.nmr.mgh.harvard.edu/>) run on a Lenovo ThinkPad X220 tablet. The following structures were traced bilaterally: caudate nucleus, nucleus accumbens, putamen, pallidum, thalamus, hippocampus, amygdala and cerebellar hemispheres, as well as the cerebellar vermis. Tracing protocols for each section followed

the Infant Brain Segmentation Manual developed by the HST/MGH Athinoula A. Martinos Center for Biomedical Imaging (de Macedo Rodrigues et al., 2015), where training in the use of Freeview software and manual tracing of infant MRI scans was received. Tracings were rendered chiefly in the coronal plane, with guidance from the axial and sagittal planes where region boundaries were indistinct in a coronal view. The volumes of the traced regions were then calculated. Total brain volume was determined by extracting the brain from the anatomical T1-weighted volumes using an in-house script. Nine brains were independently retraced for inter-rater reliability purposes. Both tracers (FLW, NML) were blind to the exposure status of the infant brains. Dice overlap measures were determined for all ROIs using FreeSurfer.

2.6 Statistical Analysis

Statistical analysis was performed using SPSS (version 22; IBM, Armonk, NY). Eight variables were considered as potential confounders: maternal age at delivery, educational status (number of years), parity, maternal marijuana use (days per month during pregnancy), smoking (number of cigarettes per day during pregnancy), alcohol use (oz of absolute alcohol consumed per day during pregnancy), and infant sex and gestational age at scan (weeks). Total brain volume was not considered a potential confounder as it was unrelated to methamphetamine exposure.

T-tests or chi-square tests for categorical variables were used to compare sample characteristics between exposed and control groups. The methamphetamine use and smoking variables both contained outliers, which were recoded to 1 unit greater than the next highest value (see (Winer, 1971)). Prenatal alcohol use was skewed and was therefore logged for multivariable analyses.

Pearson correlation was used to analyse the relation between methamphetamine exposure and ROI volume in the methamphetamine exposed group. Following this, regions showing significant association with methamphetamine exposure were analysed by means of hierarchical multiple regression using a best estimate approach. Methamphetamine was entered first into the regression; the potential confounders described above which were at least weakly related to volume ($p < 0.10$) were then entered.

3. Results

3.1 Sample characteristics

We report data for 39 infants (18 methamphetamine exposed and 21 controls). Demographic and substance exposure characteristics of the infants are summarised in Table 1. Maternal education differed between groups, with controls achieving a higher level of education than the methamphetamine group. Food security and maternal weight gain during pregnancy did not differ between groups. The 24-hr dietary recall interviews for the 39 women showed no group difference for energy (calorie intake), carbohydrates, proteins, and fat (all p 's > 0.20). The only differences found for this sample were that controls reported lower intake of cholesterol, fluoride and selenium in their diet.

The sample consisted of 18 male and 21 female infants. Infants exposed to methamphetamine were born earlier, which is consistent with previous studies (Carter et al., 2016; Ladhani et al., 2011). Although the methamphetamine group weighed less at birth, there was no between-group difference in terms of gestational age at scan (calculated as gestational age at birth + age in weeks).

Mean methamphetamine, smoking, marijuana and alcohol use by mothers of the exposed group was higher than in the control group. Although control mothers did not use methamphetamine, 62% ($n = 13$) reported smoking, 9.5% ($n = 2$) used marijuana and 4.8% ($n = 1$) drank alcohol. The 1 control mother who reported alcohol use drank about 2 drinks/occasion, which is considered light drinking and within the acceptable limits set for inclusion as a control. By contrast, all 18 of the mothers in the exposed group reported smoking, 55.6% ($n = 10$) reported using marijuana and 55.6% ($n = 10$) reported drinking alcohol during pregnancy.

Only 9 (23.1%) of the mothers in the sample had urine drug screens: 3 of the 9 were in the methamphetamine group, and all 3 admitted using methamphetamine; 2 admitted using marijuana, but all 3 denied using methaqualone. All 3 tested positive for methamphetamine, marijuana and methaqualone. The 6 control mothers denied using methamphetamine, marijuana and methaqualone, and all 6 tested negative for all drugs in the urine screen.

3.2 Inter-rater reliability of manual tracing

Volumes of traced regions and inter-rater reliability measures are reported in Table 2. Interrater reliabilities are reported as the median and range of the Dice coefficients calculated for 9 brains. The median Dice values of 10 ROIs (caudate, putamen, thalamus, and cerebellar hemispheres bilaterally, right and left hippocampus, and vermis) were greater or equal to 0.80. The remaining ROIs had Dice coefficients below 0.70. As Dice 0.80 is generally considered good interrater reliability, pallidum, nucleus accumbens, and amygdala bilaterally were discarded from further analyses.

3.3 Relation of methamphetamine exposure to subcortical regional volumes

Pearson correlation analyses investigated the associations between methamphetamine exposure and all subcortical regions which met the reliability threshold, in methamphetamine exposed infants (shown in Table 3). These analyses showed that heavier methamphetamine exposure was associated with reduced right caudate volume (Fig. 1), and reduced left caudate and bilateral thalamus volumes at a trend level. No association was observed between methamphetamine exposure and the other regions. Total intracranial volume was not significantly associated with methamphetamine exposure ($r = -0.38$, $p = 0.122$).

Potential confounding variables (see Table 4) were included in the subsequent regression analyses if they showed a correlation with ROI volume at $p < 0.10$. Cigarette smoking and alcohol exposure were associated with left and right caudate volume respectively, while gestational age at time of scan was associated with left and right thalamus volumes. Left and right caudate and thalamus volumes were then each regressed on methamphetamine, followed by the associated confounders for each ROI. Prenatal exposure to

methamphetamine was associated with reduced volume in the right caudate after controlling for the potential confounder alcohol exposure ($\beta = -0.55$, $p = 0.009$). Methamphetamine exposure was associated with left caudate volume at a trend level after controlling for the potential confounder maternal smoking ($\beta = -0.42$; $p = 0.065$). After control for gestational age at scan, methamphetamine exposure was associated with left and right thalamus volumes at a trend level (left: $\beta = -0.33$, $p = 0.094$; right: $\beta = -0.39$, $p = 0.063$). Correlation and regression analyses which excluded control mothers who drank alcohol or used marijuana showed that their exclusion made essentially no change to the findings (results not shown). Similarly, exclusion of one methamphetamine-exposed infant who was born at 31 weeks produced no substantive changes (results not shown).

4. Discussion

This study is the first to investigate the effects of prenatal exposure to methamphetamine on regional brain volumes in neonates. As hypothesised, changes were observed in the left and right caudate nuclei, with reduced volume observed as a consequence of prenatal methamphetamine exposure. Similarly, the thalamus bilaterally showed a reduction in volume in association with prenatal methamphetamine exposure. Although the association in the left caudate and the thalamus remained at a trend level when confounding variables were included in the analysis, the effect of methamphetamine on the right caudate remained significant.

These results are consistent with those obtained in previous studies in which volumetric effects of prenatal methamphetamine exposure on subcortical structures were observed in older cohorts. In a study of children aged between 5 and 15 years, the striatum and thalamus were smaller in children exposed to both methamphetamine and alcohol prenatally, with the striatal volume reduction more severe than in children exposed to alcohol alone (Sowell et al., 2010). A study of 3- to 5-year-old children demonstrated significantly lower caudate volume in children with prenatal methamphetamine exposure than in controls, although no effect in the thalamus was observed (Derauf et al., 2012b). A trend towards reduction in volume was observed in the caudates of children aged 3-16 years with prenatal methamphetamine exposure (Chang et al., 2004). In an investigation of children aged 8-11 years with multiple substance exposure, including methamphetamine, trends towards reduced caudate and thalamus volume were observed, with significantly decreased total volume (Walhovd et al., 2007). By contrast, increased striatal volume was found in 6-year-olds with *in utero* methamphetamine exposure, findings which may reflect methodological differences, given that this was the only study that performed automated segmentation using FreeSurfer (Roos et al., 2014). In adult users, volumetric alterations have been observed in a number of studies. A reduction in caudate volume was noted in methamphetamine-dependent smokers (Morales et al., 2012). Other research, however, observed increased caudate volume in recently abstinent methamphetamine users (Chang et al., 2005; Jernigan et al., 2005).

The weaker effect of methamphetamine in the left caudate than the right was unexpected but may be due to chance confounding in this sample. The association of methamphetamine with volume was weaker in the left caudate than in the right before the addition of the

confounding variables, while the association of cigarette smoking with volume was considerably stronger in the left caudate than in the right. Cigarette smoking has been shown to be associated with volume reductions in a variety of brain structures in adult smokers (Gallinat et al., 2006) and children with prenatal exposure (Ekblad et al., 2010). Given that the relative magnitudes of these effects might vary in different samples, it seems reasonable to suggest that both these exposures have bilateral impact, particularly in neonates. Findings in neonates are likely more “widespread” and may account for discrepancies in hemispheres, given that cognitive development is not refined and left brain dominance related to analytical learning develops later in life.

Previous studies of prenatal methamphetamine exposure reported volume reductions in additional regions, such as the hippocampus (Chang et al., 2004), as well as in a number of frontal cortical regions (Sowell et al., 2010). These alterations were not observed in the current study. It is worth noting that the strength of the association between methamphetamine and thalamus volume in this study might well have proved significant with a larger sample size; the same can be said of the association of methamphetamine exposure with cerebellar volumes. The strength of the association of methamphetamine with caudate volume in the current study, however, lends support to the hypothesis that prenatal methamphetamine specifically targets dopamine-rich regions. The thalamus relays outputs from the basal ganglia to the cortex (Haber, 2014) and has been shown to be profusely innervated with dopaminergic axons (García-Cabezas et al., 2007; Sanchez-Gonzalez, 2005), making it similarly vulnerable to dopamine-related insults (Salzwedel et al., 2016). This is in striking contrast to alcohol, which has been shown to be teratogenic to multiple regions of the brain (Astley et al., 2009; Coles et al., 2011; Meintjes et al., 2014; Sowell et al., 2008), and suggests that the mechanisms whereby methamphetamine and alcohol induce CNS damage are likely distinct from one another.

Reduced birth weight and lower gestational age at birth have previously been shown to be associated with prenatal methamphetamine exposure (Ladhani et al., 2011; Shah et al., 2012; Woudes et al., 2014). This may be due to the vasoconstrictive effect of methamphetamine, causing reduced blood flow across the placenta (Stek et al., 1995) and consequent restriction of nutrient and oxygen supply to the fetus (Chang et al., 2004; Nguyen et al., 2010). Analysis of placental development in our cohort showed that methamphetamine use during pregnancy was associated with increased placental size, as well as increased placenta- to birth- weight ratio, lower gestational age at birth, and increased risk of intrauterine passing of meconium, which suggests that the exposed fetus may experience prolonged periods of hypoxia-ischemia (Carter et al., 2016).

The precise mechanisms whereby *in utero* methamphetamine exposure reduces the volumes of subcortical structures are not fully understood. Methamphetamine has been shown to be neurotoxic to dopaminergic and serotonergic axons and terminals in animal (Cappon et al., 2000; Castner et al., 2005; LaVoie et al., 2004; Marshall et al., 2007) and human studies (Lee et al., 2009; McCann et al., 1998), and in mature neurons appears to involve the production of reactive oxygen species (ROS), activation of P53 and subsequent apoptosis, and dysfunction of mitochondria (Quinton and Yamamoto, 2006). Alterations in dopamine and dopamine metabolite concentrations have been observed in the striatum of rats

issue when the subjects are neonates, as incomplete myelination of the neonatal brain (Rivkin, 2000) presents a challenge in correctly identifying regions of interest.

One limitation of this study is the potential confounding effects of polysubstance exposure, with the methamphetamine-exposed infants also having higher exposure to alcohol, cigarette smoking and marijuana. This is, unfortunately, almost inevitable in studies of prenatal drug exposure (Roos et al., 2015; Sowell et al., 2010). These other exposures were, however, controlled in the multivariable analyses in this study. Moreover, as mentioned above, recruitment during pregnancy allowed for a more accurate measure of substance use. Previous studies (Chang et al., 2004; Roos et al., 2014; Sowell et al., 2010) did not control for cigarette exposure, which was shown to be a significant confounding variable in the current study.

Another limitation is that the biological measures of exposure were available for only 9 of the 39 women in this sample. Additionally, drug use may not be detectable in urine if that use occurred several days before testing. However, the urine tests for the 9 showed that the maternal interviewing was successful in eliciting accurate responses regarding methamphetamine use. Of the 105 women with urine drug tests in our larger study, results were consistent with maternal reports for 96 (91.4%) for marijuana, cocaine, opiates and methamphetamine. None of the 3 women in the current sample who tested positive for methaqualone reported its use. In this community, methaqualone is commonly mixed with other drugs prior to being sold, often without the user's knowledge. Consistent with maternal reports, no urine tests were positive for cocaine or opiates.

It should be considered that some unexamined additional factor, such as malnutrition, may have played a role in these findings. However, both exposed and control groups were recruited from the same community, and socioeconomic status (Hollingshead, 2011) did not differ between groups. Moreover, the methamphetamine and control groups did not differ in food security, weight gain during pregnancy or calorie, carbohydrate, protein and fat intake, suggesting that nutritional status was similar in the two groups. Furthermore, neither birth weight nor crown-to-heel length, both of which might be considered measures of intrauterine nutritional status, was different between exposed and control children.

The sample size was small but comparable to other studies (Roos et al., 2014; Sowell et al., 2010) and sufficient to observe statistically significant effects. It is possible that with a larger cohort additional differences might have been significant. A potential concern, as in most such studies, is the issue of multiple comparisons. Eleven ROIs were included in the final analysis. However, the association of methamphetamine with right caudate volume remained significant, prior to the addition of confounders, even after controlling for multiple comparisons. Furthermore, as mentioned previously, the significant exposure effect was predicted *a priori* and found in the part of the striatum where it was expected, which provides additional support for its validity.

Given the rapid and heterochronous nature of early brain growth (Oishi et al., 2013), regional volumes obtained in the first weeks of life are particularly challenging to measure. Segmentation of the newborn brain is more time-consuming due to lower contrast-to-noise

ratio (Gousias et al., 2012). Although the brain stem and posterior limbs of the internal capsule are myelinated in the newborn with white to gray matter contrast that is similar to the adult brain, other regions are unmyelinated with the gray/ white contrast inverted in T1-weighted images relative to adult contrast (Dubois et al., 2014; Xue et al., 2007). Despite these difficulties, we were able to demonstrate reductions in caudate and thalamus volumes in methamphetamine-exposed newborns, consistent with previously published research in older children. These reductions are thus already detectable in exposed infants in the first month postpartum. Future research is warranted to examine whether reduced subcortical volumes in methamphetamine-exposed neonates is predictive of the cognitive, behavioural and affective impairments observed in older children.

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Abbreviations

MRI	Magnetic resonance imaging
ROI	Region of interest

Highlights

- Prenatal methamphetamine exposure is associated with reduced caudate volume in human newborns
- Prenatal methamphetamine exposure is associated with reduced thalamus volume in neonates
- Volume reductions previously observed in older children are already detectable in newborns

Figure 1.
Relation of prenatal methamphetamine exposure across pregnancy to volume of the right caudate nucleus in methamphetamine exposed newborns ($n = 18$).

Table 1

Sample characteristics (N = 39)

	Methamphetamine			Control			χ^2 or <i>t</i>	<i>p</i>
	Mean	SD	Range	Mean	SD	Range		
Maternal								
Age at delivery (years)	27.0	4.2	19.8–34.0	26.7	5.9	18.8–36.4	−0.19	0.850
Education (years)	9.3	1.4	7.0–12.0	10.5	1.4	7.0–12.0	2.60	0.013
Parity	3.2	1.6	1–6	2.4	1.3	1–5	−1.70	0.098
Socioeconomic status ^a	20.2	4.7	11.0–27.0	22.1	7.2	8.0–34.5	0.96	0.342
Food security (% moderate-severe) ^b	11.8			28.6			1.60	0.206
Gestational weight gain (kg/wk)	0.4	0.3	−0.2–1.1	0.4	0.3	−0.3–0.8	0.26	0.794
Dietary caloric intake (kJ/day) ^c	9601.06	3120.35	4278.80–15,863.10	9356.24	5881.96	3741.90–28,849.80	−0.16	0.875
Infant								
Sex (% male)	33			57			2.21	0.137
Birth weight (g)	2804.2	498.9	1370.0–3590.0	2915.7	541.7	1940.0–4200.0	0.67	0.510
Head circumference (cm)	32.9	1.9	27.0–35.0	33.3	2.0	31.0–38.0	0.67	0.509
Crown-to-heel length (cm) ^d	47.6	3.5	41.0–53.0	48.8	3.4	40.0–53.0	1.08	0.287
Gestational age at birth (weeks)	37.6	2.7	31.0–41.3	39.1	2.0	33.7–42.1	2.01	0.052
Gestational age at scan (weeks)	40.5	2.1	36.7–44.0	41.6	1.9	37.6–44.6	1.65	0.107
Total intracranial volume (mm ³)	491,044	41,631	395,900–549,600	516,805	69,236	428,700–660,700	1.38	0.177
Substance use								
Methamphetamine (days/month)	6.1	3.8	0.7–12.0	0.0	0.0	0.0–0.0	−7.34	<0.001
Smoking (number cigarettes/day)	6.5 ^e	4.5	2.0–20.0	3.5 ^f	3.4	0.0–10.3	−2.42	0.021
Marijuana (days/month)	5.8 ^g	8.4	0.0–30.5	0.0 ^h	0.1	0.0–0.2	−3.18	0.003
Alcohol (oz AA/day)	0.2 ⁱ	0.4	0.0–1.4	0.0 ^j	0.0	0.0–0.1	−2.15	0.038

^a Hollingshead (2011) Four Factor Index of Social Status Scale.

^b *n* = 20 for control.

^cBased on multiple pass 24-h dietary recall interviews, quantified using FoodFinder[®].

^d*n* = 17 for methamphetamine group.

^e18/18 (100%) smoked.

^f13/21 (62%) smoked.

^g10/18 (56%) used marijuana.

^h2/21 (10%) used marijuana.

ⁱ10/18 (56%) used alcohol.

^j1/21 (5%) used alcohol.

Table 2
Volumes and interrater reliability measures

ROI	Volume (mm ³)		Dice Coefficients	
	Methamphetamine (n=18) Mean $\pm$ SD	Control (n=21) Mean $\pm$ SD	Median	Range
Overall	-	-	88.5	84.7 - 99.6
Left caudate	1241 $\pm$ 201	1300 $\pm$ 197	84.6	83.2 - 88.8
Right caudate	1175 $\pm$ 159	1264 $\pm$ 156	86.6	84.4 - 89.9
Left putamen	1679 $\pm$ 256	1806 $\pm$ 322	81.5	76.7 - 87.3
Right putamen	1720 $\pm$ 242	1798 $\pm$ 328	84.0	73.2 - 86.5
Left pallidum	650 $\pm$ 111	685 $\pm$ 123	66.8	37.7 - 76.1
Right pallidum	594 $\pm$ 91	626 $\pm$ 131	69.8	49.8 - 81.1
Left nucleus accumbens	150 $\pm$ 29	148 $\pm$ 41	38.3	18.0 - 63.4
Right nucleus accumbens	158 $\pm$ 41	147 $\pm$ 41	43.1	28.1 - 66.2
Left thalamus	4344 $\pm$ 352	4435 $\pm$ 713	90.3	85.3 - 92.1
Right thalamus	4264 $\pm$ 360	4470 $\pm$ 708	90.8	86.4 - 92.9
Left hippocampus	1187 $\pm$ 148	1149 $\pm$ 151	80.8	63.2 - 85.1
Right hippocampus	1173 $\pm$ 109	1144 $\pm$ 140	79.7	73.4 - 86.3
Left amygdala	383 $\pm$ 116	370 $\pm$ 74	64.2	44.6 - 75.6
Right amygdala	406 $\pm$ 124	374 $\pm$ 79	67.5	54.0 - 74.5
Vermis	1957 $\pm$ 383	1986 $\pm$ 386	84.7	71.4 - 89.7
Left cerebellar cortex	10207 $\pm$ 1500	10365 $\pm$ 1949	92.4	91.7 - 96.0
Right cerebellar cortex	10188 $\pm$ 1447	10501 $\pm$ 1820	93.3	88.6 - 95.8

Table 3
Association between prenatal methamphetamine exposure and volume of subcortical structures ($n = 18$)

Volume (ROI)	Methamphetamine exposure	
	<i>r</i>	<i>p</i>
Left caudate	-0.44	0.071
Right caudate	-0.62	0.006
Left putamen	0.10	0.700
Right putamen	-0.02	0.946
Left thalamus	-0.42	0.087
Right thalamus	-0.46	0.054
Left hippocampus	-0.38	0.116
Right hippocampus	0.02	0.946
Vermis	-0.10	0.686
Left cerebellum	-0.39	0.109
Right cerebellum	-0.38	0.125

r is the Pearson correlation between methamphetamine exposure and volume in methamphetamine-exposed infants. Boldface denotes significant findings.

Table 4
Association of potential confounding variables with volumes of regions showing significant associations with methamphetamine ($n = 18$)

	Maternal age (years)	Education (years)	Parity	Marijuana (days/month)	Smoking (number of cigarettes/ day)	Alcohol (oz AA/day)	Infant sex	Gestation at age at scan (weeks)
Left caudate	-0.02 (0.953)	0.09 (0.733)	-0.23 (0.355)	0.08 (0.749)	-0.42 (0.081)	0.33 (0.180)	-0.26 (0.291)	0.07 (0.796)
Right caudate	-0.17 (0.492)	-0.14 (0.594)	-0.25 (0.325)	0.25 (0.326)	-0.14 (0.585)	0.48 (0.046)	-0.32 (0.195)	0.27 (0.281)
Left thalamus	-0.25 (0.325)	-0.31 (0.216)	-0.21 (0.400)	-0.14 (0.587)	-0.14 (0.594)	0.24 (0.337)	-0.17 (0.506)	0.63 (0.005)
Right thalamus	-0.35 (0.152)	-0.30 (0.226)	-0.279 (0.262)	-0.02 (0.930)	-0.07 (0.789)	0.33 (0.182)	-0.06 (0.804)	0.56 (0.016)

Values are Pearson r (p) in methamphetamine-exposed infants. Results with a trend towards association ($p < 0.10$) are shown in boldface.