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Reduced fractional anisotropy in projection, association and commissural fibre networks in neonates with prenatal methamphetamine exposure

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Abstract

Prenatal exposure to methamphetamine is associated with neurostructural changes, including alterations in white matter microstructure. This study investigated the effects of methamphetamine

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AUTHOR CONTRIBUTION

FL Warton conceptualised the methamphetamine study, participated in subject scanning, conducted data analyses, prepared the manuscript and approved the final manuscript.

PA Taylor designed data analysis methods, supervised and reviewed data analysis, critically reviewed the manuscript and approved the final manuscript.

CMR Warton reviewed the anatomical data collection, critically reviewed the manuscript and approved the final manuscript.

CD Molteno examined and prepared the infants for the neonatal scanning, monitored the infants during the scan and reviewed the manuscript.

P Wintermark designed the procedure for preparing the infants for the neonatal scanning without sedation and provided initial training and supervision in implementing these techniques.

L Zöllei designed data collection instruments, assisted in data analysis and reviewed the manuscript.

SW Jacobson, JL Jacobson, A van der Kouwe, and EM Meintjes conceptualised and designed the infant scan study, supervised and reviewed data analysis, critically reviewed the manuscript and approved the final manuscript.

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exposure on microstructure of global white matter networks in neonates. Pregnant women were interviewed beginning in mid-pregnancy regarding their methamphetamine use. Diffusion weighted imaging sets were acquired for 23 non-sedated neonates. White matter bundles associated with pairs of target regions within five networks (commissural fibres, left and right projection fibres, and left and right association fibres) were estimated using probabilistic tractography, and fractional anisotropy (FA) and diffusion measures determined within each connection. Multiple regression analyses showed that increasing methamphetamine exposure was significantly associated with reduced FA in all five networks, after control for potential confounders. Increased exposure was associated with lower axial diffusivity in the right association fibre network and with increased radial diffusivity in the right projection and left and right association fibre networks. Within the projection and association networks a subset of individual connections showed a negative correlation between FA and methamphetamine exposure. These findings are consistent with previous reports in older children and demonstrate that microstructural changes associated with methamphetamine exposure are already detectable in neonates.

Keywords

diffusion magnetic resonance imaging; prenatal methamphetamine exposure; methamphetamine; neonate; white matter

1. INTRODUCTION

Methamphetamine abuse is one of the fastest growing illicit drug use problems worldwide, with estimates suggesting that its global use is second only to that of marijuana (Courtney & Ray, 2014; UNODC, 2017). Methamphetamine functions primarily as a stimulant of the central nervous system (CNS), altering the release and activity of the neurotransmitters dopamine, norepinephrine and serotonin (Fleckenstein, Volz, Riddle, Gibb, & Hanson, 2007; Haughey, Fleckenstein, Metzger, & Hanson, 2000; Kuhn, Angoa-Pérez, & Thomas, 2011). In current and abstinent users, it has been shown to be associated with damage in a range of brain areas. Changes in the striatum (Chang, Alicata, Ernst, & Volkow, 2007; Jan, Lin, Miles, Kydd, & Russell, 2012; London et al., 2004), hippocampus (Thompson et al., 2004), amygdala (London et al., 2004) and several cortical areas (London et al., 2004; Tanabe et al., 2009; Thompson et al., 2004) have been associated with methamphetamine abuse and linked to alterations in affective or cognitive function in a number of studies (S. J. Kim et al., 2005; London et al., 2004; Tanabe et al., 2009; Thompson et al., 2004).

In 2006, a multi-site study in the USA estimated the incidence of methamphetamine use during pregnancy to be greater than 5% (Arria et al., 2006). Methamphetamine has been shown to cause vasoconstriction and reduced blood flow to the placenta (Stek, Baker, Fisher, Lang, & Clark, 1995), which have deleterious effects on the placenta (Carter et al., 2016) and can result in fetal hypoxia (LaGasse et al., 2011). Methamphetamine use during pregnancy is associated with a range of poor pre- and post-natal outcomes (Elliott et al., 2009; Good, Solt, Acuna, Rotmensch, & Kim, 2010; Gorman, Orme, Nguyen, Kent, &

Caughey, 2014; Ladhani, Shah, Murphy, & Knowledge Synthesis Group on Determinants of Preterm/LBW Births, 2011; Nguyen et al., 2010; L. Smith et al., 2003).

Given its demonstrated neurotoxicity in adult users, it is expected that methamphetamine exposure during the vulnerable prenatal period will have severe and potentially long-lasting effects on the infant. In light of the rapid development and growth of the CNS during gestation (Salisbury, Ponder, Padbury, & Lester, 2009), it is reasonable to hypothesize significant modifications in neural structure and function in the infant following such exposure. For example, we have previously reported that prenatal methamphetamine exposure is associated with reduced subcortical volumes in neonates (Warton, Meintjes, et al., 2018).

Diffusion tensor imaging (DTI) is a non-invasive means to visualise and characterise white matter (WM) (Feldman, Yeatman, Lee, Barde, & Gaman-Bean, 2010; Le Bihan et al., 2001). It produces a number of measures associated with the structural properties of WM and its component axons, including fractional anisotropy (FA) and axial (AD) and radial (RD) diffusivity (Assaf & Pasternak, 2008). A high FA typically reflects diffusion that is chiefly parallel to the fibre bundles and restricted in the perpendicular direction and is often interpreted as an indicator of more highly ordered, healthy or mature WM (Feldman et al., 2010). Many pathological processes induce changes in WM microstructure, and alterations in diffusion characteristics are often related to functional changes (Massaro et al., 2015; Thomason & Thompson, 2011; Tortora et al., 2018). DTI is thus a powerful tool for investigating the effects of such pathologies (Alexander, Lee, Lazar, & Field, 2007; Duerden et al., 2019).

There is considerable evidence that methamphetamine induces alterations in WM microstructure in adult users. Several studies have noted reduced FA in frontal regions of recently abstinent methamphetamine users (Alicata, Chang, Cloak, Abe, & Ernst, 2009; Chung et al., 2007; Tobias et al., 2010). Reduced FA in the corpus callosum (CC), particularly in the genu, has also been observed in methamphetamine users (I.-S. Kim et al., 2009; Salo et al., 2009; Tobias et al., 2010). Findings in the basal ganglia are more equivocal, with higher AD and RD observed in caudate and putamen in one study (Alicata et al., 2009), while another observed no changes in these structures relative to comparison subjects (Lin, Jan, Kydd, & Russell, 2015).

The neuroimaging literature investigating white matter changes in children with prenatal methamphetamine exposure is sparse. Reduced FA and increased diffusivities have been observed in WM regions in children (Roos et al., 2015) and infants (Chang et al., 2016) with prenatal methamphetamine exposure compared to unexposed control subjects. Other studies, by contrast, have noted higher FA and lower diffusivity in methamphetamine-exposed children (Cloak, Ernst, Fujii, Hedemark, & Chang, 2009; Colby et al., 2012). The available literature thus demonstrates that prenatal methamphetamine exposure has significant and persistent effects on CNS microstructure, although there are inconsistencies regarding the exact locations and direction of these changes.

Given the previous findings in adult methamphetamine users and children with prenatal methamphetamine exposure, we hypothesised that *in utero* exposure would also lead to alterations in the WM of exposed neonates. One advantage of investigations in neonates is that they allow a greater separation of the effects of drug exposure from potential confounding postnatal socio-environmental influences. Given the challenging environment into which children of mothers using methamphetamine are often born (Nguyen et al., 2010; Piper et al., 2011), these influences are likely to exert an appreciable effect on neural development postnatally. In a previous seed-based tractographic analysis of the striato-orbitofrontal circuit in the current cohort of neonates, we found that increased methamphetamine exposure was associated with reduced FA in several WM connections between the striatum and midbrain, orbitofrontal cortex and associated limbic structures (Warton, Taylor, et al., 2018).

The current study used a network-based approach to investigate whole-brain microstructural alterations, quantified by diffusion and anisotropy measures, within the three major classes of WM tracts – commissural, projection and association fibres – in the brains of neonates with prenatal methamphetamine exposure, compared to non-exposed control infants from the same community. We hypothesized that this exposure would be related to lower FA in each of these WM networks after adjustment for potential confounders.

2. METHODS

2.1 Study sample

The study sample was comprised of infants born to mothers from a historically disadvantaged Cape Coloured (mixed ancestry) community in Cape Town, South Africa. The rate of methamphetamine (“tik”) abuse in this community has been reported to be as high as 58% (Wechsberg et al., 2010), the highest in South Africa (Peltzer, Ramlagan, Johnson, & Phaswana-Mafuya, 2010), and 35–43% of patients seeking treatment for drug abuse report it to be their primary drug (Meade et al., 2015; Plüddemann et al., 2013). The women were recruited between October 2011 and October 2014 from three community antenatal midwife obstetric units to participate in a prospective longitudinal study on effects of prenatal alcohol or methamphetamine exposure (S. W. Jacobson et al., 2017; Warton, Meintjes, et al., 2018; Warton, Taylor, et al., 2018). Women were screened at their antenatal visit regarding alcohol, methamphetamine and other drug use and smoking during pregnancy. As reported in Warton, Meintjes et al. (2018), volumetric structural MRI data were obtained for 39 infants (18 exposed to methamphetamine and 21 control infants). The current sample consisted of a subset for whom DTI data of adequate quality for analysis were obtained. The exposed group in the subset consisted of 11 newborns born to women using methamphetamine at least twice/week at recruitment; the control group consisted of 12 newborns from the same community who had not been exposed to methamphetamine or other drugs of abuse *in utero*, except for marijuana, and who had no or minimal prenatal exposure to alcohol.

Demographic and other background data were collected during the antenatal visits, and the women were interviewed three times (once at recruitment and twice more before delivery) regarding their methamphetamine, alcohol and other drug use, and cigarette smoking. Use of

methamphetamine and other drugs was reported as days/month. Alcohol consumption was determined using a timeline follow-back approach and summarized in terms of average oz absolute alcohol (AA)/day (1 oz AA $\approx$ 2 standard drinks) (S. W. Jacobson, Chiodo, Sokol, & Jacobson, 2002; S. W. Jacobson et al., 2008), and smoking was reported as number of cigarettes/day.

Women were excluded if they met any of the following criteria: < 18 years of age, multiple gestation pregnancy, HIV positive, or receiving treatment for medical conditions, including hypertension, heart disease, epilepsy, or diabetes. Infant exclusionary criteria were neural tube defects, seizures and chromosomal abnormalities (Carter et al., 2016).

Urine samples were collected from the last 105 women enrolled in the latter part of the larger study (S. W. Jacobson et al., 2017) to assess the validity of maternal drug use reports (Carter et al., 2016) using the AccTest™ 6+2 drugs of abuse panel (DTA Pty, Ltd., Cape Town, South Africa), an immunochemical assay which detects metabolites of drugs that are commonly used in the study community (cocaine, methaqualone, amphetamines, methamphetamine, opiates and marijuana (THC)). The assay also assesses pH and creatinine as a test for sample adulteration. None of the women refused urine drug testing. Although urine drug test samples were only available for 4 women in the current study, the assays from the larger longitudinal study cohort ($n = 105$ samples) validated the maternal reports of drug use used here (Carter et al., 2017). Results for that group were consistent with maternal reports of marijuana, methamphetamine, cocaine, and opiates for 97 (92.4%) of those tested. Only 2 of 99 (2.0%) women denying methamphetamine use tested positive for that substance, and 5 of 89 (3.6%) women denying marijuana tested positive for THC. Among 8 women testing positive for methamphetamine, 6 also tested positive for methaqualone despite denying using it. An additional 2 women denying all drug use also tested positive for methaqualone. In this community, methaqualone is commonly mixed with methamphetamine or marijuana prior to being sold, often without the user's knowledge. The barbiturate-like qualities of methaqualone counteract some of the activating negative side effects of methamphetamine, such as anxiety, jitteriness, and racing thoughts. Consistent with maternal reports, no urine tests were positive for cocaine or opiates.

Written informed consent was obtained from each mother. Human subjects approval for the study was obtained from the ethics committees at Wayne State University and the Faculty of Health Sciences at the University of Cape Town.

2.2 Structural Brain Scans

Infants were scanned without sedation on a Siemens 3T Allegra scanner at 1–5 weeks of age (median = 2.6 weeks), except for 1 premature infant born at 31 weeks gestation, whose scan was delayed until 9 weeks postpartum (gestational age at scan = 40.0 weeks; sample mean = 41.1 weeks). Mothers and infants were transported to the Cape Universities Brain Imaging Centre (CUBIC) for the scan. Before scanning, the Brazelton *Neonatal Behavioral Assessment Scale* (NBAS; Brazelton, 1984) was administered by CDM, a senior developmental paediatrician, trained and certified to administer the test (S. W. Jacobson et al., 2017). The infants were then weighed, and head circumference and crown-to-heel length were measured. Because the NBAS and measurement procedures are tiring, their

administration made it easier for the infant to fall asleep and remain asleep in the scanner without sedation. The infant was then swaddled and fed and allowed to fall asleep. The infant was placed supine on an MRI-compatible vacuum cushion (VacFix®, S&S Par Scientific, Houston, TX) that fits snugly around the whole body. Earplugs were inserted and foam ear pads were placed over the ears to protect the infant from and diminish the noise of the scanner. The NBAS item scores were averaged to generate six clusters: Orientation, Range of state, Motor, Autonomic stability, Regulation of state, and Abnormal reflexes (see J. L. Jacobson, Fein, Jacobson, & Schwartz, 1984).

The infant was then placed in the scanner and immobilised by means of the VacFix® cushion, in accordance with a protocol for neonatal neuroimaging adapted from Wintermark et al (Wintermark, Labrecque, Warfield, DeHart, & Hansen, 2010). The infant's head was positioned within the bird-cage coil (described below), and his/her head was further secured with rolled towels or foam cubes to limit head and body movements and provide additional sound protection. A probe monitoring pulse and oxygen saturation was attached to the infant's foot, and was monitored throughout the scanning process by CDM or our research nurse, who remained in the scanning room for the duration of the procedure.

A circularly polarised bird-cage coil, custom-built for neonatal scanning, was used to transmit and receive the signal. Two diffusion weighted imaging (DWI) sets with opposite (AP/PA) phase encoding directions were acquired with a twice refocused spin echo EPI (echo planar imaging) sequence (Reese, Heid, Weisskoff, & Wedeen, 2003). For 5 infants (1 exposed, 4 controls) the following scanning parameters were used: TR 9500 ms, TE 86 ms, 50 slices of 80x80 voxels (each voxel 2x2x2 mm³). For the remaining infants, a navigated DTI sequence was used, which performed real-time motion detection and correction (Alhamud et al., 2012). The parameters in the latter sequence were identical to the first, with the exception of TR = 10,026 ms (which includes the navigator acquisition time). In all cases, AP and PA acquisitions each contained four $b = 0 \text{ s mm}^{-2}$ reference scans and 30 DW gradient directions with $b = 1000 \text{ s mm}^{-2}$.

For anatomical imaging, a multiecho FLASH sequence (van der Kouwe, Benner, Salat, & Fischl, 2008) was used, with protocol parameters as follows: TR 20 ms, TE 1.46/ 3.14/ 4.82/ 6.5/ 8.18/ 9.86/ 11.54/ 13.22 ms, 128 x 144 x 144 voxels, and 1 mm isotropic resolution. Two anatomical acquisitions were obtained with flip angles of 5° and 20°, respectively.

2.3 Data processing and parameter estimation

DWI data were inspected visually for motion and slices with motion-induced signal dropout; individual volumes with dropout slices were discarded. Matched volumes were removed across the AP and PA sets, ensuring that the same diffusion directions appeared in both sets. A minimum of 12 pairs of DWIs remained for each infant. The number of discarded volumes were similar across groups (13 ± 4 for the methamphetamine exposed group; 14 ± 7 for controls). The FSL tools *eddy_correct*, *topup* and *apply_topup* were applied to reduce effects of subject motion, eddy current distortion and EPI distortion (S. M. Smith et al., 2004). AFNI's (Cox, 1996) *3dDWItoDT* was used to fit the DTs and to estimate tensor parameters, such as FA, MD, eigenvalues (L_i , $i = 1,2,3$; $AD = L_1$; $RD = [L_2+L_3]/2$) and directional eigenvectors (e_i , $i = 1,2,3$). FreeSurfer's (<http://surfer.nmr.mgh.harvard.edu/>)

mri_ms_fitparms programme was used to combine the multiple echoes from the FLASH sequence into a single anatomical volume and also to estimate T1 and PD images.

2.4 Selection of regions of interest and tractographic analysis

Five WM network groups were analysed: commissural fibres, which included the corpus callosum, projection fibres in left and right hemispheres separately, and association fibres in left and right hemispheres separately. These networks were defined by placing spherical target regions of interest (ROIs) in one control subject's DWI space. A nonlinear alignment between that subject's b0 volume and each other subject's b0 volume was calculated, following which the target ROIs were mapped to each subject's DWI space, producing in each subject five networks of homologous target ROI sets. ROI placement was visually checked in each subject. Target ROIs for each WM network were placed in a manner following an early DTI-tractographic study of infants (Taylor et al., 2015). Briefly, twelve target ROIs were placed along in the bilateral extensions of the corpus callosum as six left-right homologous pairs (Fig. 1A). Eight target ROIs were placed in the left projection fibres, and eight homotopically located ROIs in the right projection fibres (Fig. 1B). Ten target ROIs were placed in the left association fibres, and ten homotopic ROIs in the right association fibres (Fig. 1C). Target location was determined based on an initial estimate of likely WM bundle locations, using a "mini-probabilistic" tractographic approach which combined deterministic tractography and DT uncertainty measures (Taylor et al., 2015).

Probabilistic tractography was then performed to estimate the WM most likely associated with pairs of target ROIs in each network group and to determine quantitative measures of structural properties in these WM connections. Using FATCAT software in AFNI (Taylor & Saad, 2013), uncertainties in DT eigenvectors and FA were estimated via 3dDWUncert, using 300 iterations. 3dTrackID (Taylor, Cho, Lin, & Biswal, 2012) was then used to perform 5000 Monte Carlo iterations of brute force whole brain tractography. The following propagation parameters were used: a maximum angle of propagation of 55° between voxels with FA > 0.1, the standard FA threshold for WM in infants (Hüppi & Dubois, 2006). This algorithm finds tracts connecting pairs of targets at each iteration and records which voxels are intercepted by those bundles. All voxels through which a minimum (> 1% of Monte Carlo iterations) of tracts passed were included to define WM-ROIs associated with each pair of targets. WM-ROIs found between the same target regions in every subject were included for further analysis. Mean and SD of the DTI parameters FA, AD, and RD were calculated for each WM-ROI.

Although partial volume averaging in voxels containing both white and grey matter (GM) could affect DTI parameters in WM-ROIs, the extent of these effects are not expected to differ across WM-ROIs or participants and as such should not introduce any bias into our results. Specifically, voxels containing only a small amount of WM may fail to meet the tractography propagation FA threshold value of 0.1, disallowing WM tracts from propagating through them. Exclusion of such "mixed" voxels from WM-ROIs could potentially lead to WM-ROI volumes being somewhat smaller than if all WM were included. Alternatively, inclusion in the WM-ROIs of "mixed" voxels that meet the FA threshold and

through which a minimum of tracts pass, could result in slight overestimation of WM-ROI volumes but lowering of mean FAs.

2.5 Statistical analysis

Demographic characteristics were entered into the data set using SPSS (version 23; IBM, Armonk, NY). Eleven variables were considered as potential confounders: maternal marital status, parity, educational status (highest grade level completed) and socioeconomic status (SES; Hollingshead, 2011), marijuana use (days/month during pregnancy), smoking (cigarettes/day during pregnancy) and alcohol use (oz of absolute alcohol/day during pregnancy), and infant sex, birthweight (g) and gestational age at birth and at scan (weeks). Data were examined for skewness and outliers were recoded to one unit greater than the highest value (methamphetamine, alcohol, marijuana and cigarette smoking; see Winer (1971). *T*-tests or χ^2 tests for categorical variables were used to compare sample characteristics between exposed and control groups. Throughout the paper, results were regarded as significant at $p < 0.05$.

Multivariate statistical analysis was performed using the afex package (Analysis of Factorial Experiments) in R, as implemented in AFNI's 3dMVM programme (Chen, Adelman, Saad, Leibenluft, & Cox, 2014). The association of prenatal methamphetamine exposure (days/month) with network FA was examined in each of the five WM networks. To control for the fact that DTI data in five infants were acquired using a different sequence, acquisition sequence was included as a categorical variable in the initial multivariate general linear model analysis. Potential confounding variables showing even a weak association ($p < 0.10$) with FA in any network were included in subsequent multiple regression analyses. Total intracranial volume (TIV) was additionally controlled for in a final step to ensure that any observed microstructural differences were not an indirect effect of reduced cortical volume. Analyses were repeated excluding the five infants whose DTI data were acquired using the non-navigated DTI sequence. Following the network level analysis, the effect of methamphetamine exposure on each WM-ROI in each network was analysed, with the potential confounding variables meeting the $p < 0.10$ criterion included in the multiple regression. This analysis was performed to determine whether the effect of methamphetamine within each network was due to an effect seen diffusely across the network or whether effects in sub-regions were driving the observed methamphetamine effect. The primary aim of the *post hoc* evaluation was not to investigate individual connections, as in Warton, Taylor et al. (2018), but to analyse patterns of WM change within the networks examined.

Associations of methamphetamine exposure with AD and RD were similarly examined first across the networks to determine whether significant associations of methamphetamine exposure on FA were related to either axial or radial diffusivity. Acquisition sequence was again included in an initial multivariate general linear model analysis, followed by adjustment for confounding variables and TIV. AD and RD in individual WM-ROIs were then analysed using the procedure described above.

Finally, we used Spearman's rho to examine associations of NBAS scores with FA in each of the five networks.

3. RESULTS

3.1 Sample characteristics

Table 1 shows the sample characteristics of the cohort. The mothers in the two groups did not differ on age, parity, or socioeconomic status. Both groups were socioeconomically disadvantaged and poorly educated with maternal education slightly lower in the methamphetamine group than the controls. On average, the mothers of the infants in the exposed group used methamphetamine on 7.1 days/month during pregnancy, as contrasted to the control mothers who did not use it at all. The mean GA for the three visits were recruitment: 25.1 ± 4.9 weeks; visit two: 29.9 ± 5.4 , and visit three: 34.2 ± 3.7 weeks. There were no between group differences in GA at any of the three visits (all p 's > 0.20). At recruitment, pregnant women in the exposed group used methamphetamine 3.4 ± 1.9 days/week (range: 2–7). At visit two, mean weekly usage of methamphetamine was 1.6 ± 1.6 days/week (range: 0–4), and at the final prenatal visit, mean usage was 0.3 ± 0.5 days/week (range: 0–1). Frequency of usage at recruitment was very highly correlated with visit two ($r = 0.88$, $p = 0.004$) and also between visits two and three ($r = 0.99$, $p = 0.011$). Although all of the mothers in the methamphetamine group smoked cigarettes compared to 67% ($n = 8$) of the controls, smoking was generally light for both groups, with mothers in the methamphetamine group tending to smoke slightly more cigarettes than those in the control group. While 36% ($n = 4$) of the mothers in the methamphetamine group used marijuana and 46% ($n = 5$) drank alcohol during pregnancy (< 2 oz AA/ day across pregnancy; $n = 3$ used both alcohol and marijuana), 17% ($n = 2$) of control mothers used marijuana and all abstained from alcohol use during pregnancy except for 1 mother who drank 1–2 drinks on 2 occasions during the pregnancy. None of the mothers reported cocaine, opiate, SSRI, or benzodiazepine use during pregnancy, and only one in the methamphetamine group used methaqualone (“mandrax”) on one occasion. The maternal drug use reports were validated in a larger study comparing these data to urine assays (Carter et al., 2016).

The methamphetamine and control groups did not differ in terms of infant sex (methamphetamine group 5 males; control group 7 males), birthweight, or gestational age at birth or at the scan (gestational age at birth + age in weeks). Total intracranial volume did not differ between groups, neither did average nor maximum displacement during the DTI acquisitions. Nor were there differences between the methamphetamine and control groups on the six NBAS clusters administered prior to the scan (Orientation, Range of state, Motor, Autonomic stability, Regulation of state, and Abnormal reflexes; p 's ranges from 0.38 to 0.90).

3.2 Tractographic connections

Probabilistic tractography produced several WM-ROI connections between pairs of target ROIs that were common to all infants. In the commissural network, three connections were present in all infants. Ten WM-ROI connections were present in all infants in both the left and right projection fibre networks. In the left association fibre network, 12 connections were common to all infants, while 9 connections were common to all infants in the right association network. Except for two WM-ROIs in the right projection fibre network, tract volumes (both absolute and normalized for TIV) did not differ between groups – WM-ROI

connection 004–007 was larger in the exposed than control group (mean $\pm$ SD: exposed = 1889 ± 766 mm³; controls = 1229 ± 775 mm³; $p = 0.05$), while 007–008 was smaller (exposed = 2084 ± 406 mm³; controls = 2723 ± 886 mm³; $p = 0.04$).

3.3 Association of prenatal methamphetamine exposure with FA in WM networks

The association of methamphetamine exposure with FA in each of the five WM networks is shown in Table 2 and Figure 2. Effect sizes are reported as the median value of the unstandardized betas for all WM-ROIs in each network. An initial regression controlling for acquisition sequence (DTI sequence used) revealed that higher prenatal methamphetamine exposure was significantly associated (at $p = 0.05$) with lower FA bilaterally in the projection and association fibre networks, while the association of methamphetamine with lower FA in the commissural fibre network fell short of conventional levels of statistical significance ($p = 0.10$). Although birthweight was associated with FA in some networks, it was not included as a confounder because it was highly collinear with gestational age at scan, and the latter was more strongly associated with FA in all networks. Following the addition of the confounding variables in the analysis, higher methamphetamine exposure was significantly associated with lower FA in all five WM networks (Table 2, all of which remained significant after controlling for TIV. Notably, bilateral findings in the projection and association networks remained significant after Bonferroni adjustment for comparisons in five networks ($p = 0.01$). Excluding the five subjects who were scanned using a non-navigated DTI sequence did not substantively alter the results (see Table 2), although associations in right and left projection networks fell short of significance after adjustment for TIV. Similarly, exclusion of one methamphetamine-exposed infant born at 31 weeks produced no essential changes (results not shown). To determine whether infant sex or alcohol exposure modified the relation between methamphetamine exposure and FA, interactions between methamphetamine and sex and between methamphetamine and alcohol exposure were examined in each network. The interaction effect was not significant for either infant sex or alcohol exposure in any network (p values ranged from 0.12–0.91).

Associations between prenatal methamphetamine and FA in the individual WM-ROIs within each network were then examined. The individual WM-ROIs within each network showing at least weak associations (at $p = 0.10$ before or after control for confounders and/or TIV) of methamphetamine exposure with FA are shown in Table 3 (each WM-ROI is defined by the pair of target ROIs it connects; see Fig.1 for reference of locations). After control for confounders and TIV, increased methamphetamine exposure was significantly associated with lower FA in one WM-ROI in the commissural fibre network. In the projection fibre networks, higher methamphetamine exposure was significantly associated with lower FA in two of the 10 WM-ROIs in the left hemisphere and seven of the 10 WM-ROIs in the right hemisphere, with one additional WM-ROI in each hemisphere falling short of significance. In the association fibre networks, a significant negative association between methamphetamine exposure and FA was observed in six of the 12 left hemisphere WM-ROIs and five of the 9 right hemisphere WM-ROIs, with an additional one left hemisphere WM-ROI and three right hemisphere WM-ROIs falling short of significance.

3.4 Association of prenatal methamphetamine exposure with AD and RD in WM networks

Networks which showed an association between methamphetamine exposure and FA were further analysed to investigate whether these associations were driven by an association of methamphetamine with either AD or RD. In multiple regressions with acquisition sequence, confounding variables and TIV, higher prenatal methamphetamine exposure was associated with lower AD in the right association network ($B = -1.64 \times 10^{-3}$, $p = 0.007$) and the left projection network, although the latter fell short of significance ($B = -2.87 \times 10^{-4}$, $p = 0.08$). Higher RD was associated with methamphetamine exposure in the right projection ($B = 7.64 \times 10^{-3}$, $p = 0.04$), and left ($B = 4.29 \times 10^{-3}$, $p = 0.05$) and right ($B = 5.05 \times 10^{-3}$, $p = 0.05$) association networks.

Individual WM-ROIs within each network which showed an association between methamphetamine exposure and FA were similarly analysed to investigate whether this association was driven by AD or RD. In multiple regressions with acquisition sequence, confounders and TIV, higher methamphetamine exposure was associated with lower AD in 001–007 in the left projection fibre network ($B = -9.36 \times 10^{-3}$, $p = 0.007$) and higher AD in 003–007 in the right association fibre network ($B = 7.02 \times 10^{-3}$, $p = 0.04$). Several connections showed a positive association (at $p = 0.10$) between methamphetamine exposure and RD, and the results of these analyses are shown in Table 4. In the left projection fibre network, higher RD in 004–006 was associated with higher methamphetamine exposure. In the right projection fibre network, 001–005, 002–004, 004–005 and 004–006 showed a significant association of methamphetamine exposure with higher RD, while the association in 002–003 fell just short of significance. In the left association fibre network, higher RD in 001–003 and 006–009 was associated with methamphetamine exposure, while the association in 005–007 fell short of significance. In the right association fibre network, higher methamphetamine exposure was associated with higher RD in 001–002, 003–007 and 005–007.

3.5 Associations of NBAS scores with FA in WM networks.

Spearman's rho revealed that an increase in abnormal reflexes was associated with lower FA in the left projection fibre network ($r = 0.44$, $p = 0.04$), and short of conventional levels of significance in the right ($r = 0.37$, $p = 0.08$), with that in the right being attributable to increasing RD ($r = 0.37$, $p = 0.09$). NBAS performance was not associated with FA in any of the other networks (all p 's > 0.10).

4. DISCUSSION

In a previous analysis of the current cohort, methamphetamine exposure was shown to be associated with reduced FA in specific white matter connections between striatal and limbic regions and the orbitofrontal cortex (Warton, Taylor, et al., 2018). The current study sought to investigate the effects of prenatal methamphetamine exposure on global WM networks by using a whole-brain tractographic approach to examine the three major classes of WM in the CNS: commissural fibres, and projection and association fibres bilaterally. Following regression to adjust for potential confounding variables, higher methamphetamine exposure was associated with lower FA in all five networks. Higher methamphetamine was related to

reduced AD in the right association and left projection fibre networks and with higher RD in the right projection and left and right association fibre networks. Within each network, a subset of WM-ROIs showed a significant negative correlation between methamphetamine and FA. These included fibres in the posterior callosal extensions; in the corticospinal tracts, the internal capsule, the optic radiation and superior and posterior thalamic radiations in the projection networks; and the uncinate, occipitofrontal and superior and inferior longitudinal fasciculi in the association networks [see (Jellison et al., 2004)]. At the individual connection level, methamphetamine exposure was associated with AD in one WM-ROI in each of the right association and left projection fibre networks, and with RD in several WM-ROIs.

These results are consistent with previous studies that examined WM characteristics in an older cohort from the same geographic region. Roos and colleagues observed lower FA with higher prenatal methamphetamine exposure in several WM tracts in 6- to 7-year-old children, including the external capsule, sagittal stratum and fornix, which connect striatal, frontal and limbic regions (Roos et al., 2015). Prenatal methamphetamine was associated with higher RD in these regions. Lower FA and higher diffusivities were observed at 1 month in the corona radiata of 1-month-old infants with combined methamphetamine and tobacco exposure compared to infants with tobacco exposure only or controls (Chang et al., 2016).

Not all findings in prenatally exposed children are consistent, however. An investigation of a sample of 3- to 4-year-old children with prenatal methamphetamine exposure found lower diffusivity in frontal and parietal WM (Cloak et al., 2009). Another study found higher FA, likely attributable to lower RD, in major WM bundles, including the CC, internal and external capsules and corona radiata in 5- to 18-year-old children with prenatal methamphetamine exposure, of whom 81% had also been exposed to alcohol (Colby et al., 2012). Notably these findings remained largely unchanged when alcohol exposure clinical severity was controlled for, localizing robustly to the entire length of the left corticospinal tract. The reasons for these inconsistencies are unclear. One possible explanation may be methodological: the former study extracted mean DT parameters in fixed-size regions of interest that were manually drawn on the FA and ADC maps (Cloak et al., 2009), while the latter performed a voxel-wise analysis on a common FA skeleton (Colby et al., 2012). These methods may be more sensitive to detecting localised changes than our tractography approach that averages measures along the entire length and volume of the tract. However, using a similar tract-based spatial statistics approach as that employed by Colby et al. (2012), Roos and colleagues (2015) found *lower* FA, with higher RD and AD, in 6- to 7-year-old methamphetamine exposed children compared to controls – also in the left external capsule where FA increases were reported by Colby and colleagues. One advantage of the current tractography-based approach is that all analyses, except for initial placement of spherical targets, are performed in native space, making it less sensitive to co-registration issues encountered in voxel-wise approaches.

Interpretation of the diffusion tensor measurements and the changes therein is complex. FA is often interpreted as a measure of the structural integrity of WM, with higher FA suggesting more optimal structural organization (Beaulieu, 2002). Lower FA has been

observed in WM tracts of patients with a range of psychiatric and neurodegenerative disorders (Akbar et al., 2016; Gan et al., 2016; Mayo et al., 2017; Won et al., 2016), but the exact biochemical and structural nature of the pathology underlying the reductions is not directly apparent from this index (Assaf & Pasternak, 2008). FA alterations may be related to disruption in myelin structure or damage to the axons (Wozniak & Lim, 2006) or to changes in fluid content in the examined region (Assaf & Pasternak, 2008). Evaluation of additional diffusion measures, such as AD and RD, can provide more information. Reductions in FA may be the result of lower AD or increased RD (Alexander et al., 2007), and these measures are differentially affected by the underlying pathology, with AD being more sensitive to axonal degeneration and RD more severely affected by alterations in myelination (Fjell et al., 2008; Song et al., 2003).

Higher methamphetamine was associated with lower FA in the current study in all five major WM networks examined. In all but one, higher methamphetamine exposure was associated with higher RD, suggesting that the change in FA may be primarily attributable to alterations in myelination. This interpretation is consistent with evidence from rat studies that found that prenatal methamphetamine exposure is associated with reduced myelination and myelin content (Melo, Moreno, Vázquez, Pinazo-Durán, & Tavares, 2006; Melo, Pinazo-Durán, Salgado-Borges, & Tavares, 2008) and that methamphetamine can induce oligodendroglial cell death *in vitro* (Genc et al., 2003). Our findings are also consistent with reports of reduced FA and increased RD in adult methamphetamine users (Alicata et al., 2009; I.-S. Kim et al., 2009). By contrast, our data are not consistent with evidence of increased AD in studies of older children with prenatal methamphetamine exposure (Colby et al., 2012; Roos et al., 2015) and of methamphetamine abuse in adults (Alicata et al., 2009; I.-S. Kim et al., 2009). In the current study, methamphetamine exposure was associated with lower AD in two networks. This finding is consistent with evidence of smaller axons in rats treated prenatally with methamphetamine (Melo et al., 2008). In addition, prenatal treatment with amphetamines induces significant terminal and axonal loss in the striatum of rats (Bowyer & Schmued, 2006) and baboons (Villemagne et al., 1998) and reduction of axon density in the medial prefrontal cortex (Kadota & Kadota, 2004). Given that our data come from newborns, it is possible that greater effects on axonal structure, indicated by AD, may become evident later in development. The precise mechanisms of methamphetamine damage to WM are likely multifactorial.

Interpretation of diffusion measures in neonates is further complicated by the fact that the neonatal brain is far from fully developed. Axonal connections are organised into fibre bundles in the last trimester of gestation, but the myelination process is initiated in the second half of pregnancy and is only partially complete at birth (Dubois et al., 2014). In addition, the maturation of WM in the infant brain is regionally variable, with a general progression of maturation in posterior-to-anterior and central-to-peripheral directions (Oishi et al., 2011). Diffusion indices change with WM maturation, such that FA increases while AD, RD and MD decrease (Qiu, Mori, & Miller, 2015), which may be the result of reduced brain water, increases in fibre diameter and myelination, more cohesive fibre tract arrangement and greater axonal packing (Mabbott, Noseworthy, Bouffet, Laughlin, & Rockel, 2006). The reduced FA in the current study might, therefore, be considered to be an indication of delayed maturation in the WM of exposed neonates. Lending credence to this

interpretation are a number of preclinical studies which have found delays in somatic development (McDonnell-Dowling, Donlon, & Kelly, 2014), locomotor control (Acuff-Smith, Schilling, Fisher, & Vorhees, 1996) and sensory-motor development (Slamberová, Pometlová, & Charousová, 2006), and slowed maturation of frontal cortical density (Tavares & Silva, 1996) in rats following amphetamine administration during gestation. Furthermore, the developmental trajectories of FA and diffusivity measures were found to be altered in corona radiata of infants with combined methamphetamine and tobacco exposure compared to controls (Chang et al., 2016). Although differences in diffusivity measures following prenatal methamphetamine exposure have been observed at several time points in childhood (Chang et al., 2016; Colby et al., 2012; Roos et al., 2015), these may not represent a delay in maturation of WM that persists into adulthood. Investigations of WM in adults with prenatal exposure, including long-term follow-up of exposed children, are needed to more fully explore this question.

WM microstructure and connectivity are of critical functional importance. WM pathways in the CNS are responsible for the transmission of information across networks and the integration and coordination of the activity of multiple individual regions (Turken et al., 2008). A substantial body of literature supports the role of WM in cognition. Higher FA has been shown in school-age children to be associated with higher IQ, as well as better performance on tasks of visuospatial information processing and sustained attention (Mabbott et al., 2006; Muetzel et al., 2015). Higher WM integrity (measured by diffusion parameters) in the corona radiata, superior longitudinal fasciculus, posterior thalamic radiation and cerebral peduncle is associated with greater cognitive control, selective attention and interference suppression in school-age children (Chaddock-Heyman et al., 2013). Better verbal ability is associated with higher FA in the superior longitudinal fasciculus bilaterally and the left anterior thalamic radiation and with lower RD in the superior longitudinal fasciculi, the inferior longitudinal fasciculus and uncinate fasciculus in the left hemisphere and in forceps major (Tamnes et al., 2010). Higher FA in fronto-parietal connections, particularly in the superior longitudinal fasciculus, is associated with better spatial working memory performance (Vestergaard et al., 2011). In infants, higher FA and lower RD in anterior and superior thalamic radiations, anterior cingulum, arcuate fasciculus and temporo-parietal connections are related to better working memory performance (Short et al., 2013). In the current study, lower FA in the projection fibre networks was associated with an increase in abnormal reflexes in the NBAS.

Prenatal methamphetamine exposure in the current study was associated with poorer WM integrity in a number of the above-mentioned connections, including the corona radiata, thalamic radiations, longitudinal fasciculi and uncinate fasciculus, and might, therefore, be expected to be related to dysfunction in several domains of cognitive and emotional function that do not emerge until later in development. This prediction is supported by previous studies that have shown alterations in WM structure as a consequence of use of or exposure to methamphetamine to be associated with a number of functional deficits. In adult users, lower FA in the left midcaudal superior corona radiata was associated with several clinical indices of depression and affective disorder (Tobias et al., 2010); reduced FA in right frontal white matter was associated with impairment in executive function (Chung et al., 2007); and poorer cognitive control correlated with lower FA in the genu of the corpus callosum (Salo

et al., 2009). A recent study showed that 6- to 7-year-old children with prenatal methamphetamine exposure scored more poorly on IQ assessments and several cognitive domains, including learning and memory (Kwiatkowski et al., 2018). In children with prenatal exposure, altered FA in the external capsule, sagittal stratum and fornix/stria terminalis was associated with poorer motor coordination, cognitive control and executive function (Roos et al., 2015). It is important to note, however, that reduced structural integrity of WM, as measured by FA, may not necessarily be associated with poorer functional outcomes. Further investigation is, therefore, warranted regarding the degree to which methamphetamine exposure-related alterations in WM structural connectivity that are evident in the newborn period predict deficits that become evident during childhood and adulthood.

To our knowledge, this is the first study to use DTI tractography to investigate whole-brain changes in major WM networks in neonates with prenatal exposure to methamphetamine. Studies of drug exposure effects in neonates have a major potential advantage over studies at older ages. Children of women who abuse methamphetamine during pregnancy are almost invariably born into a disadvantaged and dysfunctional environment (Piper et al., 2011), which has been shown to exert further damaging influences on development (LaGasse et al., 2012; Twomey et al., 2013). Evaluation of prenatal methamphetamine exposure during the newborn period permits an assessment relatively free of the potential confounding influences associated with the postnatal environment.

The women whose infants were scanned in the current study were recruited prospectively during pregnancy, allowing a more accurate, contemporaneous measure of frequency of methamphetamine use, compared with retrospective studies of older children in which measurement of alcohol and drug use by the mother is likely to be less precise and less valid (Fortin, Muckle, Jacobson, Jacobson, & Bélanger, 2017; S. W. Jacobson et al., 2002). Measurement of methamphetamine use during pregnancy makes a detailed quantitative analysis of associations with diffusion properties more feasible. Among the few previous studies of prenatal methamphetamine exposure, only one investigated potential associations between methamphetamine and diffusion properties (Cloak et al., 2009).

Although our sample size was small, it is comparable to previous studies on this topic (Roos et al., 2015), and alterations were observed in regions similar to those reported in prior studies (Colby et al., 2012; Roos et al., 2015). One limitation, almost inevitable in any study of prenatal drug exposure, is the potential confounding effects of polysubstance exposure, which can lead to alterations in CNS structure and function (Alpár, Di Marzo, & Harkany, 2016; Ekblad et al., 2010; Jacobsen et al., 2007; Meintjes et al., 2014; Minnes, Lang, & Singer, 2011; Rivkin et al., 2008; Taylor et al., 2015; Willford, Chandler, Goldschmidt, & Day, 2010). However, the methamphetamine and control groups were drawn at the same time from the same community and because multiple detailed maternal reports were obtained during pregnancy, we were able to include continuous measures of these substances as potential confounding variables in the statistical analyses. Unfortunately, urine sample testing for drug use was begun in the latter part of the larger cohort study, so that assays were only performed on four women in the current sample. Samples from the full cohort, as well as repeated sample testing for each woman, would have enabled stronger validation of

the maternal drug use reports. However, the assays from the larger cohort were consistent with the maternal reports in that group, providing support for the reports as valid measures of drug use in this cohort (Carter et al., 2016).

The findings presented here are consistent with previously published results showing reduced FA and increased radial diffusion in a number of major WM connections (Chang et al., 2016; Roos et al., 2015). The current study is also consistent with our findings in corticostriatal WM connections in the current sample, linking these alterations to increased methamphetamine exposure (Warton, Taylor, et al., 2018). Given that the affected tracts have considerable functional significance, it is likely that these changes will have a serious long-term impact on the exposed children. Further research into the precise cognitive and emotional changes associated with such findings will be essential to inform the necessary therapeutic interventions.

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Data availability:

The data supporting the results of this study are available upon reasonable request from the corresponding author.

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Figure 1.

Locations of target ROIs, with WM-ROI connections shown in top panel. Mini-probabilistic tractography was used to create homologous target locations, following which ROIs were mapped to each subject's native DW space for tractography. **A.** Target ROIs for connections in the commissural network, shown in sagittal (top) and axial (bottom) views. **B.** The top image shows targets for right projection fibres in sagittal view; the bottom image shows left and right projection targets in axial view. **C.** The top image shows targets for right association fibres in sagittal view; the bottom image shows left and right association targets. (Figure reprinted from Taylor et al., 2015).

Figure 2. Mean network FA vs. methamphetamine exposure (days/ month during pregnancy) for all subjects (left; $N=23$) and exposed subjects only (right; $n=11$). A) Commissural fibre network; B) Left projection fibre network; C) Right projection fibre network; D) Left association fibre network; E) Right association fibre network.

Table 1.

Sample characteristics ($N=23$)

	Methamphetamine ($n = 11$)				Controls ($n = 12$)			
	Mean	SD	Range	Mean	SD	Range	χ^2 or t	p
Maternal								
Age (years)	27.2	3.9	21.4 – 32.6	25.1	5.4	18.8 – 36.4	-1.05	0.305
Education (highest grade)	9.4	1.2	7.0 – 11.0	10.6	1.1	9.0 – 12.0	2.56	0.018
Parity	3.1	1.6	1 – 6	2.3	1.2	1 – 4	-1.44	0.165
Socioeconomic status ^a	21.0	3.2	16.5 – 27.0	21.8	6.7	11.0 – 31.5	0.33	0.741
Infant								
Sex (% male)	45.5				58.3		0.38	0.537
Birthweight (g)	2806.8	600.5	1370.0 – 3590.0	2795.8	485.2	1940.0 – 3470.0	-0.05	0.962
Gestational age at birth (weeks)	37.3	3.0	31.0 – 40.7	39.0	1.7	36.6 – 42.1	1.67	0.110
Gestational age at scan (weeks)	40.6	2.1	37.3 – 43.1	41.6	1.9	37.6 – 44.1	1.24	0.227
Total intracranial volume (mm ³)	491755	59253	427200 – 608600	496725	51191	428700 – 633500	0.22	0.831
Average displacement (mm) ^b	1.1	1.4	0.2 – 4.8	0.5	0.5	0.1 – 1.8	-1.38	0.182
Maximum displacement (mm) ^b	1.2	1.4	0.2 – 4.8	0.7	0.8	0.2 – 3.0	-1.11	0.279
Neonatal Behavioral Assessment Scale								
Orientation ^c	4.8	1.0	3.6 – 6.2	4.9	0.9	3.8 – 6.6	0.13	0.898
Range of state ^d	4.3	0.6	3.0 – 5.3	4.4	0.7	3.0 – 5.3	0.55	0.589
Motor	4.8	0.4	4.3 – 5.3	4.8	0.4	4.0 – 5.5	-0.17	0.868
Autonomic stability ^d	5.1	0.5	4.3 – 5.7	5.2	0.5	4.7 – 6.0	0.75	0.460
Regulation of state ^d	4.2	1.0	3.0 – 6.5	3.9	1.2	2.0 – 5.5	-0.58	0.566
Abnormal reflexes	5.0	2.0	2.0 – 8.0	4.3	2.0	2.0 – 8.0	-0.90	0.380
Substance use during pregnancy								
Methamphetamine (days/month)	7.1	3.5	1.5 – 12.0	0.0	0.0	0.0 – 0.0	-7.04	0.000
Smoking (number cigarettes/day)	6.5 ^e	5.4	2.0 – 20.0	3.3 ^f	2.8	0.0 – 7.7	-1.78	0.089

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	Methamphetamine (<i>n</i> = 11)				Controls (<i>n</i> = 12)			
	Mean	SD	Range		Mean	SD	Range	χ^2 or <i>t</i> <i>p</i>
Marijuana (days/month)	4.4 ^g	9.6	0.0 – 30.5		0.0 ^h	0.1	0.0 – 0.2	-1.58 0.129
Alcohol (oz AA /day)	0.2 ⁱ	0.4	0.0 – 1.4		0.0 ^j	0.0	0.0 – 0.1	-1.26 0.222

^aFour factor index of social status (Hollingshead, 2011);

^bAverage and maximum motion during DTI acquisitions;

^cData acquired for 9/11 exposed and 12/12 controls;

^dData acquired for 11/11 exposed and 11/12 controls;

^e11/11 (100%) and

^f8/12 (66.7%) smoked cigarettes;

^g4/11 (36.4%) and

^h2/12 (16.7%) used marijuana;

ⁱ5/11 (45.5%) and

^j1/12 (8.3%) drank alcohol during pregnancy.

Table 2.

Association of methamphetamine exposure with FA in the five networks

Network	All Participants ($N = 23$)					Participants imaged using navigated DTI sequence ($N = 18$)				
	B_{acq} (E-03)	p_{acq}	$B_{acq,conf}$ (E-03)	$p_{acq,conf}$	$B_{acq,conf,TTV}$ (E-03)	$p_{acq,conf,TTV}$	B (E-03)	p	B_{conf} (E-03)	p_{conf}
Commissural	-1.90	0.09	-1.85	0.02	-1.84	0.03	-1.83	0.10	-1.34	0.04
Left projection	-1.54	0.05	-1.61	0.009	-1.89	0.01	-1.64	0.08	-2.05	0.02
Right projection	-2.66	0.04	-3.53	0.02	-3.69	0.01	-2.65	0.06	-3.28	0.05
Left association	-1.75	0.03	-2.37	0.006	-2.10	0.01	-2.02	0.03	-2.12	0.02
Right association	-2.11	0.02	-2.82	0.002	-2.97	0.009	-2.26	0.03	-2.34	0.03
									-2.49	0.06

B values are the median of the non-standardised betas output by AFNI's 3dMVM tool for all WM-ROIs in the network. Subscripts denote control variables adjusted for in the regression: Acq: acquisition sequence; Conf: confounders, namely infant gestational age at scan, infant sex, socioeconomic status (Hollingshead, 2011), maternal education, and maternal alcohol and marijuana use during pregnancy. TTV: total intracranial volume. Bold denotes significance at $p = 0.05$.

Table 3.

WM-ROIs showing associations of FA with methamphetamine exposure ($N=23$)

Network	WM-ROI	Methamphetamine FA (mean $\pm$ SD)	Control FA (mean $\pm$ SD)	B_{FA} (E-03)	p_{FA}	$B_{\text{Acq,conf}}$ (E-03)	$p_{\text{Acq,conf}}$	$B_{\text{Acq,conf,TIV}}$ (E-03)	$p_{\text{Acq,conf,TIV}}$
Commissural	011-012	0.277 $\pm$ 0.019	0.292 $\pm$ 0.060	-3.41	0.159	-6.75	0.022	-6.71	0.035
	001-007	0.244 $\pm$ 0.015	0.254 $\pm$ 0.025	-1.92	0.082	-2.77	0.008	-2.72	0.009
	004-006	0.253 $\pm$ 0.019	0.261 $\pm$ 0.022	-2.41	0.005	-3.27	0.001	-3.24	0.003
	007-008	0.194 $\pm$ 0.016	0.193 $\pm$ 0.019	-1.37	0.111	-2.26	0.040	-2.16	0.067
Right projection	001-005	0.255 $\pm$ 0.014	0.277 $\pm$ 0.043	-3.01	0.099	-4.10	0.051	-4.51	0.047
	001-007	0.241 $\pm$ 0.013	0.248 $\pm$ 0.025	-1.47	0.167	-2.24	0.051	-2.43	0.050
	002-003	0.185 $\pm$ 0.023	0.201 $\pm$ 0.032	-2.74	0.073	-3.71	0.026	-4.26	0.016
	002-004	0.252 $\pm$ 0.013	0.268 $\pm$ 0.051	-2.57	0.207	-4.61	0.087	-4.95	0.091
	004-005	0.249 $\pm$ 0.011	0.268 $\pm$ 0.024	-2.27	0.036	-2.91	0.007	-3.48	0.001
	004-006	0.251 $\pm$ 0.015	0.264 $\pm$ 0.026	-2.76	0.005	-3.49	0.001	-3.91	0.000
	004-007	0.253 $\pm$ 0.012	0.273 $\pm$ 0.036	-2.81	0.063	-4.28	0.018	-4.56	0.020
	007-008	0.183 $\pm$ 0.019	0.194 $\pm$ 0.023	-2.76	0.011	-3.56	0.005	-3.35	0.012
Left association	001-003	0.174 $\pm$ 0.021	0.187 $\pm$ 0.020	-2.28	0.040	-1.97	0.039	-1.77	0.078
	002-007	0.238 $\pm$ 0.015	0.239 $\pm$ 0.015	-1.12	0.138	-1.42	0.086	-1.30	0.143
	003-007	0.235 $\pm$ 0.013	0.245 $\pm$ 0.027	-2.11	0.051	-2.66	0.029	-3.02	0.021
	004-007	0.234 $\pm$ 0.015	0.232 $\pm$ 0.034	-1.79	0.160	-3.34	0.009	-3.20	0.018
	005-007	0.188 $\pm$ 0.016	0.192 $\pm$ 0.021	-1.72	0.078	-3.09	0.004	-3.24	0.005
	006-007	0.215 $\pm$ 0.025	0.222 $\pm$ 0.019	-2.25	0.047	-2.45	0.086	-2.23	0.143
	006-008	0.203 $\pm$ 0.020	0.206 $\pm$ 0.021	-1.61	0.134	-2.34	0.025	-2.42	0.032
	006-009	0.230 $\pm$ 0.019	0.248 $\pm$ 0.051	-3.00	0.155	-4.40	0.067	-5.13	0.045
Right association	007-009	0.232 $\pm$ 0.017	0.236 $\pm$ 0.017	-2.01	0.010	-2.41	0.007	-28.4	0.001
	001-002	0.197 $\pm$ 0.023	0.214 $\pm$ 0.026	-3.06	0.018	-3.78	0.005	-4.23	0.003
	002-006	0.218 $\pm$ 0.018	0.224 $\pm$ 0.026	-2.04	0.065	-1.77	0.131	-2.18	0.080
	002-007	0.239 $\pm$ 0.013	0.249 $\pm$ 0.029	-1.94	0.095	-2.97	0.042	-3.21	0.042
	002-009	0.244 $\pm$ 0.017	0.248 $\pm$ 0.033	-2.11	0.097	-2.82	0.054	-2.97	0.062
	003-007	0.233 $\pm$ 0.014	0.238 $\pm$ 0.023	-1.38	0.140	-2.05	0.050	-2.01	0.075
	005-007	0.176 $\pm$ 0.010	0.182 $\pm$ 0.016	-1.33	0.044	-2.17	0.001	-2.23	0.002

Network	WM-ROI	Methamphetamine FA (mean ± SD)	Control FA (mean ± SD)	B_{acq} (E-03)	p_{acq}	$B_{\text{acq,conf}}$ (E-03)	$p_{\text{acq,conf}}$	$B_{\text{acq,conf,TIV}}$ (E-03)	$p_{\text{acq,conf,TIV}}$
	006-007	0.232 ± 0.025	0.238 ± 0.038	-3.07	0.028	-4.70	0.014	-3.80	0.037
	006-008	0.217 ± 0.020	0.228 ± 0.023	-2.88	0.006	-2.97	0.004	-3.22	0.004

B values are non-standardised betas output by AFNI's 3dMVM tool. Subscripts denote control variables adjusted for in the regression: Acq: acquisition sequence; Conf: confounders, namely infant gestational age at scan, infant sex, socioeconomic status (Hollingshead, 2011), maternal education, and maternal alcohol and marijuana use during pregnancy. TIV: total intracranial volume. Bold denotes significance at $p = 0.05$.

Table 4.

Association of methamphetamine exposure with RD in individual WM-ROIs ($N=23$)

Network	WM-ROI	Methamphetamine RD (mean $\pm$ SD)	Control RD (mean $\pm$ SD)	B_{acq} (E-03)	p_{acq}	$B_{\text{acq,conf}}$ (E-03)	$p_{\text{acq,conf}}$	$B_{\text{acq,conf,TIV}}$ (E-03)	$p_{\text{acq,conf,TIV}}$
Left projection	004-006	1.081 $\pm$ 0.042	1.059 $\pm$ 0.076	4.80	0.116	6.33	0.044	7.25	0.031
	001-005	1.005 $\pm$ 0.048	0.964 $\pm$ 0.069	5.88	0.075	6.89	0.018	7.71	0.013
	002-003	1.231 $\pm$ 0.088	1.178 $\pm$ 0.104	1.04	0.043	9.26	0.055	9.29	0.076
Right projection	002-004	0.964 $\pm$ 0.028	0.949 $\pm$ 0.076	4.20	0.135	6.23	0.078	7.57	0.041
	004-005	1.071 $\pm$ 0.051	1.038 $\pm$ 0.070	5.92	0.073	7.64	0.018	8.78	0.010
	004-006	1.098 $\pm$ 0.059	1.071 $\pm$ 0.079	4.72	0.151	6.63	0.063	8.03	0.032
Left association	001-003	1.256 $\pm$ 0.095	1.194 $\pm$ 0.079	10.0	0.035	8.02	0.036	8.64	0.037
	005-007	1.209 $\pm$ 0.065	1.186 $\pm$ 0.083	5.97	0.117	6.51	0.090	7.30	0.079
	006-009	1.298 $\pm$ 0.094	1.256 $\pm$ 0.120	8.06	0.163	14.	0.009	15.1	0.014
Right association	001-002	1.202 $\pm$ 0.071	1.156 $\pm$ 0.075	8.08	0.033	10.6	0.001	11.1	0.001
	003-007	1.100 $\pm$ 0.041	1.080 $\pm$ 0.082	5.46	0.080	8.42	0.008	8.61	0.012
	005-007	1.204 $\pm$ 0.055	1.173 $\pm$ 0.067	6.56	0.036	8.37	0.013	8.64	0.017

B values are non-standardised betas output by AFNI's 3dMVM tool. Subscripts denote control variables adjusted for in the regression: Acq: acquisition sequence; Conf: confounders, namely infant gestational age at scan, infant sex, socioeconomic status (Hollingshead, 2011), maternal education, and maternal alcohol and marijuana use during pregnancy. TIV: total intracranial volume. Bold denotes significance at $p = 0.05$.