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Neuroanatomical characteristics of youths with prenatal opioid and poly-drug exposure

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ABSTRACT

Neuroanatomical and cognitive differences have been documented during childhood between children with prenatal opioid- and poly-drug exposure and controls in small samples. We investigated whether these differences persisted in larger samples of youth at older ages. Quantitative MRI and cognitive data were compared between 38 youths in the risk group and 44 youths in the non-exposed group (aged 17 to 22 years) who had been followed prospectively since birth. Most drug-exposed youths (84%) moved to permanent foster or adoptive homes before one year of age. The drug-exposed group displayed smaller neuroanatomical volumes (0.70 *SD* difference in total brain volume, $p = 0.001$), smaller cortical surface areas and thinner cortices than the comparison group. The birth weight accounted for some of the intergroup differences. Neuroanatomical characteristics partially mediated group differences in cognitive function. The present study cannot differentiate between causal factors but indicates persistent neurocognitive differences associated with prenatal opioid or poly-drug exposure.

1. Introduction

We have previously documented lesser neuroanatomical volumes and white matter microstructural maturation in a small subsample ($n = 14 + 14$) of adopted children (8 to 13 years of age) with prenatal opioid or poly-drug exposure compared to controls (Walhovd et al., 2007; Walhovd et al., 2010). Researchers have not determined whether these differences reflect delayed development or continue throughout childhood and into youth and whether these results can be replicated in larger samples. Moreover, researchers have not determined whether these differences are modulated by the type of drug to which the subject was exposed, demographic characteristics (e.g., age, sex and parental socio-economic status), perinatal features (e.g., birth weight) or post-natal risk. The present study aimed to examine these issues in a large cohort of individuals who have now reached the late teens and young adulthood. Based on histological, cell culture and animal studies (Harlan and Song, 1994; Hu et al., 2002; Lu et al., 2012; Wang and Han, 2009), as well as the known trajectories of brain development (Tamnes et al., 2013), we hypothesized that broad differences would also be observed in a larger sample of subjects at older ages. Our purpose is to investigate the outcomes for this vulnerable group to facilitate better clinical practice and future research into reasons for the identified differences.

A substantial increase in the use of prescribed and illegal opioids has been observed over the past 15 years (Manchikanti et al., 2010); in particular, the number of women using opioids during pregnancy has more than quadrupled in the US between 2000 and 2009 (Patrick et al., 2012). An increasing number of studies have demonstrated that children with prenatal opioid or poly-substance exposure are at increased risk of negative outcomes, e.g., neonatal abstinence syndrome (NAS), reduced gestational age and birth weight, visual deficiencies, decreased fine motor abilities, behavioural and emotional regulation problems, and, possibly, reduced cognitive abilities (Logan et al., 2011; Mactier et al., 2014; McGlone et al., 2014; Nygaard et al., 2017; Ornoy et al., 2001; Patrick et al., 2012; Walhovd et al., 2015). With few exceptions, previous clinical studies have mainly investigated relatively young children (Nygaard et al., 2017). The lack of knowledge about possible negative long-term consequences of prenatal opioid or poly-substance

Abbreviations: CA, cortical surface area; CT, cortical thickness; FASD, foetal alcohol spectrum disorder; MRI, magnetic resonance imaging; NAS, neonatal abstinence syndrome

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exposure in children and how these outcomes change over time indicates a need for longitudinal studies beyond childhood.

Knowledge of the long-term brain development of offspring after prenatal opioid or poly-substance exposure is very limited. Neuroanatomical studies of infants with opioid or poly-substance exposure have found altered neural tract development (Monnelly et al., 2018; Walhovd et al., 2012c), smaller total brain volume (Yuan et al., 2014) and hippocampal spectral abnormalities (Christmas et al., 2015). We have previously found that school-aged children born to mothers who used opioids and poly-substances during pregnancy had smaller neuroanatomical volumes (Walhovd et al., 2007) and lower fractional anisotropy than non-exposed children (Walhovd et al., 2010). These neuroanatomical differences were moderately related to lower cognitive and behavioural functioning. Children who were exposed to opioids during prenatal period were recently shown to exhibit smaller basal ganglia, thalamus and cerebellar white matter and different bold activation than the comparison group (Sirnes et al., 2018; Sirnes et al., 2017). The only published neuroanatomical study of adolescents in such risk groups found no differences in whole brain volume, but the heroin- and/or cocaine-exposed group had a larger hippocampal volume than the group of adolescents without such exposure (Riggins et al., 2012). However, that study found this increased hippocampal volume to be related to lower scores on a memory test. In contrast to the findings of most of these studies, the only neuroanatomical study of children born to mothers with opioid and poly-substance addiction who were detoxified before or during pregnancy did not find any trends towards neuroanatomical differences relative to the comparison group (Walhovd et al., 2015).

This prospective study investigated the neuroanatomical characteristics of youths born to mothers who used opioids and poly-substances during pregnancy compared to a comparison group without any known prenatal risk factors. Most of the prenatally drug-exposed youths moved to permanent foster or adoptive homes at an early age. Thus, these individuals were likely exposed to few of the postnatal psychosocial risk factors often associated with growing up with parents with opioid addiction. To the best of our knowledge, no previous studies have investigated the neuroanatomical characteristics of youths born to mothers with opioid and poly-substance use during pregnancy but with minimized postnatal risk. The relatively low number of children with opioid or poly-substance exposure and differing degrees of postnatal risk participating in previous neuroimaging studies has limited the researchers' opportunities to consider possible moderating and mediating factors that have been investigated in the present study, such as the type of drug to which the child was exposed, demographic characteristics (e.g., age, sex and parental socio-economic status), perinatal features (e.g., birth weight), postnatal risk factors (e.g., changes in the care environment) and how neuroanatomical characteristics mediate cognitive and behavioural differences between groups. Based on previous findings (Sirnes et al., 2017; Walhovd et al., 2007), we hypothesized that the participating youths who were born to mothers with opioid and poly-substance use during pregnancy would display smaller neuroanatomical volumes than the controls. We also investigated the intergroup differences in cortical surface area (CA) and cortical thickness (CT) and how these neuroanatomical features mediated group differences in cognitive and behavioural functions. Based on previous findings on cortical thickness, we tentatively hypothesized that the exposed group would display regionally thinner cortices and, partially based on the overall lower birthweight in the exposed group and partially based on previously reported smaller neuroanatomical volumes (Sirnes et al., 2017; Walhovd et al., 2007) we tentatively hypothesized regionally smaller cortical surface areas in the exposed group than in the controls.

2. Methods

2.1. Participants

The present sample was recruited from a longitudinal prospective study of infants who were exposed to heroin and other drugs in utero (for details, see Moe, 2002; Moe and Slinning, 2001; Slinning, 2004). That project initially included 78 prenatally drug-exposed children and 58 children without any known biological prenatal risk factors. The drug-exposed children were consecutively recruited from Aline Infant and Family Center in Oslo, where they were enrolled in a perinatal risk project during the period from 1992 to 1996. The Aline Infant and Family Center in Oslo is a social service institution for families with children aged 0–2 years. The majority (76.9%) of participants were enrolled in the perinatal risk project at Ullevål Municipal Hospital by the second or third trimester of pregnancy, and the remaining participants were born at other hospitals. The biological mothers were referred to the perinatal risk project because of concerns about substance abuse from medical or social staff at the municipal health services. Because one aim of that study was to assess child outcomes under conditions of adequate care, the comparison group of non-exposed children was recruited from a nonclinical setting of local maternal and child health centres in Norway, where biomedical vulnerability and social risk factors were minimal. Inclusion criteria for the comparison group were that the child was born without biomedical risk, the child had not experienced unusual sleep or feeding problems during the first 6 months of life, and the birth mother had not used alcohol or illicit drugs during pregnancy. None of the mothers in the comparison group used tobacco daily.

Out of the original 136 children who were included in that study as infants, 11 were not invited to participate as youths because their parents had requested to withdraw from the study at a prior time point. Of the 125 invited youths, 98 (78%) participated in the present study. Seven of these individuals participated in cognitive testing only, as they preferred not to undergo scanning, and one was excluded from scanning due to the presence of a metal implant. Of the 90 youths who were scanned, one was excluded from all analyses based on a metal artefact on MRI (caused by a piercing), and seven were excluded from the primary analyses: four of these children had been evaluated in infancy to have foetal alcohol syndrome or foetal alcohol spectrum disorder (FASD), and 3 exhibited neuroanatomical findings; see below. The seven youths excluded from the study were more frequently from the drug-exposed group ($n = 6$) and had earlier gestational ages and worse general cognitive scores at 8½ years of age than the included participants. Ultimately, the total number of participants included in the primary analyses in the present study were 38 drug-exposed youths in the risk group (20 girls, 53%) and 44 non-exposed youths in the comparison group (13 girls, 30%) (Chi square = 4.52, $p = 0.03$).

FASD and the presence of neuroanatomical abnormalities may be related to maternal opioid or poly-substance use during pregnancy. Thus, the analyses were re-performed while including these seven youths to reveal the profile of the total sample and to clarify the possible confounding factors of serious prenatal alcohol exposure and neuroanatomical abnormalities. The flow chart in Fig. 1 depicts the inclusion and dropout of participants in this study.

The information about drug use by the mothers in the present study was based on the women's medical and social records and self-reports. With the heavy nature of maternal substance abuse during pregnancy, many had trouble reporting specific information about the dose, frequency and timing of their drug abuse. In addition, they may have been afraid of losing the custody of their newborn children because of their drug use. For these reasons, we have only included what was deemed the most reliable information, specifically the women's main drug of choice and any additional drugs that were used during pregnancy (Supplementary material and Supplementary Table A2). The biological mothers of the youths in the exposed group used a wide range of drugs.

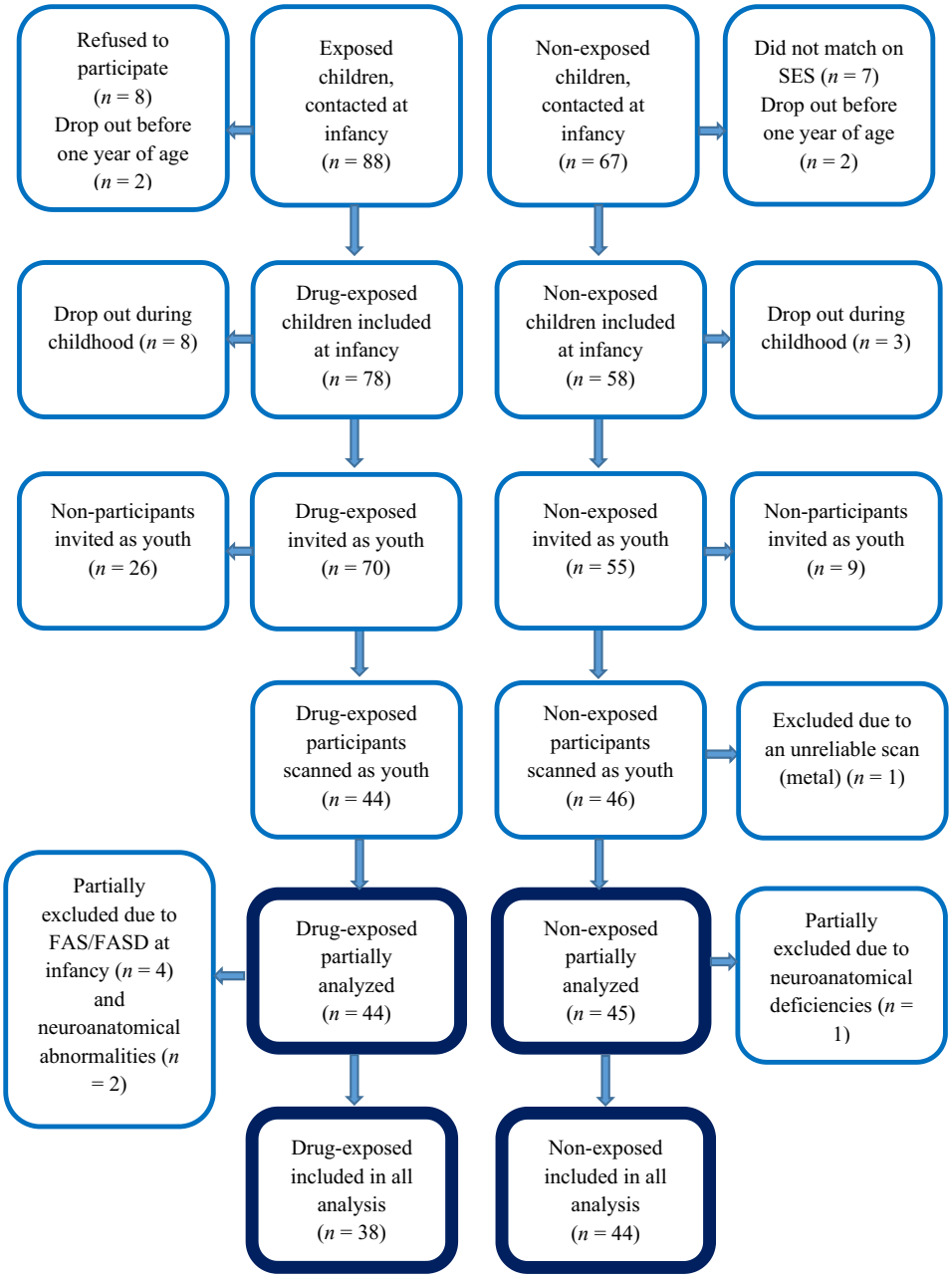

Fig. 1. Flow chart of the inclusion and dropout of participants.

The most common main drug of choice, aside from tobacco (n = 38, 100%), was opioids (heroin) (n = 18, 47%) followed by alcohol (n = 5, 13%), benzodiazepines (n = 4, 11%) and amphetamines (n = 4, 11%). On average, these mothers had used 3.4 (range 2 to 6) different drugs, including tobacco, during pregnancy. Most of the exposed youths (n = 28, 74%) had NAS, as recorded from the children's medical records. Eight (21%) of the youths in the exposed group and one in the comparison group had a birth weight < 2500 g. The risk group had worse perinatal outcomes (lower gestational age, lower birth weight and smaller head circumference), lower caregiver education, and shorter height than the comparison group (Table 1).

Whereas all youths in the comparison group lived with their biological families throughout the study period, most youths in the exposed group were either adopted or had moved to permanent foster homes before the age of one year (n = 32, 84%). Two youths in the exposed group lived with their biological mother at the time of the most recent assessment, one of whom had done so throughout childhood. The County Social Welfare Board made the decision concerning custody of the child after the child protective services in Norway had evaluated the mothers in the substance-exposed group regarding their ability to participate in a rehabilitation program for drug and alcohol addiction, as well as their ability to adequately care for their children. As is common in clinical samples, both historical and concurrent information about the care environment were lacking.

As shown in Table 1, the average age of non-exposed youths was younger than that of drug-exposed youths, although substantial overlap in age ranges was observed (see statistical analyses). An age-matched comparison group would be preferable. However, sustaining the advantage of having followed the comparison group from birth was prioritized, as this comparison group had been regularly assessed using the same measurements as the drug-exposed group. Furthermore, this approach avoided selection bias. Therefore, this study was performed on the original comparison group, and differences in age between the groups were accounted for statistically.

Table 1
Descriptive information about the sample.

	Drug-exposed (n = 38)			Non-exposed (n = 44)			Test of significant differences
	Mean	*SD*	Range	Mean	*SD*	Range	*p*
Gestational age (weeks)	38.4	2.3	31.0–42.0	40.6	1.2	38.0–42.5	< 0.001
Birth weight (grams)	3155.1	718.0	1160–4380	3753.9	436.0	2620–4615	< 0.001
Head circumference (cm)	34.1	1.9	28.0–37.0	35.7	1.2	32.0–38.0	< 0.001
Caregivers' education level[a]	1.6	0.8	0–3.0	2.1	0.7	0.5–3.0	0.001
Age at scanning (years)	19.5	1.4	17.6–22.0	18.5	0.4	17.3–19.1	< 0.001
Height (cm)[b,c]	170.8	9.3	154–193	179.3	7.6	165–193	< 0.001
Weight (kg)[b,c]	66.6	15.5	44–117	74.8	15.3	55–130	0.020

The significance of mean intergroup differences was evaluated using Student's *t*-test.

[a] The caregivers' education level represents the mean education level; 0 indicated that none of the caregivers had received any secondary education, whereas 3 indicated that both caregivers had received tertiary education of four years or more.

[b] $n_{Drug\text{-}exposed\ group} = 36$.

[c] The drug-exposed individuals were on average 5.4 cm shorter (95% CI = 1.9 to 8.9 cm, $p = 0.003$) and weighted 5.1 kg less (95% CI = −2.6 to 12.8 kg, $p = 0.19$) than the non-exposed individuals after controlling for sex and age.

The participants who were included in all analyses (n = 82) showed better results than the non-participants (n = 47) on many measures (Supplementary Table A1). Compared to the non-participants, the participants had more frequently converted to a different caregiver before one year of age; had a higher gestational age, higher birth weight and greater head circumference at birth; had caregivers with higher socioeconomic status at one year of age; and had greater general cognitive abilities based on previous assessments at 1, 2, 3, 4½ and 8½ years of age. However, the included participants and non-participants did not differ significantly in terms of study group, sex, heroin exposure or NAS occurrence.

2.2. Procedures

At this stage of the current longitudinal study, the participating youths underwent several cognitive tests and a clinical interview in one day and most often then underwent MRI scanning 1–6 weeks later (mean = 37 days later, SD = 51 days, range −11 to 445 days). All scans were reviewed by a radiologist, and in three cases (see above), the participants were excluded based on gross neuroanatomical deviations: one had a large arachnoid cyst, one had a corpus pineal cyst, and the third participant showed postoperative changes after resection of a left-sided temporal arachnoid cyst without any conspicuous changes in the proximal parenchyma. The youths received a payment of 1000 Norwegian kroner (approximately 110 Euros) for their participation. All participants were above the legal age of consent in Norway and signed a written consent form. This project was approved by the Regional Committees for Medical and Health Research Ethics (no. 2012/1630).

2.3. MRI acquisition and analyses

MRI data were collected using a 3-T MRI scanner (Magnetom Skyra, Siemens AG, Erlangen, Germany) equipped with a 24-channel Siemens coil. Three-dimensional T1-weighted MP-RAGE sequences were used for volumetric and cortical surface analyses with the following parameters: repetition time = 2300 ms; echo time = 2.98 ms; inversion time = 850 ms; flip angle = 8°; band width = 240 Hz/pixel; field of view = 256 mm; and scan time = 9 min 50 s. Each volume consisted of 176 sagittal slices with a voxel size of 1.0 × 1.0 × 1.0 mm. Manual inspection of all scans revealed no gross movement artefacts. For one participant, manual inspection revealed a flawed segmentation of the right hippocampus, which was corrected via manual editing (see Supplementary material). The image volumes were processed using FreeSurfer version 5.3 software (https://surfer.nmr.mgh.harvard.edu/). This process includes the removal of non-brain tissue, automated Talairach transformation, intensity correction, whole-brain volumetric segmentation (Fischl et al., 2002; Fischl et al., 2004), cortical surface reconstruction (Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 1999a), parcellation (Desikan et al., 2006; Fischl et al., 2004) and estimation of intracranial volume (Buckner et al., 2004) (see Supplementary Fig. A1 for an example of automated segmentation). Cortical reconstruction yielded measures of cortical thickness, surface area and volume. Cortical maps were resampled, mapped to a common surface, smoothed using a circularly symmetric Gaussian kernel with a full-width half-maximum of 10 mm (Fischl et al., 1999b), and subjected to statistical analyses.

2.4. Behavioural and functional measures

Two subtests of the Wechsler Abbreviated Scale of Intelligence™ (WASI) (Zhu, 1999), matrix reasoning and vocabulary, were used to measure general cognitive abilities (IQ). The Rey Complex Figure Test (RCFT) (Meyers and Meyers, 1995) was used to measure the delayed recall of visual stimuli. The digit span subtest from the Wechsler Adult Intelligence Scale – Third Edition (WAIS) (Wechsler, 2003) was used to measure working memory. An anti-saccade test (Miyake et al., 2000) using arrows on a computer screen was performed to measure visual inhibition ability. A visual 3-back task with pictures was used to measure the ability to update short-term memory over a temporal sequence and to monitor visual stimuli (Miyake et al., 2000). Adult self-report (18-59) (ASR) (Achenbach and Rescorla, 2003) questionnaires were completed by the participants to assess their externalizing, internalizing and attention problems. For more information about the behavioural and functional measures, see the Supplementary material and the study by Nygaard et al. (2017).

2.5. Statistical analyses

The possible influence of skewed data was tested by comparing the results between 1000 bootstraps and the original sample, and only negligible differences in the conclusions were found. Thus, we chose to perform parametric tests on the original data (Fagerland and Sandvik, 2009).

Estimations of intergroup differences in neuroanatomical volumes were analysed using general linear models (GLMs) in IBM SPSS statistical software version 22. The final *p*-values were adjusted ad hoc, as suggested by Hochberg and Benjamini (1990), using the statistical program R, version 3.2.2 to avoid the risk of type I errors related to multiple analyses. To avoid a skewed representation of the data, we included the results of both bivariate analyses and analyses controlling for sex and age. GLMs including the two possible interaction effects of sex and group as well as age and group were analysed. To further ensure that the observed intergroup differences were not caused by the

inclusion of a skewed and unrepresentative comparison group, the analyses were re-performed while excluding participants with incomparable ages across groups (Supplementary material).

Perinatal factors, such as birth weight, may be a factor mediating some of the negative consequences of prenatal opioid exposure (Leitner et al., 2000; Mactier et al., 2014; Walhovd et al., 2012a). Birth weight, gestational age and head circumference are highly related, as also observed in the present study, with correlations between 0.69 and 0.85. Although all perinatal information was gathered from the children's medical records, there are uncertainties about the reliability of the youths' gestational age, especially because substance-using mothers often have an unstable life in which information about gestational age is not as reliable as that for non-risk children. The most reliable perinatal measure was thus expected to be birth weight. Controlling for perinatal factors in the analyses of intergroup differences may remove some of the possible causal relation between prenatal drug exposure and neuroanatomical features at youth. Therefore, we analysed whether birth weight mediated the intergroup differences in neuroanatomical volumes instead of considering birth weight as a covariate. We used the Hayes process computational tool for SPSS, model 4 (Hayes, 2012a), considering sex and age as covariates, to analyse the mediating effect of birth weight. We also used Hayes model 4, with sex and age as covariates, to investigate whether neuroanatomical features mediated group differences in cognitive and behavioural functioning.

As very little is known about brain development specifically following prenatal opioid exposure, analyses were also performed separately on the group of youths who had mothers who used heroin as their main drug of choice during pregnancy. We were not able to analyse the differences between youths who were living with their biological mother and youth living in foster or adoptive homes because only one participant stayed with the biological mother through childhood. Thus, the time of the most recent change of caregiver and the number of caregiving changes after hospital discharge following birth were evaluated to investigate the relationship between postnatal environment and neuroanatomical volumes within the risk group. Educational level was higher among the parents in the comparison group than among the caregivers of the drug-exposed youths (Table 1). Thus, analyses were also conducted to investigate how parental education level influenced the results.

Separate GLM analyses were performed for CA and CT using FreeSurfer version 5.3 (https://surfer.nmr.mgh.harvard.edu/), with each vertex across the brain surface considered as a dependent variable, group as the independent variable of interest, and sex and age as covariates. We did not find any significant interaction effects of group and sex or of group and age on CA or CT. Thus, the slopes were assumed to be similar across groups. These results were tested against an empirical null hypothesis in which multiple comparisons across the surface were taken into account using Monte Carlo simulations with a z-distribution with 10,000 iterations as implemented in FreeSurfer (Hagler et al., 2006; Hayasaka and Nichols, 2003), synthesized with a cluster-forming threshold of $p \leq 0.05$ (two-sided). Due to the combination of a skewed distribution between groups and possible interaction effects, the results from the bivariate analysis controlling for sex as well as the analysis controlling for both sex and age are presented; in addition, the results of re-analyses performed while excluding participants of incomparable ages across groups are provided (see the Supplementary material). Clusters of vertices with significant intergroup differences in cortical features were exported as regions of interest (ROIs) for further evaluation of their relation to cognitive and behavioural measures.

3. Results

3.1. Intergroup differences in neuroanatomical volumes

Table 2 shows the mean volumes of brain structures and intergroup differences controlled for sex and age. All intergroup differences showed smaller neuroanatomical volumes in the drug-exposed group. The intergroup differences in neuroanatomical volume were significant ($p < 0.05$) after controlling for sex and age for the whole brain, cerebral cortex, cerebral white matter, amygdala, basal ganglia, pallidum, thalamus, corpus callosum, and cerebellar white matter. However, the intergroup differences in the volume of the amygdala and corpus callosum were no longer significant after adjusting the *p*-values for multiple comparisons. None of the intergroup differences in volume were significant when including intracranial volume as a covariate in the models in addition to age and sex (results not shown). Thus, the intergroup differences in neuroanatomical volumes (Table 2) did not appear to be region-specific but rather seemed to be related to generally smaller brain volumes among youths born to mothers who used drugs during pregnancy.

Similar GLMs analysing the intergroup differences in neuroanatomical volumes as above were performed while including either the interaction effect of sex and group or the interaction effect of age and group as predictors. There were no significant interaction effects of sex and group or of age and group when including group, age and sex as covariates.

3.2. Intergroup differences in cortical surface area

Fig. 2 shows the results of vertex-wise analyses of group differences in CA, both bivariate and after regressing out sex or sex and age. All significant intergroup differences based on both bivariate analyses and after regressing out covariates showed that the risk group had smaller CA than the comparison group. The bivariate vertex-wise analyses showed that the risk group had smaller CA than the comparison group over a large percentage of the cortex (42% of the left and 30% of the right hemisphere). The inclusion of sex as a covariate diminished this finding, but 19% of the left and 13% of the right hemisphere continued to show significantly smaller CA in the risk group. Upon accounting for both sex and age, the risk group had smaller CA in 9 clusters, five in the left and four in the right hemisphere (28% of the left and 26% of the right hemisphere). These regions included a large cluster in the rostral middle and superior frontal gyri and the insula in the left hemisphere as well as part of the inferior parietal cortex, the precuneus and the cuneus in the right hemisphere. The remaining intergroup differences were located in smaller clusters in the superior parietal cortex, fusiform gyrus, posterior cingulate cortex, precuneus, and pericalcarine cortex in the left hemisphere as well as the pars opercularis gyrus, the rostral middle frontal gyrus, the insula, the lateral occipital cortex and the fusiform gyrus in the right hemisphere. No significant differences in CA were observed when the intracranial volume was entered as a covariate in addition to sex and age.

3.3. Intergroup differences in cortical thickness

The bivariate vertex-wise analyses showed that the risk group had thinner cortices than the comparison group bilaterally in the precentral gyrus and in a small cluster in the left rostral middle frontal gyrus and the right precuneus cortex (Fig. 3). After accounting for both sex and age, there were three clusters with intergroup differences: in the left precentral gyrus, in the inferior parietal cortex, and surrounding the right precentral and postcentral gyri. These three clusters continued to show a significantly thinner cortex, albeit to a smaller extent, in the risk group when intracranial volume was entered as an additional covariate (all *p*-values ≤ 0.004).

3.4. Covariates and subgroup analyses

A matrix of correlations between possible covariates and between these covariates and specific neuroanatomical volumes are presented in Table 3.

The drug-exposed group had lower birth weight than the

Table 2
Mean (*SD*) brain volumes in mm^3 and tests of the significance of intergroup differences.

Volumes	Comparison group (n = 44)		Poly-substance-exposed group (n = 38)		Group differences after controlling for sex and age		
	M	*SD*	*M*	*SD*	*b*	*p*	Adjusted *p*
Whole brain	1,257,460	94,501	**1,165,048**	**135,955**	**0.70**	**0.001**	*0.004*
Cerebral cortex	561,848	44,492	**513,901**	**54,473**	**0.82**	**< 0.001**	*0.003*
Cerebral white matter	482,614	46,022	*451,815*	*72,474*	*0.52*	*0.020*	*0.036*
Hippocampus	9364	824	*8904*	*1021*	0.40	0.108	0.119
Amygdala	4116	510	*3809*	*548*	*0.45*	*0.048*	0.061
Accumbens	1744	224	*1590*	*242*	*0.54*	*0.023*	*0.036*
Basal ganglia	26,028	2313	**23,718**	**2778**	**0.79**	**0.001**	*0.004*
Thalamus	16,029	1352	**14,684**	**1854**	**0.74**	**0.001**	*0.004*
Corpus callosum	3303	422	3179	576	*0.48*	*0.050*	0.061
Cerebellar cortex	114,166	10,933	*108,202*	*11,889*	0.26	0.253	0.252
Cerebellar white matter	33,458	3715	*31,058*	*4294*	*0.59*	*0.014*	*0.030*

Descriptive statistics show the mean brain volumes of the comparison and poly-substance-exposed groups and the results of bivariate tests of the significance of intergroup differences. Regression coefficients for intergroup differences were calculated using a univariate linear regression analysis considering sex and age as covariates. The brain volumes were standardized (Z-values) before entering the data into the models. Thus, *b* is comparable to Cohen's *d* for the standardized effect size. All intergroup differences were in the direction of smaller brain volumes in the drug-exposed group. Significant intergroup differences between the drug-exposed group and the comparison group determined using bivariate and multiple general linear models are shown in *italics* ($p \leq 0.05$) or **bold** ($p \leq 0.001$). Adjusted *p* represents the *p* values determined after adjusting for multiple analyses (n = 11 tests) as suggested by Hochberg and Benjamini (1990).

comparison group (Table 1). We performed a mediation analysis to investigate whether some of the previously described main effects of group on neuroanatomical volumes (Table 2) could be explained by differences in birth weight. Thus, we used mediation analyses to divide the previously observed intergroup differences into an indirect mediating effect of birth weight and a direct effect of group. We found that most of the mediating effects were in the expected direction, in which birth weight explained some of the previously described intergroup differences (Table 4). However, none of the mediating effects were significant. The direct effects of group on the whole brain volume

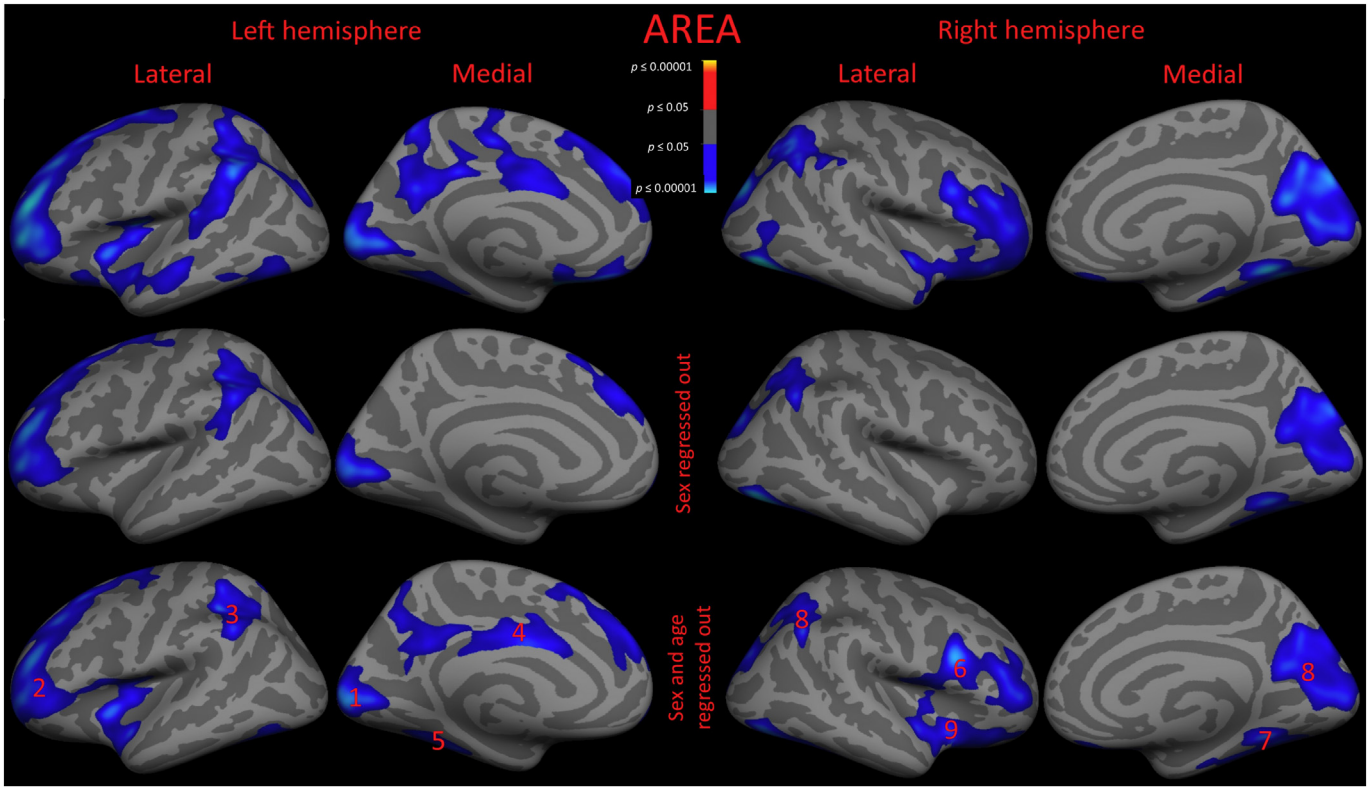

Fig. 2. Differences in cortical surface area between youths born to mothers with opioid or poly-substance use during pregnancy (n = 38) and controls (n = 44). The group differences are projected onto an inflated brain (left panels: lateral view, right panels: medial view) using FreeSurfer version 5.3 software (https://surfer.nmr.mgh.harvard.edu/). Because several possible confounders correlated with prenatal drug exposure, the analyses performed using general linear models were repeated after regressing out different variables. Thus, the results are shown without any corrections (top), after controlling for sex, and after controlling for sex and age. The blue colour indicates a cluster with a significantly smaller cortical surface area in the risk group than in the comparison group. The annotations indicate the significant clusters. Left hemisphere: pericalcarine cortex (1), rostral middle and superior frontal gyri (2), superior parietal cortex (3), posterior cingulate cortex and precuneus (4) and fusiform gyrus (5). Right hemisphere: pars opercularis and rostral middle frontal gyri (6), lateral occipital cortex and fusiform gyrus (7), inferior parietal cortex, precuneus and cuneus (8) and insula (9).

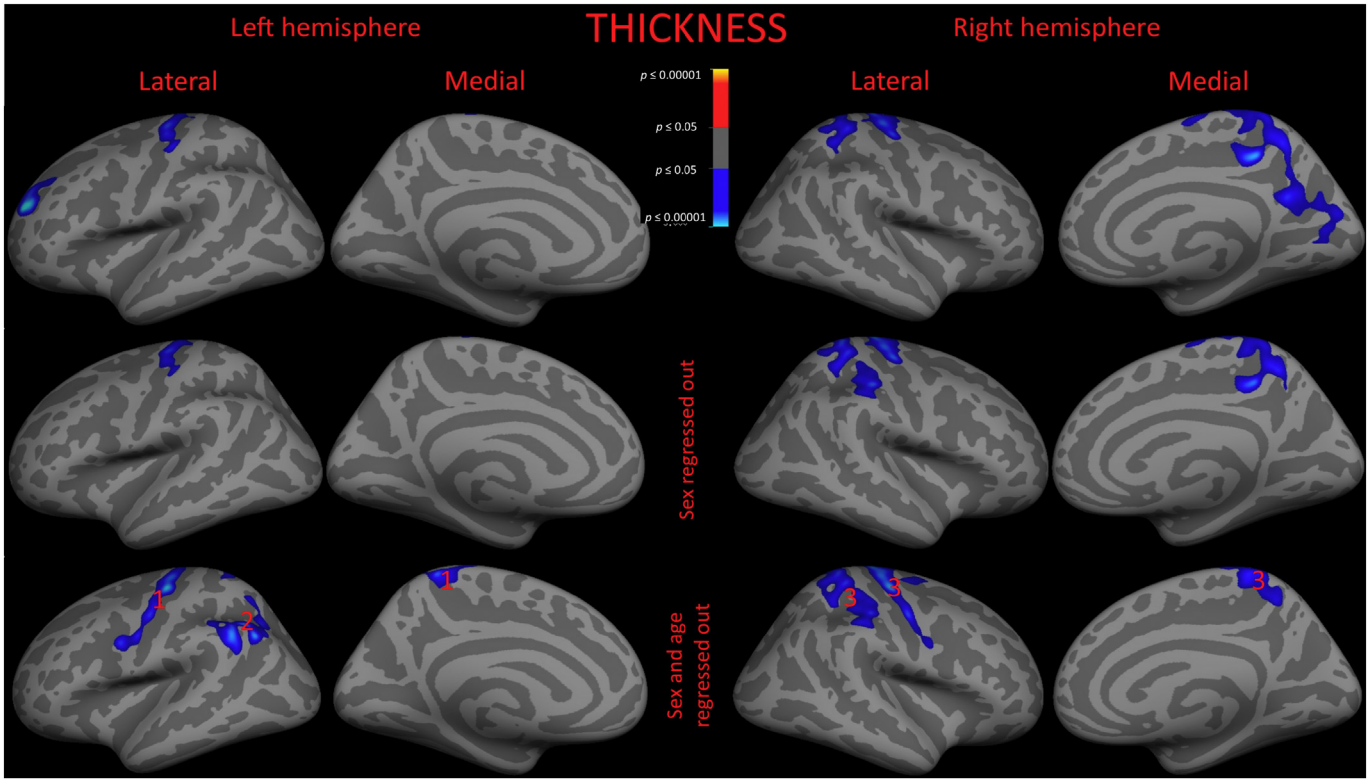

Fig. 3. Differences in cortical thickness between youths born to mothers with opioid or poly-substance use during pregnancy (n = 38) and controls (n = 44). The group differences are projected onto an inflated brain (left panels: lateral view, right panels: medial view) using FreeSurfer version 5.3 software (https://surfer.nmr.mgh.harvard.edu/). Because several possible confounders correlated with prenatal drug exposure, the analyses performed using general linear models were repeated after regressing out different variables. Thus, the results are shown without any corrections (top), after controlling for sex, and after controlling for sex and age. The blue colour indicates a cluster with a significantly thinner cortex in the risk group than in the comparison group. The annotations indicate the significant clusters. Left hemisphere: precentral gyrus (1) and inferior parietal cortex (2). Right hemisphere: precentral and postcentral gyri (3).

as well as the volumes of the cerebral cortex, cerebral white matter, basal ganglia, thalamus, corpus callosum and cerebellar white matter remained significant after removing the indirect effect of birth weight (Table 4). However, the direct effect of group on the volumes of the cerebral white matter, corpus callosum and cerebellar white matter were not significant after controlling for multiple analyses (Table 4).

Caregivers' education levels were not related to any neuroanatomical volumes (Table 3). When controlling for caregivers' education in addition to sex and age, most effect sizes of intergroup differences in neuroanatomical volumes were similar to the values presented in Table 2, except that cerebellar white matter volume (b = 0.48, p = 0.059) was no longer significantly different between the groups.

NAS occurred more frequently among mothers who used heroin as their main drug of choice (89%) during pregnancy compared to those using other drugs as their main drug of choice (60%) (Chi square = 4.08, p = 0.043). NAS was not related to any other covariates (Table 3), but NAS did correlate with several neuroanatomical volumes within the risk group (Table 3). After controlling for age and sex, NAS occurrence was related to a larger cerebellar cortex volume (b = 0.68, p = 0.046) within the risk group. However, this relation was not significant after adjustment for multiple comparisons.

Although 32 of the participants in the risk group moved to a stable foster- or adoptive home before one year of age, five participants changed caregivers after one year of age and one participant lived together with the biological mother throughout childhood. However, significant correlations between the age at the most recent change of caregiver and any of the other possible covariates (except sex) or any neuroanatomical volumes were not observed (Table 3). There were no significant differences in neuroanatomical volumes between participants with zero or one change of caregiver (n = 14) and participants with more than one change of caregiver after hospital discharge following birth (n = 23, among whom four had more than two caregiver changes).

All analyses presented above were performed while excluding the seven participants with FASD or neuroanatomical abnormalities. When the analyses were repeated by including all participants with interpretable MR images (n = 89), nearly identical results were obtained compared to the findings presented above (Supplementary material, Supplementary Tables A3–A5 and Supplementary Figs. A2 and A3).

Analyses were repeated while excluding participants born to mothers with a main drug of choice other than heroin. Similar to the results obtained from the total sample, the opioid-exposed group (n = 18) displayed smaller volumes, CT, and CA than the comparison group (n = 44). The effect sizes of the intergroup differences in neuroanatomical volumes after controlling for sex and age were predominantly larger than or similar to those presented above, as well as after excluding the possible mediating effect of birth weight. Very similar cortical regions to those identified in the full sample showed intergroup differences in CA and CT. See the Supplementary material, Supplementary Tables A3–A5 and Supplementary Figs. A2 and A3 for more details.

Similar differences in neuroanatomical volumes, CA and CT between the risk and comparison groups to those presented above (Table 2) were observed when excluding participants outside the age range of the other group (Supplementary material, Supplementary Tables A6 and A7 and Supplementary Figs. A2 and A3). Thus, the aforementioned findings obtained from the analyses of the original sample showing that the risk group had smaller neuroanatomical volumes, CA and CT do not seem to be due to a skewed sample.

Table 3
Correlation matrix between relevant covariates and neuroanatomical volumes among participants without FASD or neuroanatomical abnormalities (n = 82).

	1	2	3[b]	4[c]	5[c]	6	7	8	9	10
Covariates * covariates										
1. Group[a]										
2. Sex[a]	0.24*									
3. Age at most recent change in caregiver[b]		0.39*								
4. Heroin as the main maternal drug of choice[a,c]		−0.05	0.07							
5. Neonatal abstinence syndrome[a,c]		−0.21	−0.11	0.33*						
6. Gestational age (weeks)	0.51***	−0.02	−0.10	0.35*	0.12					
7. Birth weight (gram)	0.46***	0.02	−0.19	0.23	0.09	0.73***				
8. Birth head circumference (cm)	0.44***	0.10	−0.18	0.07	−0.01	0.66***	0.82***			
9. Caregivers' education level	0.36***	−0.03	−0.28	0.03	−0.04	0.18	0.04	0.10		
10. Age at scanning (years)	−0.48***	−0.12	−0.08	−0.30	−0.10	−0.39***	−0.44***	−0.26*	−0.08	
Volume * covariates										
Whole brain	0.37***	0.52***	0.04	−0.07	−0.30	0.22*	0.17	0.25*	0.12	−0.04
Cerebral cortex	0.44***	0.46***	0.03	0.02	−0.36*	0.28**	0.22*	0.30*	0.20	−0.12
Cerebral white matter	0.25*	0.48***	0.05	−0.11	−0.19	0.14	0.08	0.17	0.02	0.06
Hippocampus	0.24*	0.31**	0.18	0.10	−0.18	0.28**	0.16	0.20	0.01	−0.09
Amygdala	0.28**	0.50***	0.15	−0.16	−0.33*	0.17	0.15	0.21	−0.07	−0.06
Accumbens	0.32**	0.38***	0.02	−0.06	−0.31	0.24*	0.21	0.24*	0.11	−0.10
Basal ganglia	0.42***	0.34**	0.16	−0.02	−0.35*	0.28**	0.26*	0.28**	0.11	−0.14
Thalamus	0.39***	0.42***	0.10	−0.13	−0.30	0.32**	0.21	0.30**	0.09	−0.09
Corpus callosum	0.13	0.21	−0.13	−0.04	−0.13	−0.10	−0.12	−0.04	−0.08	0.21
Cerebellar cortex	0.26*	0.51***	0.01	−0.12	−0.38*	0.09	0.17	0.16	0.12	−0.15
Cerebellar white matter	0.29**	0.38***	−0.10	−0.22	−0.24	0.14	0.14	0.17	0.18	−0.01

Pearson's correlation coefficients.

[a] Group was defined as 0 = drug-exposed or 1 = control; sex as 0 = girls or 1 = boys; heroin as the main drug of choice as 0 = yes or 1 = no; and neonatal abstinence syndrome as 0 = yes or 1 = no.

[b] Ranked ages, n = 37 (only in the drug-exposed group).

[c] n = 38 (only in the drug-exposed group).

* $p \leq 0.05$.

** $p \leq 0.01$.

*** $p \leq 0.001$.

Table 4
Analyses of whether birth weight mediated the intergroup differences in brain volumes when controlling for age and sex (n = 44 + 38).

Volumes	Direct effect		Indirect effect	
	b	p[a]	b	95% CI
Whole brain	0.63	0.006	0.10	−0.09 to 0.28
Cerebral cortex	0.74	0.002	0.10	−0.11 to 0.29
Cerebral white matter	0.47	0.048	0.07	−0.15 to 0.26
Hippocampus	0.32	0.221	0.10	−0.11 to 0.34
Amygdala	0.36	0.127	0.11	−0.07 to 0.32
Accumbens	0.44	0.077	0.13	−0.10 to 0.37
Basal ganglia	0.70	0.006	0.14	−0.03 to 0.34
Thalamus	0.65	0.007	0.12	−0.05 to 0.31
Corpus callosum	0.56	0.032	−0.10	−0.43 to 0.12
Cerebellar cortex	0.18	0.459	0.11	−0.05 to 0.29
Cerebellar white matter	0.52	0.039	0.09	−0.09 to 0.26

Notes. Mediation analyses were performed using model 4 from the Hayes (Hayes, 2012b) process computational tool for SPSS. All models considered group as a predictor, birth weight as a mediator, and sex and age at scanning as covariates. All brain volumes were standardized (z-values) before entering the data for analysis. Positive regression coefficients (b) indicate smaller brain volumes in the drug-exposed group.

[a] After controlling for multiple analyses (n = 11 tests), the direct effect was significant for the volumes of the whole brain (p = 0.020), cerebral cortex (p = 0.017), basal ganglia (p = 0.020) and thalamus (p = 0.020).

3.5. Relation between neuroanatomical measures and functioning

Bivariate and partial correlations between neuroanatomical features, including neuroanatomical volumes, ROIs for CA and CT, and behavioural and cognitive functioning, are shown in Supplementary Table A8. ROIs were defined as areas with significant intergroup differences based on the vertex-wise analyses. All cognitive and behavioural measures were significantly related to one or more neuroanatomical measures, with general cognitive functioning, as measured by IQ on the WASI, typically exhibiting the highest correlations with most of the neuroanatomical volumes and ROIs for CA and CT (partial r from 0.02 to 0.48). Supplementary Fig. A3 presents a scatterplot of the relation between IQ and the volume of the whole brain.

All intergroup differences in cognitive scores and behavioural measures showed lower functioning among the risk group, and all bivariate differences were significant ($p \leq 0.05$). After controlling for age and sex, the risk group had lower cognitive scores on the WASI ($b_{z\text{-}value} = 1.06, p < 0.001$), the RCFT ($b_{z\text{-}value} = 0.87, p = 0.001$), the digit span test ($b_{z\text{-}value} = 0.90$, $p < 0.001$) and the 3-back test than the comparison group ($b_{z\text{-}value} = 0.78$, $p = 0.002$), whereas the group differences on the anti-saccade test ($b_{z\text{-}value} = 0.43$, $p = 0.078$) and total self-reported behavioural functioning ($b_{z\text{-}value} = 0.48$, $p = 0.085$) were not significant.

The mediating effects of neuroanatomical features on the group differences in general cognitive functioning are presented in Table 5. The worse general cognitive function of the risk group was partially mediated by smaller volumes of the whole brain, cerebral cortex, amygdala, accumbens and thalamus. The group difference in general cognitive function was also partially mediated by seven of the clusters of smaller CA in the risk group. Group differences in visual memory were partially mediated by the smaller CA in the insula in the right hemisphere ($b_{z\text{-}value} = 0.16$, 95% CI [0.00 to 0.41]), but were not significantly mediated by any of the other neuroanatomical features. The cluster of smaller CA superior parietal in the left hemisphere partially mediated the group difference in digit span test performance ($b_{z\text{-}value} = 0.22$, 95% CI [0.02 to 0.53]). The volume of the amygdala partially mediated the group differences in performance on the anti-saccade test ($b_{z\text{-}value} = 0.10$, 95% CI [0.00 to 0.32]). None of the neuroanatomical measures significantly mediated the group differences in updating functioning measured by the 3-back test. Almost all of the

Table 5
Analyses of whether neuroanatomical measures mediate the intergroup differences in general cognitive abilities (IQ) after controlling for age and sex (n = 82).

	Direct effect		Indirect effect	
	b	*p*	*b*	95% CI
Volumes				
Whole brain	0.91	> 0.001	0.15	0.00 to 0.38
Cerebral cortex	0.79	0.002	0.27	0.09 to 0.54
Cerebral white matter	1.01	> 0.001	0.05	−0.06 to 0.23
Hippocampus	1.02	> 0.001	0.04	−0.02 to 0.19
Amygdala	0.97	> 0.001	0.09	0.00 to 0.29
Accumbens	0.94	> 0.001	0.12	0.01 to 0.31
Basal ganglia	0.95	> 0.001	0.11	−0.03 to 0.31
Thalamus	0.92	> 0.001	0.14	0.00 to 0.34
Corpus callosum	1.10	> 0.001	−0.04	−0.23 to 0.05
Cerebellar cortex	1.06	> 0.001	0.00	−0.12 to 0.06
Cerebellar white matter	1.05	> 0.001	0.02	−0.11 to 0.19
Cortical area ROIs				
lh, pericalcarine	1.01	> 0.001	0.05	−0.15 to 0.24
lh, rostral middle frontal	0.70	0.004	0.36	0.14 to 0.66
lh, superior parietal	0.80	0.002	0.26	0.08 to 0.53
lh, posterior cingulate and precuneus	0.77	−0.002	0.29	0.10 to 0.57
lh, fusiform	0.88	> 0.001	0.18	0.02 to 0.44
rh, pars opercularis	0.77	0.003	0.29	0.09 to 0.57
rh, lateral occipital	0.82	0.002	0.24	0.06 to 0.50
rh, inferior parietal	0.68	0.009	0.38	0.16 to 0.69
rh, insula	0.89	> 0.001	0.17	−0.00 to 0.40
Cortical thickness ROIs				
lh, precentral	0.94	> 0.001	0.12	−0.12 to 0.40
lh, inferior parietal	0.97	> 0.001	0.09	−0.15 to 0.34
rh, precentral	1.06	> 0.001	0.00	−0.27 to 0.29

The regression coefficient (*b*) was obtained from mediation analyses performed using model 4 from the Hayes (Hayes, 2012b) process computational tool for SPSS. All models considered group as a predictor, neuroanatomical measure as a mediator, sex and age at scanning as covariates, and general cognitive abilities as measured by the Wechsler Abbreviated Scale of Intelligence as a dependent variable. Thus, the total group differences in cognitive abilities are divided between the direct effect and the indirect mediating effect. General cognitive abilities were standardized (z-values) before entering the data for analysis. Thus, the regression coefficients are interpreted as the difference in the number of standard deviations in IQ between groups. Positive regression coefficients indicate worse cognitive performance of the drug-exposed group. lh = left hemisphere; rh = right hemisphere; ROI = region of interest from vertex-wise analyses of intergroup differences in cortical surface area and thickness.

group differences in total self-reported behavioural problems were mediated by the ROI localized to the left inferior parietal cortex ($b_{z\text{-}value}$ = −0.43, 95% CI [−0.98 to −0.06]), whereas differences in the basal ganglia exerted the opposite mediating effect ($b_{z\text{-}value}$ = 0.20, 95% CI [0.01 to 0.47]). The direct effects of group on cognitive function, which were significant before considering the indirect mediating effects, remained significant after accounting for the mediating effects.

4. Discussion

4.1. Main findings

Consistent with our hypothesis, the present study found that youths with opioid and poly-drug exposure in utero exhibit smaller neuroanatomical volumes, CA and CT than controls. The replication and extension of the findings from previous studies (Sirnes et al., 2017; Walhovd et al., 2007; Yuan et al., 2014) using the present larger sample of older participants suggests that these intergroup differences are stable alterations rather than signs of delayed development. The intergroup differences in brain volume appeared to be a general feature across multiple neuroanatomical regions, including both cortical and subcortical regions. Most of the direct effects of group on neuroanatomical volumes remained significant after accounting for the mediating effect of birth weight. Neuroanatomical features partially mediated the group differences in cognitive functioning.

4.2. Intergroup differences

The finding of smaller neuroanatomical volumes corresponds to previous findings in a subsample (n = 28) of the present participants when they were 8 years younger (Walhovd et al., 2007), in a study of 16 infants born to mothers who used opioids during pregnancy (Yuan et al., 2014), and in a study of 16 children aged 10–14 years (Sirnes et al., 2017). The largest effect sizes were observed in grey matter of both cortical and subcortical regions. As described in these previous studies (Sirnes et al., 2017; Walhovd et al., 2007; Yuan et al., 2014), very large group differences in basal ganglia volume were observed.

The risk group had a smaller CA across approximately one quarter of the cortex. The intergroup differences in CA were stable across subgroups and were independent of sex and age. A smaller CA was observed bilaterally in the rostral middle frontal gyrus, insula, inferior and superior parietal cortices, fusiform gyrus and precuneus cortex; the pericalcarine cortex in the left hemisphere; and the cuneus cortex and pars opercularis in the right hemisphere. To the best of our knowledge, no previous studies have investigated CA in individuals born to mothers with opioid or poly-drug abuse during pregnancy.

As found in the subsample approximately 8 years prior to the present scan (Walhovd et al., 2007; Walhovd et al., 2008), the risk group has a smaller CT. However, the previous study found reduced CT in the drug-exposed children in the anterior cingulate and lateral orbitofrontal cortex in the left hemisphere, but the areas displaying a significantly thinner cortex in the risk group from this larger and older sample primarily included the precentral gyrus bilaterally and the left inferior parietal cortex.

Thus, the results of the present study support previous findings showing that this risk group generally had smaller neuroanatomical structures, including both cortical and subcortical structures, than the comparison group. This finding contrasts the results from a study of children born to opioid- and poly-substance-dependent mothers who were detoxified during pregnancy; in that study, no differences in children's neuroanatomical volumes or general cognitive abilities were observed in the risk group compared to the non-risk comparison group (Walhovd et al., 2015). None of the children born to detoxified mothers had NAS, and their mean birth weights were well within the normal range (Haabrekke et al., 2014).

The findings of smaller neuroanatomical structures in the risk group than in the comparison group in the present study may be related to previously reported worse clinical outcomes in similar risk groups compared to control groups, e.g., in neuropsychological functioning (Lester and Lagasse, 2010; Ornoy et al., 2010), visual function (Gupta et al., 2012; Hamilton et al., 2010; McGlone et al., 2014; Walhovd et al., 2015), fine motor abilities (Bunikowski et al., 1998; Davis and Templer, 1988; Hans and Jeremy, 2001; Logan et al., 2011; Wahlsten and Sarman, 2013) and perinatal factors such as birth weight (Creanga et al., 2012; Mactier et al., 2014). These results are also consistent with the findings of animal and cell culture studies showing that prenatal opioid exposure can alter the myelin sheath in the developing brain (Sanchez et al., 2008), disrupt neuronal migration and/or cell survival (Harlan and Song, 1994), affect genetically programed cell death in the hippocampus by influencing specific proteins in apoptotic signal-transduction pathways (Wang and Han, 2009), decrease dendrite length and branch number in pyramidal neurons in the somatosensory cortex (Lu et al., 2012), alter synaptic neuroplasticity (Beltran-Campos et al., 2015), and disrupt several important neurotransmitter systems (De Montis et al., 1983; McGinty and Ford, 1980; Robinson, 2002; Robinson et al., 1997). Studies of both human infants and rodents have also found possible epigenetic modifications associated with opioid use (Vassoler

et al., 2014; Wachman et al., 2014).

4.3. Delayed development or persistent differences from birth?

One important question is whether the smaller neuroanatomical structures of the drug-exposed group are related to developmental differences, e.g., delayed development, or to persistent differences existing from birth. CT is known to decrease with age beginning from childhood and throughout the adult lifespan (Amlien et al., 2016; Brown et al., 2012; Fjell et al., 2015a; Fjell et al., 2009; Raznahan et al., 2011; Shaw et al., 2008; Westlye et al., 2010). The present sample was aged between 17 and 23 years; thus, they were much younger than the age at which positive developmental cortical thinning would be expected to become a more negative factor due to the ageing process (Fjell et al., 2015a; Westlye et al., 2010). The participants were also much older than the time of the expected peak of CA at approximately 12 years of age (Amlien et al., 2016; Brown et al., 2012). There is also little overlap between the regions of CA that were previously found to correlate with age (Amlien et al., 2016) and the regions showing the greatest intergroup differences in CA in the present study. Thus, the age of the participants indicates that it is not probable that the present findings of smaller neuroanatomical volumes, CA and CT in the risk group are due to a delay in development.

Another aspect indicating that the findings are most likely related to early established differences rather than developmental delay is that most of the intergroup differences in cortical structures were in CA to a greater extent than CT. CT is influenced by postnatal developmental processes, e.g., selective pruning (Bourgeois and Rakic, 1993; Huttenlocher and Dabholkar, 1997; Petanjek et al., 2011) and an increase in the myelin coating of fibres within and near deeper cortical layers (Benes et al., 1994; Sowell et al., 2004). In contrast, CA is primarily related to neuron formation and migration during foetal life (Rakic, 2000). The folding of the surface of the brain, referred to as gyrification, creates a large cortical surface area. The gyrification of the brain primarily increases during the third trimester and then remains very stable during later development (White et al., 2010). Thus, the findings of widespread intergroup differences in CA indicate that the neuroanatomical differences between the groups may have already been present at birth.

4.4. Birth weight

The lower birth weight of the participants with prenatal opioid- or poly-drug exposure than the controls, both in the present study and as commonly found in other studies (Creanga et al., 2012; Mactier et al., 2014), also indicates that the observed intergroup differences may have existed at birth. Variations in birth weight within the normal range, after controlling for gestational age, was positively associated with subsequent total neuroanatomical volumes and CA, although to a lesser extent with CT, in two large studies (Raznahan et al., 2012; Walhovd et al., 2012a). Birth weight is related to several possible covariates of poly-drug use by the mother, such as maternal stress (Monk et al., 2012), maternal food intake (Stein et al., 1972), smoking (England et al., 2001) and alcohol use during pregnancy (Dörrie et al., 2014). However, maternal use of opioids or multiple drugs also likely influences birth weight (Creanga et al., 2012; Haabrekke et al., 2014). Thus, birth weight may have mediated some of the possible negative consequences of prenatal poly-drug exposure. Both Raznahan et al. (2012) and Walhovd et al. (2012a) identified a positive correlation between birth weight and CA in the left cingulate and inferior parietal cortex and in the right precuneus cortex; these regions are similar to regions shown to display a smaller CA in the drug-exposed youths in the present study. However, both studies also observed a relation between birth weight and several CA regions in which no intergroup differences in CA were found in the present study, e.g., the right medial orbitofrontal cortex. In addition, several regions showing intergroup differences in CA in the present study were not related to birth weight in previous studies, e.g., the left superior parietal cortex and rostral middle frontal gyrus (Raznahan et al., 2012; Walhovd et al., 2012a). Moreover, birth weight mediated only a small part of the intergroup differences in neuroanatomical volumes in the present study (Table 4). For the subgroup of children born to mothers using heroin as their main drug of choice, none of the mediating effects of birth weight were significant, and 1/3 of these effects were even negative (Supplementary Table A5). Thus, birth weight is not a substantial, or the only, mediating factor related to the observed intergroup differences.

4.5. Change in caregiver

The combination of having been moved to a stable caregiving environment before one year of age among the majority of the drug-exposed youths and the provision of intensive professional care by Aline Infant and Family Center before transfer should have minimized the effects of a detrimental postnatal environment. The foster and adoptive parents in the present study were specially selected and trained to care for children at risk and had a high socioeconomic status compared to the common characteristics of foster parents and the general population in Norway (Moe and Slinning, 2001; Statistics Norway, 2015). Thus, most of the youths in the risk group likely grew up in typical, stable and caring family environments. The lack of any significant relation between any measured neuroanatomical volume and age at the most recent change of caregiver or the number of changes of caregivers supports the hypothesis that the observed intergroup differences are not mainly due to differences in the caregiving environment.

4.6. Neuroanatomical features of participants with known opioid exposure

Significant bivariate relations between the mother's main drug of choice during pregnancy (heroin vs other drug) and any neuroanatomical volume were not observed. Thus, the opioid-exposed group exhibited very similar neuroanatomical volumes to the combined poly-substance-exposed group (Supplementary Table A3), and similar effect sizes for the intergroup differences were observed after controlling for sex and age, as presented in the primary analyses (Supplementary Table A4). Notably, the effect sizes were not smaller, but rather were larger, than when analyses were performed including all drug-exposed participants. Thus, we cannot exclude the possibility that a larger sample would show more distinct differences for opioids compared to other drugs.

Notably, the birth mothers in the risk group were poly-substance users. Some of these birth mothers whose main drug of choice was not heroin may have also used some heroin during pregnancy. One limitation of many studies of prenatal opioid and poly-substance exposure, including the present study, is the lack of data from toxicological tests performed regularly throughout pregnancy. More mothers may have used heroin than were reported, as these mothers were in a situation in which the authorities would evaluate whether the child should be assigned to another caretaker. The mothers may have deduced that it would be preferable to report the abuse of other drugs with less prejudice regarding their use while remaining silent about their heroin abuse. Although other drugs, such as alcohol, nicotine and benzodiazepines, can cause similar symptoms, NAS is thought to mainly occur after prenatal opioid exposure (Jansson and Velez, 2012), not, for example, from marijuana or cocaine exposure (Behnke et al., 2013). According to other studies, approximately 60–80% of new-borns who are exposed to heroin or methadone in utero have NAS (Patrick et al., 2012). Specifically, 74% of drug-exposed children were reported to have NAS, whereas only 53% of their mothers reported heroin use. This discrepancy indicates underreporting of opioid use in the present study. Prenatal alcohol exposure exerts highly neurotoxic effects (Donald et al., 2015; Wang and Kroenke, 2015). As is common for opioid-addicted persons (Delano et al., 2013; Messinger et al., 2004), mothers

using heroin as their main drug of choice had relatively low levels of alcohol use during pregnancy (Supplementary material). This distributional skewness of alcohol use should thus correspond to more normal neuroanatomical features in opioid-exposed youths than in youths born to mothers who abused other drugs during pregnancy. Despite this skewness, the opioid-exposed group had similar or worse neuroanatomical outcomes than the other drug-exposed group. Thus, the similarities in the results between the total group and the subgroup of participants whose mothers used heroin as their main drug of choice cannot be directly interpreted as a difference in effects between heroin and other drugs.

4.7. Relations between neuroanatomical features and function

The risk group of youths displayed lower cognitive and behavioural functioning than the comparison group. More detailed information about the youths' cognitive function is presented in previously published articles (Nygaard et al., 2017) or a study in progress (Nygaard et al., In progress). However, we investigate here whether these functional outcomes may be related to neuroanatomical features.

We found moderate correlation between better cognitive functioning and larger neuroanatomical volumes, consistent with the findings from several previous studies (e.g., Haier et al., 2004; Pangelinan et al., 2011; Pennington et al., 2000; Walhovd et al., 2005; Wickett et al., 2000; Witelson et al., 2006). The correlations were very similar to those in prior studies, such as a prior meta-analysis finding of 0.33 for the correlation between total brain volume and intelligence (McDaniel, 2005). However, no previous study has investigated how neuroanatomical features mediate cognitive differences between people with prenatal opioid or poly-substance exposure and comparison groups. We found that neuroanatomical features partially mediated the group differences in cognitive abilities. The mediating effects were the most pronounced where the relations between neuroanatomical features and cognitive abilities are known to be highest. The mediating effect appeared greatest in the cerebral cortex, smaller in the subcortical grey regions and smallest or non-significant in the white matter or cerebellum, in accordance with prior studies of the relation between these volumes and cognitive functioning (Andreasen et al., 1993; Haier et al., 2004; Pennington et al., 2000). For the most part, the mediating effects were strongest for general cognitive abilities and were less clear for more specific measures of cognitive abilities such as memory or executive functioning. This result is consistent with the observations of prior studies showing that the higher the g-loading of a test, the greater the correlations between its results with such broad measures of neuroanatomical volumes (Pangelinan et al., 2011; Wickett et al., 2000).

We found positive relationships between general cognitive functioning and CA in all of the clusters with smaller CA in the risk group, and seven of the nine clusters partially mediated the group differences in general cognitive functioning. Some overlap was observed between these mediating clusters in the present study and the regions found to be related to general cognitive abilities in a large study by Fjell et al. (2015b), e.g. the posterior portion of the cingulate cortex and the precuneus cortex in the left hemisphere, bilaterally in the fusiform gyrus, and the insula in the right hemisphere. Some overlap was also observed between the mediating ROIs with intergroup differences in CA in the present study and a parieto-frontal network found to likely underlie general cognitive abilities in a prior comprehensive multimethod review (Jung and Haier, 2007); the related brain areas include the bilateral parietal regions, rostral middle frontal cortex and fusiform gyrus. Thus, these intergroup differences in CA in these regions may be related to the findings of lower cognitive abilities in the risk group in the present study, both in childhood (Nygaard et al., 2015) and now in youth (Nygaard et al., 2017).

A thicker cortex was related to better cognitive and behavioural outcomes, but the only significant mediating effect was of the ROI of the left inferior parietal cortex on behaviour. As cortical thinning is observed to be monotonous throughout development and ageing and as cortical thickness has been observed to vary across at-risk individuals and healthy persons, the direction of cortical thickness-functional relationships identified has also varied across studies (Ameis et al., 2014; Ducharme et al., 2012; Ducharme et al., 2011; Karama et al., 2009; Narr et al., 2009; Ostby et al., 2012; Shaw et al., 2006a; Shaw et al., 2006b; Squeglia et al., 2013; Tamnes et al., 2011; Walhovd et al., 2012b; Wallace et al., 2012; Zielinski et al., 2014). In the present study, the thinner cortex in the risk group might be related to the findings of more frequent behavioural problems in the risk group than in the comparison group, both in childhood (Nygaard et al., 2016) and now in youth (Nygaard et al., In progress).

4.8. Other strengths and limitations

This neuroanatomical study of youths born to mothers with opioid or poly-drug abuse during pregnancy is larger than most MR studies of such risk groups, and it includes participants who are older than those examined in any previous related studies. The longitudinal prospective design of this study, as well as the initial inclusion of all eligible drug-exposed participants within a specific geographic area, ensures less sampling bias and more information about non-participants than is commonly reported. Because the participants generally had better prior test results than the dropouts (Supplementary Table A1) and seven participants with FASD or neuroanatomical abnormalities were excluded from analysis, the total sample of originally included drug-exposed children probably had worse neuroanatomical features than the subsample of participating youths in this study.

We chose to use the original comparison group that has been followed prospectively in the same manner as the risk group since birth. However, the comparison group did not have the same age and sex distribution as the risk group at follow-up. We therefore controlled for age and sex in all analyses and re-analysed the subsample with similar age and sex distributions, and all subgroup analyses showed similar results. Thus, the findings were probably not due to distributional differences between the groups.

The present comparison group may have exhibited better functioning than the general population in Norway, as indicated by the mean cognitive abilities above the norms (Nygaard et al., 2017) and higher educational levels among the parents of the comparison group than among both the Norwegian population (Statistics Norway, 2015) and the caregivers of the risk group. However, the above norm levels of cognitive abilities may be partially due to a Flynn effect because of the approximately 15–20-year gap between the time of the norms and the testing of the youths in the present sample. The similar findings of intergroup differences in neuroanatomical volumes between controlling and not controlling for parental education indicate that the observed results are not due to a higher parental education level in the comparison group.

Smoking could be a confounding factor, which was not controlled for because all mothers of the drug-exposed children smoked during pregnancy. However, other studies have found that smoking does not completely explain the reduced foetal growth in prenatally opioid-exposed children (Mactier et al., 2014). Previous studies have observed relations between prenatal nicotine exposure and smaller neuroanatomical volumes and lesser cortical thickness (England et al., 2017). These findings appear to be less pronounced, e.g., a study by El Marroun et al. (2014) reported effect sizes of total brain volume differences that were approximately half the sizes found in the present study.

Clinical studies such as the present study cannot specify the causal mechanisms underlying their findings. The brains of the risk group may be smaller due to a combination of genetic vulnerability (Rimol et al., 2010), prenatal drug exposure and other environmental factors before (Dörrie et al., 2014) and after birth (Zatorre et al., 2012). These factors probably interact in a transactional process throughout life (Sameroff,

2010). These in-depth realistic and complex models of development are impossible to examine in a clinical study of a limited sample size.

4.9. Conclusions

The findings of smaller neuroanatomical volumes, and regionally smaller cortical areas and a thinner cortex in the present study are consistent with previous studies of neuroanatomical features of opioid- and poly-drug-exposed children (Monnelly et al., 2018; Sirnes et al., 2017; Walhovd et al., 2007; Walhovd et al., 2008; Walhovd et al., 2012c; Walhovd et al., 2010; Yuan et al., 2014). These findings extend previous results by showing that these differences are likely not due to a developmental delay but rather persist into youth and young adulthood. Furthermore, using a larger sample than previously investigated, we did not identify other mediating or risk factors that could explain the findings, e.g., type of drugs, birth weight, changes in caregivers, or socioeconomic factors. We also found that the neuroanatomical features partially mediated the lower cognitive functioning in this risk group. As clinical, animal and cell culture studies have revealed possible negative consequences of prenatal opioid or poly-drug exposure, we recommend that there should be increased focus on the possible long-term and persistent negative consequences of prenatal drug exposure, and well-designed trials of alternative interventions to reduce prenatal drug exposure should be prioritized, e.g., residential treatment of pregnant women with drug dependency and detoxification (Walhovd et al., 2015).

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Transparency document

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