Pediatric Neurology 52 (2015) 326–332

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Original Article

Child Neuroanatomical, Neurocognitive, and Visual Acuity Outcomes With Maternal Opioid and Polysubstance Detoxification

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ABSTRACT

BACKGROUND: Maternal opioid and polysubstance use during pregnancy is associated with an increased risk of child neurocognitive and visual problems and neuroanatomical differences. We hypothesized that, in contrast to findings from a previous study of children born to mothers not detoxified, children born to detoxified mothers would not show gross neuroanatomical and neurocognitive differences. **METHODS:** Mothers with opioid and polysusbstance abuse problems and their infants (n = 11 + 12) were recruited from residential treatment institutions. Comparison mothers and infants (n = 12 + 12) were recruited from child health centers. The studies were approved by the Regional Committee of Medical Research Ethics. Children had magnetic resonance imaging scanning, neurocognitive, and visual acuity testing at 4.5 years. Neuroanatomical, cognitive, and visual acuity characteristics were compared across groups by analysis of variance and general linear models. **RESULTS:** There were no significant differences across groups in neuroanatomical volumes, or cortical thickness, area, or volume. There were no differences in general neurocognitive functioning, but significantly lower left eye visual acuity, and a trend toward lower binocular visual acuity, in the drug-exposed relative to the comparison group. **CONCLUSIONS:** The present study does not demonstrate gross differences relative to a comparison group in neuroanatomical and general neurocognitive characteristics of children born to mothers with opioid and polysubstance abuse who were detoxified during pregnancy. However, visual acuity was significantly lower in the drug-exposed group, requiring attention. There is a pressing need for additional and larger studies of long-term and specific child outcomes in this at-risk group.

Keywords: opioid, detoxification, brain, MRI, neurocognitive, vision, development, outcome

Pediatr Neurol 2015; 52: 326-332

Introduction

Children born to women using opioids and illicit drugs during pregnancy are at increased risk for neuropsychological and mental health difficulties.[1-6] Although some of these difficulties may be associated with increased postnatal risk,[7] maternal opioid and polysubstance abuse may also directly affect the developing central nervous system prenatally.[8-12] A few years ago, we published the first articles showing that children born to mothers with opioid and polysubstance abuse during pregnancy who were raised by adoptive parents in optimized environments nonetheless showed significantly lower neuroanatomical volumes, white matter

Article History:
Received September 4, 2014; Accepted in final form November 18, 2014
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http://dx.doi.org/10.1016/j.pediatrneurol.2014.11.008

microstructural maturation, and neurocognitive function than a comparison group.[13,14] We have also recently documented altered neural tract development in methadone-exposed children.[15]

It is not clear to what extent the observed group's differences and difficulties are due to the direct teratogenic effects of opioid and polysubstance exposure during pregnancy, the indirect effects of psychosocial risk associated with the lifestyle of maternal substance use, or genetic vulnerabilities. In all likelihood, no human clinical study can fully disentangle these effects. Opioid maintenance therapy (OMT) has been the preferred treatment for opioid dependence during pregnancy since the early 1970s, and recent numbers suggest that maternal opioid use is rising.[16] Thus it is paradoxical that we know little of the long-term development of children born to opioid-dependent women.[17] In addition to OMT, one option for opioid- and substance-dependent pregnant women may be detoxification. The safety of detoxification has been debated, but few studies exist to document outcomes. Recent exceptions report significant increases in birth weight and gestational age relative to children born to mothers with illicit drug use at delivery.[18,19] However, long-term outcomes are unknown.

In the present article, we examine brain and neurocognitive outcomes of children born to mothers who were hospitalized and detoxified during their pregnancies, hence reducing prenatal opioid and drug exposure. The parents retained custody after birth (see the following section). Although lessening prenatal exposure, postnatal environments are assumed to retain risk factors. We describe the brain and neurocognitive outcomes of these children at age 4.5 years. Furthermore, we discuss these data relative to brain and neurocognitive outcomes of the children in our previous study cohort, who had drug exposure throughout much of their fetal life, but whose postnatal environments were optimized. Gross neuroanatomical differences and neurocognitive correlates were found in children with opioid and polysubstance exposure throughout pregnancy,[13] and there are known central nervous system pathways that may cause these directly prenatally.[8-10] Hence, our hypothesis was that the present children, whom had considerably less prenatal exposure, would evince less neuroanatomical and neurocognitive differences despite less optimized postnatal environments.

Participants and methods

The sample consists of mothers and their infants born in between 2004 and 2008. A more detailed description of the sample and birth outcomes is given elsewhere.[19] The focus of this article is neuroanatomical and neurocognitive outcomes of children whose mothers were detoxified during pregnancy relative to a nonrisk comparison group. The mothers in the substance-associated risk group were recruited from five different residential treatment institutions in Norway. The mothers in the comparison group were recruited from child health centers in Oslo. Originally, 33 mothers of 34 children were recruited for the study group and 30 for the comparison group. In the present sample, we included only children who had neurocognitive testing at 4.5 years (risk group n = 22, comparison group n = 26), who consented to magnetic resonance imaging (MRI) scanning (risk n = 18, comparison n = 18). For some of these, usable MRI data were not obtained (risk n = 1, comparison n = 6) because they did not complete the scanning (e.g. expressed fear of lying down in the scanner, scanning noises, excess movement). Hence, useable MRI data were obtained for 29 children (risk n = 17, comparison n = 12). Furthermore, in the risk group, we included only children whose mothers themselves had reported using illicit drugs during pregnancy and underwent detoxification. For one of the mothers of these 17 children, data on drug use were missing, and three mothers stated that they had not used any illicit drugs during their pregnancies (e.g., one used prescription methadone on a daily basis throughout pregnancy, two said the used because of their residential treatment partner's drug use or fear of relapse). One child in the risk group had a venous malformation in the left orbita, also affecting soft tissue of the left eyeball. There was a left temporal lobe meningoencephalocele and dysplastic changes in the same area, previously documented and likely present at birth. Neural tube defects may in and of themselves be associated with prenatal drug exposure, including opioids,[20] and one case of spina bifida was included in an independent sample of children prenatally exposed to maternal opioid and polysubstance abuse previously published.[13] However, because the present case involved anomalies in the cerebrum, we chose to exclude this child from the present analyses. Hence, data for 12 children were included in the risk group. There was one fraternal twin pregnancy in the risk group; all others were singleton pregnancies. A subset of analyses on birth parameters was rerun with and without the twins included. At the time of the 4.5-year follow-up, three of the children included in the risk group were in foster care, whereas the others lived with their biological parents. A flow chart depicting the study and participant exclusion/inclusion is given in Supplementary Figure 1. The study was approved by the Regional Committee of Research Ethics, and parents and caregivers gave informed consent.

Residential treatment and detoxification

In Norway, there are currently multiple treatment opportunities for pregnant women with substance dependence. For pregnant women who are already enrolled in the OMT program, it is recommended that they continue the medication during pregnancy,[21,22] although the women also have the option of tapering off if they wish. Multiple inpatient clinics specialize in medically supervised detoxification in a residential setting where pregnant women with untreated substance dependence get medical and psychological support to become drug-free during their pregnancies. Pregnant women in OMT who wish to taper off as well as women with opioid and polysubstance dependence who are not in OMT can voluntarily receive help in these residential clinics. In addition, Norwegian legislation since 1996 (cf. Social Service Law § 6-2a, replaced by the Act for Municipal Health and Care Services, Section 10-3 in January 2012) authorizes detention of pregnant substance-using women in residential treatment to protect the fetus. In general, the institutions in the study provide medical supervision of the mothers where possible abstinence is monitored closely. To prevent severe abstinence, opioid agonists and pain relief medication are prescribed in a transitional phase and tapered off. When treating a pregnant woman with substance dependence, her individual state and situation is taken into careful consideration. Hence, a detailed common detoxification protocol unfortunately cannot be provided, except in the situations described here. Close monitoring as well as a supporting environment are provided. While staying in residential care, the mothers and in some cases their partners live together with other families. They receive help and guidance from professional therapists with regard to nutrition, housekeeping, and economy as well as social interaction and psychological treatment. The parents have the possibility of staying in the residences with their children up to 1 year after birth.

Maternal, drug exposure, and birth characteristics

Of the 11 women included in the risk group, seven were in residential treatment on a voluntarily basis, whereas four were admitted to treatment based on the Social Service Law §6-2a. All mothers gave written consent to participate in the study. The mean number of days of pregnancy at the time of admission was 149 (standard deviation [SD] = 69, range 64-255). Three of the mothers were admitted into treatment in their first trimester (≤84 days), four in their second trimester (85-182 days), and four in their third trimester (≥183) days. All were detoxified as part of the institutional treatment.

Data on substance abuse were collected in pregnancy, usually during the third trimester, through personal interviews using The European Addiction Severity Index, fifth edition.[23] A structured interview providing a more thorough assessment of the use of substances, nicotine, and alcohol during pregnancy was designed for the purpose of the current study and also administered. None of the 12 women in the comparison group reported use of illicit substances during their pregnancies. Two reported sporadic smoking (one two to three times per week, and one two to three times per month), restricted to the first trimester. For the first trimester, some maternal alcohol use was reported for eight comparison children: three, less than once a month; three, one to three times a month; one, once a week; and one, two to three times a week. By maternal report, the following data were obtained for the risk group: eight of the children were exposed to opioid use (i.e., heroin in the first trimester, two also in the second trimester, and for one extending into the third trimester). Nine of the children were exposed to maternal use of sedatives in the first trimester, and two in the second trimester, and none in the third trimester. None reported use of cocaine. For six children, maternal amphetamine use was reported, for one extending into the second trimester. For nine children, first trimester cannabis use was reported and for two extending in the second trimester. For four children, use of additional substances was reported in the first trimester. For all risk group children, daily or near-daily maternal smoking was reported in the first and second trimesters, whereas for five children mothers reported no smoking in the third trimester. Maternal alcohol use was reported for four children, one frequent (six to seven times per week), and three sporadic (for two, less than once a month, and for one, one to three times per month) in the first trimester only. In both the study and comparison groups, all (n = 11 + 12 available) reported having attended all regular maternity checkups. Because women were detoxified during pregnancy, no children were born with Neonatal abstinence syndrome (NAS). Six of the mothers in the risk group versus none in the comparison group reported single parenthood. Additional sample characteristics are provided in Table 1.

MRI acquisition and analyses

MRI data were collected using a 12-channel head coil on a 1.5 T Siemens Avanto scanner (Siemens Medical Solutions, Erlangen, Germany). The pulse sequence used for morphometric analysis was a three-dimensional T1-weighted Magnetization Prepared Rapid Gradient Echo (Grappa2). (Please see the supplementary material for additional details on MRI acquisition and analysis.) Only scans deemed free of gross movement artifacts were included. The image volumes were processed with the FreeSurfer software package (version 5.3; http://surfer.nmr.mgh.harvard.edu/), including volumetric segmentation,[24,25] (see Fig 1 for example segmentations) and cortical surface reconstruction.[26-28] In addition, estimated intracranial volume[29] was computed. The cortical reconstruction yields measures of cortical thickness, area, and volume throughout the cortical mantle. Maps were resampled, mapped to a common surface, smoothed using a circularly symmetric Gaussian kernel with a full-width half-maximum of 15 mm,[30] and submitted to statistical analyses.

Cognitive measures

The Norwegian edition of the Wechsler Preschool and Primary Scale of Intelligence, third edition,[31] was administered.

Visual acuity

A basic measure of visual acuity was obtained by use of the Lea Symbols 10-line folding distance chart (www.good-lite.com), designed for testing children age 2-4 years. The tests yields a visual acuity score for each eye as well as for binocular vision. (Please see Supplementary material for additional details on visual acuity testing.) The Lea Chart is considered one of the most popular and reliable preliterate acuity charts, and the 15-line version has shown good correspondence with findings on ophthalmological examination, with useful cutoff points having been found to be 0.8 where higher sensitivity is preferable, or 0.63 for a good level of specificity.[32] Because the equipment was unavailable at the time of testing, two children in the control group did not complete the visual acuity test.

Statistical analyses

One-way analysis of variance was run to test for differences in birth, demographic, and vision sample characteristics displayed in Table 1. For subcortical volumes, univariate analyses of variance were performed with age and sex as covariates to test for group effects, whereas for IQ and cognitive scaled scores, where age and sex are taken into account in the norm material on which these standardized scores are based, analyses of variance were run without covariates. For MRI cortical analyses, separate general linear models were run with cortical thickness, area, and volume, respectively, at each vortex across the brain surface as dependent variables, and group as the independent variable of interest with sex and age included as covariates. The results were tested against an empirical null

TABLE 1.
Sample Characteristics of the Two Groups

	Risk Group (5 F/7 M)			Comparison Group (3 F/9 M)			
	Mean	SD	Range	Mean	SD	Range	*P*
Birth weight (g)	3385	459	2450-3960	3753	346	3060-4316	0.062
Birth head circumference (cm)	35.2	1.3	32-37	35.6	1.4	33-38	0.530
Gestational age (weeks)	39.6	1.1	38-41	40.8	0.9	40-42	0.010
Maternal education (years)	10.9	2.6	9-18	16.3	2.1	12-19	0.000
Age at study (months)	55.3	1.1	54-57	54.8	0.9	54-56	0.157
WWPSI-III IQ	94.9	7.2	86-107	99.4	8.0	84-111	0.163
Performance IQ	95.6	10.2	75-112	100.7	9.1	86-118	0.210
Verbal IQ	98.2	8.8	80-110	100.0	10.0	84-118	0.639
Vision*							
Left eye	0.60	0.20	0.20-0.80	0.80	0.19	0.50-1.25	0.029
Right eye	0.59	0.21	0.10-0.80	0.71	0.20	0.40-1.00	0.192
Both eyes	0.65	0.22	0.10-0.80	0.80	0.09	0.63-1.00	0.063

Abbreviations:
F = female
M = male
SD = standard deviation
WWPSI-III = Wechsler Preschool and Primary Scale of Intelligence, third edition
P-values are from analyses of variance with group as factor. Sex was controlled for birth weight and head circumference.
* Not available for two in the comparison group. When excluding risk group twins (1 F/1 M), birth weight (M = 3374, SD = 507), head circumference (M = 35.1, SD = 1.4), and gestational age (M = 40.0, SD = 0.9) remained similar, and *P* values (n = 10 and n = 12) were 0.076, 0.484, and 0.043, respectively.

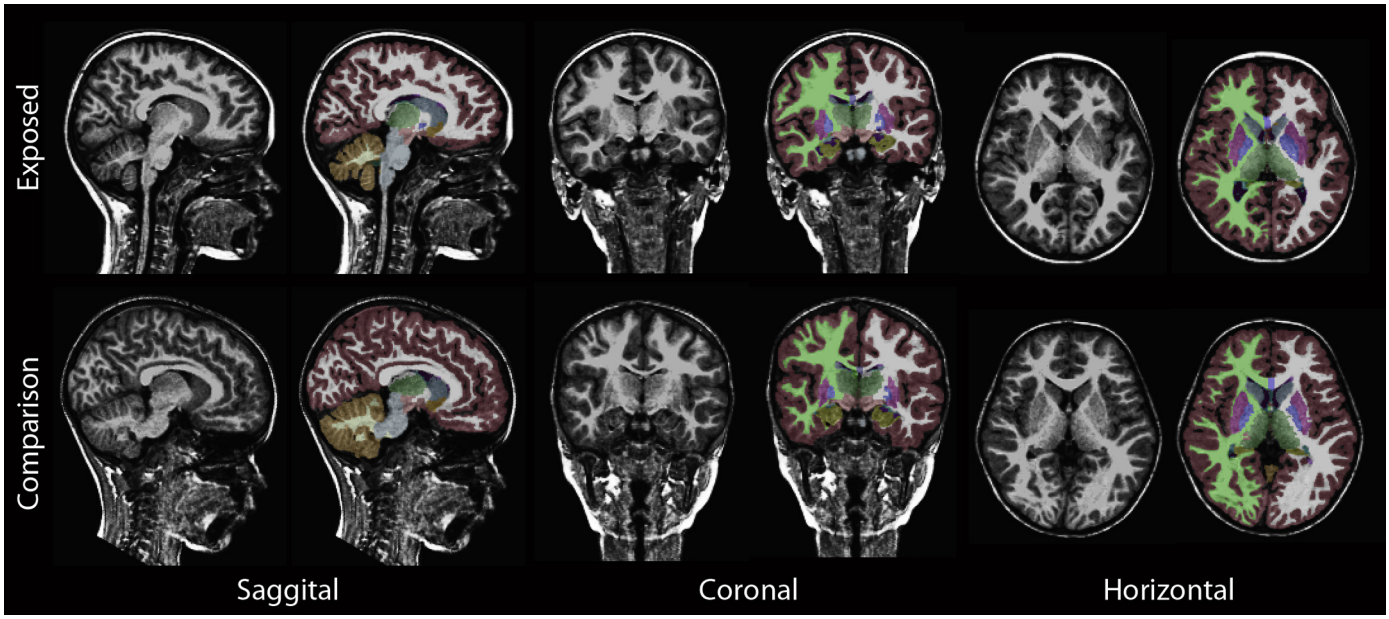

FIGURE.
Sample brain scans and segmentations. The top panel shows samples from a reconstructed scan and whole brain segmentation from one child in the risk group; the lower panel shows samples from one child in the comparison group. Sagittal, coronal, and horizontal views are shown from left to right.

distribution of maximum cluster size across 10,000 iterations using Z Monte Carlo simulations as implemented in FreeSurfer[33,34] synthesized with a cluster-forming threshold of $P < 0.05$ (two-sided), yielding correction for multiple comparisons across the surface.

Results

One-way analyses of variance showed significant differences in terms of gestational age and maternal education in the risk group as well as poorer sight when using the left eye in the risk group ($P \leq 0.05$, see Table 1 for group values). There was also a trend ($P < 0.10$) toward significantly lower birth weight ($P = 0.062$) and lower score for visual acuity when using both eyes ($P = 0.063$). There were not significant differences ($P > 0.10$) in head circumference at birth; sex distribution; age of testing at 4.5-year follow-up; full-scale, performance, or verbal IQ; or visual acuity when only using the right eye. Because group differences for visual acuity varied by eye, paired-sample t tests were performed to check if there was a significant difference in left and right eye visual acuity per se, but this was not the case, either in the sample as a whole (degree of freedom = 21, t = −1.497, $P = 0.149$) or in the risk group (degree of freedom = 11, t = −0.375, $P = 0.715$) nor in the control group (degree of freedom = 9, t = −1.595, $P = 0.145$). Analyses on birth parameters were rerun excluding the pair of twins in the risk group. The significant ($P < 0.05$) differences in gestational age remained, as did the trend ($P < 0.10$) toward lower birth weight in the risk group ($P = 0.076$).

Neuroanatomical volumes, including estimated intracranial volume, putamen, pallidum, caudate, hippocampus, amygdala, accumbens area, thalamus, cerebellar cortex, and cerebellar white matter of the two groups are shown in Table 2. Univariate analyses of variance controlling for the effects of sex and age showed no effect of group on either volume.

General linear models with cortical thickness, area, and volume, respectively, as dependent variables, with sex and group as fixed factors, and age as a continuous covariate revealed no effects of group that survived corrections for multiple comparisons. For descriptive purposes, means and standard deviations for cortical parcellation volumes for the risk and comparison groups are provided in Supplementary Table 1. Analysis of variance showed no significant ($P < 0.05$) difference in volume between groups for either parcellation volume. A trend ($P < 0.10$) was observed for smaller temporal pole volume in the risk group, but given the high number of parcellations, this trend would not survive corrections for multiple comparisons.

Discussion

We did in general not find significant cognitive or neuroanatomical differences between a group of children born to mothers with opioid and polysubstance abuse problems who were detoxified during pregnancy and a comparison group. These findings appear in contrast to the previously reported differences for a group of children who were exposed to opioid and polysubstance abuse throughout pregnancy,[13] although a direct quantitative comparison is hampered by sample differences, such as age of study. The previously studied group had greater prenatal exposure and generally less optimized prenatal conditions, but was raised in optimized environments. The children were taken into foster care at an early age and later adopted by those same parents, whose socioeconomic status was similar to that of the comparison group.[13] The presently studied group had less prenatal drug exposure,[19] but was for the most part raised by the biological mothers, probably

TABLE 2.
Neuroanatomical Volumes (mm^3) of the Two Groups

	Risk Group (5 F/7 M)		Comparison Group (3 F/9 M)		*P*
	Mean	SD	Mean	SD	
Intracranial volume	1,441,676	134,514	1,444,121	126,216	0.232
Putamen	11,798	1245	12,280	867	0.696
Pallidum	3810	395	3714	363	0.302
Caudate	8073	1145	7884	581	0.444
Hippocampus	7585	851	7640	935	0.478
Amygdala	2571	360	2634	241	0.769
Accumbens	1436	145	1444	220	0.969
Thalamus	13,544	1265	13,646	1164	0.726
Cerebellar cortex	109,845	13,797	109,610	10,695	0.558
Cerebellar white	20,715	2564	21,805	2216	0.456
Corpus callosum	2332	320	2497	237	0.445

Abbreviations:
F = female
M = male
SD = standard deviation
P-values are for the effect of group in univariate analyses of variance with neuroanatomical volume as dependent variable, group as fixed factor, and age and sex as covariates.

in a less optimized postnatal environment. In contrast to our previous study,[13] the mothers in the risk group in this study had significantly lower education, for instance. That their children did not show differences in general cognitive function and neuroanatomical volumes relative to a nonrisk comparison group, then, may indicate that maternal detoxification in a residential setting is a promising way of facilitating positive neurodevelopmental outcome of these children.

The reduced opioid and polysubstance exposure may have a positive effect on neuroanatomical volumes and cognitive scores. As cell culture and animal studies have shown, opioids may have negative, including apoptotic, effects[9-11] on fetal brain development, and with lessened exposure, it is possible that these effects can be negligible rather than pronounced. Furthermore, unlike in our previously studied cohort,[13] none of the present children was born with or treated for NAS, the absence of which may also influence their relative development positively.

However, several uncertainties and limitations remain. First, there is a possibility that the measures we utilized do not capture important differences across groups (e.g., in specific aspects of attention, executive function, and speed processing not measured). For instance, later developing functions,[35] including executive functions, may be affected,[36] and the present study does not address these or other specific cognitive abilities. This is also true for other neuroanatomical characteristics, and differences may potentially exist in, for example, white matter microstructure[14,37] or other aspects of brain anatomy and function. The present study is inadequately powered to rule out subtle differences across groups, and the cognitive scores and neuroanatomical volumes in part show tendencies to be lower in the risk group, albeit for the most part far from statistically significant with these small numbers. However, our previous study[13] was not very differently powered (14 + 14 compared with 12 + 12) and showed differences across a number of similar structures as well as in regional cortical thickness and cognitive function. If such major differences were present in the current sample, they would likely have been evident even with the relatively small sample, hence it is deemed likely that at least the group difference is lower. This could be due in part to a less well-functioning comparison group. Their cognitive scores are about average for the population norms, but often those who volunteer for research participation show above-average functioning relative to the general population.[38-40] The extent to which the previously studied comparison group was higher functioning than the present group is, unfortunately, uncertain because the tests used in that study had outdated population norms.[13] The educational level of the mothers in the present comparison group, however, was above average, and there is no reason to believe that their children were a poorly functioning group overall.

Given lesser differences relative to a comparison group, several factors could influence this result, in addition to the reduced drug exposure alone. With residential treatment, maternal nutrition and health care are optimized. This may in turn affect the developing fetus positively. The birth weight of the present risk group was, albeit lower than that of the comparison group, well within the normal range, as was gestational age at birth. Birth weight is in and of itself a significant predictor of later brain development, including gross brain volume, basal ganglia volumes, and cortical surface area.[41,42] There is reason to believe that the greater birth weight in the present risk group relative to the previous may have an effect on increasing later neuroanatomical volumes.

One difference was found across the presently compared groups: risk group children showed poorer performance on a vision screening test. The results of the vision screening, though, indicated more problems and below normal range performance in the drug-exposed group. For left eye visual acuity, this group difference reached significance, with poorer results in the risk group. For right eye visual acuity, the difference was not significant, and for visual acuity when using both eyes, there was a trend toward group difference. It is a limitation of the present study that these results varied, albeit not significantly, across eyes; there was also notable variance within the comparison group. We unfortunately do not have an overview of the factors causing this variance. However, the lower visual acuity in part observed in the risk group gives reason for concern because vision problems have repeatedly been shown in opioid-exposed children.[43,44] Animal

studies have shown detrimental effects of prenatal methadone on neurotransmitters and mu-receptor affinity[45,46] that may have adverse effects on vision. In a recent report, summed raw scores for picture completion and vocabulary did not deviate across a group of OMT- and nicotine-exposed 4 year olds relative to a comparison group.[47] It is unknown however whether general cognitive function as measured here would deviate in that sample, and comparison of scores is not possible because picture completion is not included in the present study. That study reported deviance in smooth pursuit by eye tracking. The present result as well as those of others for sight suggests that visual problems of opioid- and polysubstance-exposed children may be found also at a more basic level, that of visual acuity. Visual acuity problems may go unnoticed in small children and potentially also affect cognitive development and performance. We find it likely that the differences in visual acuity can in part be due to early drug exposure, and health personnel should be alert to potential visual problems in children exposed to opioids and other substances in utero, also in cases where exposure is reduced by detoxification and NAS is avoided.

The cognitive and neurodevelopmental characteristics of these children need to be followed further as more complex neurocognitive functions develop and can be reliably tested only later.[36] The increasing rates of maternal opioid use indicate that reducing the public health burden of maternal opioid use in pregnancy, NAS and associated factors should be of high priority.[16] In addition to Patrick et al.'s[16] concerns about treatment costs associated with NAS, it is important to recognize that costs may extend well beyond longer stays in hospital and special care units.[48] Although OMT has been the preferred treatment for opioid dependence during pregnancy since the early 1970s, this study indicates that maternal detoxification in a residential setting may also be a viable option to enhance the outcomes of children. Although a likely contributing factor to the success of detoxification here was the long-term individualized treatment in a residential setting through the remainder of pregnancy and birth, this also constitutes a limitation of the present research in that we cannot provide a detailed common detoxification protocol. The present study lacks power to support strong conclusions, and the need for further research to examine the short- and long-term developmental consequences of opioid and polysubstance abuse, OMT, and maternal detoxification is critical.

Conclusion

In sum, these children born to mothers with opioid and polysubstance abuse problems who were detoxified in a residential setting during pregnancy exhibited normal cognitive functioning and not significantly different neuroanatomical characteristics relative to a comparison group at 4.5 years. However, the study indicates also that this group of children may exhibit visual acuity problems. It is important that health personnel are alert to this, and that children are followed for a prolonged period to also detect possible problems in later neurocognitive development. Although this study of children with a lesser degree of prenatal drug exposure, in contrast to our previous study of children exposed to drugs throughout pregnancy,[13] did not reveal general differences relative to a comparison group, this should not be taken as an indication that a smaller degree of drug exposure may not affect brain and cognitive development. There may still be effects on other and more specific measures not studied here. Furthermore, there is substantial heterogeneity in risk groups, which can unfortunately not be well-investigated in a small sample such as the current.

We are grateful to all participating families and children. We thank Bibbi Juell and Unni Rosenkilde for assistance with recruitment of the participating families.
Funding source: This work was funded by grants from the Norwegian Research Council (including project numbers 190411 and 213762) to KBW and AMF; financial support was also given to the study by the Regional Center for Child and Adolescent Mental Health and the University of Oslo.
Financial disclosure: The authors have no financial relationships relevant to this article to disclose.
Conflict of Interest: The authors have no conflicts of interest to disclose.

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Appendix: Participants and methods

A flow chart depicting the overall study and participant exclusion/inclusion is given in Supplementary Figure 1.

Additional information on MRI analyses

The pulse sequence used for morphometric analysis was a three-dimensional T1-weighted Magnetization Prepared Rapid Gradient Echo (Grappa2) with the following parameters: repetition time/echo time/time to inversion/flip angle = 2400 ms/3.61 ms/1000 ms/8°, matrix 192 × 192, field of view = 240. Each volume consisted of 160 sagittal slices with a voxel size of 1.25 × 1.25 × 1.20 mm. Scan time was 4 minutes, 18 seconds. One to four Magnetization Prepared Rapid Gradient Echo series were acquired and reviewed for quality; the best was chosen for analysis. Only scans deemed free of gross movement artifacts were included (see Supplementary Figure 1 for exclusions based on unusable MRIs).

The image volumes were automatically corrected for spatial distortion because of gradient nonlinearity[1] and B_1 field inhomogeneity,[2] and resampled to isotropic 1-mm voxels and processed with the FreeSurfer software package (version 5.3; http://surfer.nmr.mgh.harvard.edu/). This processing includes removal of non-brain tissue, automated Talairach transformation, intensity correction, volumetric segmentation,[3] and cortical surface reconstruction[4-6] and parcellation.[7,8] All volumes were inspected for accuracy. Because no gross errors were found, we did not perform any manual edits, to avoid possible processor bias in this small group analysis. For subcortical volumes, briefly, the volume segmentation procedure automatically assigns a neuroanatomical label to each voxel in an MRI volume based on probabilistic information automatically estimated from a manually labeled training set.[9,10] In addition, estimated intracranial volume[11] was computed. The cortical reconstruction yields measures of cortical thickness, area, and volume throughout the cortical mantle. Maps were resampled, mapped to a common surface, smoothed using a circularly symmetric Gaussian kernel with a full-width half-maximum of 15 mm[12] and submitted to statistical analyses.

Additional information on testing of visual acuity

The Lea Symbols test of visual acuity consists of four shapes presumed familiar to children—a circle, a house, an apple, and a square. The chart is graded in decadic logarithmic steps and each of its 10 lines contains five symbols, except for the first, which contains four. In each line, the distance between the symbols is equal to their width, whereas the distance between one line and the next is equal to the height of the symbols in the lower row. The symbols are presented from the top row downward, and the child is encouraged to name all as they are pointed out.[13] Visual acuity was tested at the prescribed distance of 3 m, and first assessed in a monocular fashion via occlusion by patching the nontested eye. If a mistake was made, the child was asked to name the symbols in the line above the last line in which the error was made. If three of four symbols were correctly named, the child was asked to continue with the following lines. The test was stopped at the line in which no more than two symbols were identified. The test was repeated with the other eye occluded, and then finally with both eyes open. The visual acuity score for each eye, as well as for binocular vision, was defined as the last row in which at least three symbols were correctly identified.

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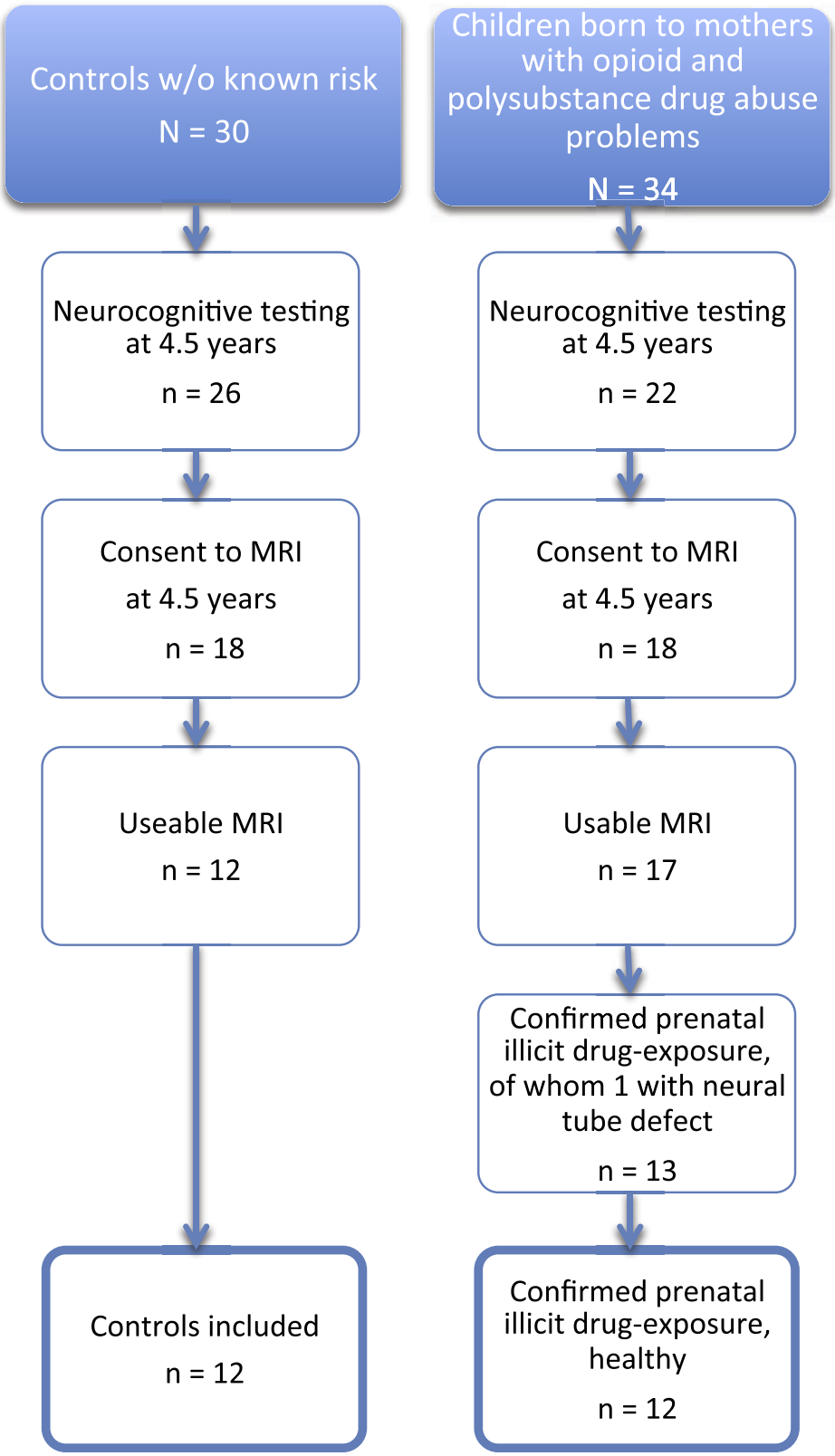
SUPPLEMENTARY TABLE 1.
Means and Standard Deviations for Volumes of Different Cortical Parcellations Averaged Across Hemispheres

Cortical Parcellation Volume	Risk Group (n = 12)		Comparison Group (n = 12)	
	Mean	SD	Mean	SD
Banks of the superior temporal sulcus	2939	430	2981	550
Caudal anterior cingulate	2288	528	2386	407
Caudal middle frontal	7506	1205	7639	1376
Cuneus	3751	655	3783	703
Entorhinal	1809	491	1806	497
Frontal pole	1583	210	1622	164
Fusiform	12,133	1952	12,112	2346
Inferior parietal	17,575	2391	17,806	1548
Inferior temporal	12,875	2424	12,443	1537
Isthmus cingulate	3254	476	3314	491
Lateral occipital	14,684	2501	14,354	1974
Lateral orbitofrontal	8929	1609	8982	1021
Lingual	8208	1414	8492	1379
Medial orbitofrontal	6646	731	6819	618
Middle temporal	13,476	1856	14,024	1694
Paracentral	4350	635	4368	502
Parahippocampal	2399	429	2389	389
Pars opercularis	5646	1054	5141	799
Pars orbitalis	3191	366	3070	309
Pars triangularis	4820	763	4888	703
Pericalcarine	2320	444	2471	613
Postcentral	11,194	1859	11,929	1236
Posterior cingulate	3995	742	4006	467
Precentral	14,374	1552	14,790	2487
Precuneus	12,722	1456	12,857	1930
Rostral anterior cingulate	2923	498	2870	456
Rostral middle frontal	19,906	2282	20,881	2706
Superior frontal	27,085	2648	26,534	3425
Superior parietal	16,941	2228	16,606	2379
Superior temporal	14,097	1981	13,518	1586
Supramarginal	13,666	2182	13,860	1859
Temporal pole	2309	365	2563	256
Transverse temporal	1262	114	1191	237

Abbreviation:
SD = standard deviation
Analysis of variance did in no case show significant ($P < 0.05$) difference in volume between groups. A trend was observed for smaller temporal pole volume in the risk group ($P = 0.060$), which remained in follow-up analysis controlling for age and sex ($P = 0.065$).



SUPPLEMENTARY FIGURE 1.
The flow chart depicts the overall study with inclusion and exclusion of participants for the present article, resulting in the final number of 24 participants (12 control children and 12 children in the risk group).