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Brain development after intrauterine exposure to lithium: A magnetic resonance imaging study in school-age children

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Abstract

Objective: Lithium is often continued during pregnancy to reduce the risk of perinatal mood episodes for women with bipolar disorder. However, little is known about the effect of intrauterine lithium exposure on brain development. The aim of this study was to investigate brain structure in children after intrauterine exposure to lithium.

Methods: Participants were offspring, aged 8–14 years, of women with a diagnosis of bipolar spectrum disorder. In total, 63 children participated in the study: 30 with and 33 without intrauterine exposure to lithium. Global brain volume outcomes and white matter integrity were assessed using structural MRI and diffusion tensor imaging, respectively. Primary outcomes were total brain, cortical and subcortical gray matter, cortical white matter, lateral ventricles, cerebellum, hippocampus and amygdala volumes, cortical thickness, cortical surface area and global fractional anisotropy, and mean diffusivity. To assess how our data compared to the general population, global brain volumes were compared to data from the Generation R study ($N = 3243$).

Results: In our primary analyses, we found no statistically significant associations between intrauterine exposure to lithium and structural brain measures. There was a non-significant trend toward reduced subcortical gray matter volume. Compared to the general population, lithium-exposed children showed reduced subcortical gray and cortical white matter volumes.

Conclusion: We found no differences in brain structure between lithium-exposed and non-lithium-exposed children aged 8–14 years following correction for multiple testing. While a rare population to study, future and likely multi-site studies with larger datasets are required to validate and extend these initial findings.

KEYWORDS
bipolar disorder, brain, child, lithium, magnetic resonance imaging, pregnancy

1 | INTRODUCTION

Lithium is a first-line treatment option for individuals with bipolar disorder.[1] Since the onset of bipolar disorder is mostly in late adolescence or early adulthood,[2] the disorder typically presents in the early child-bearing years of women. Preconceptional pharmacological treatment may be continued during pregnancy to prevent perinatal bipolar episodes. Especially in the postpartum period, women with bipolar disorder have a high risk of recurrent mood episodes.[3] Lithium use during pregnancy reduces this risk, but the benefits need to be carefully weighed against the risk of potentially harmful consequences for the unborn child. Since lithium freely crosses the placenta and lithium concentrations equilibrate between maternal and fetal circulation, maternal lithium therapy results in fetal lithium exposure.[4] There is evidence for the teratogenicity of lithium during the 1st trimester.[5–7] Moreover, associations are reported between intrauterine exposure to lithium and preterm birth, large for gestational age neonates and neonatal complications.[5,6,8]

There is currently no information on the effect of intrauterine lithium exposure on the brain development of the child. Few studies have investigated neuropsychological development of children after intrauterine lithium exposure. These studies have been reassuring and show generally normal development of lithium-exposed offspring.[9–11] Van der Lugt et al. (2012) was the first to use standardized validated tests to assess neuropsychological development in 15 children that were prenatally exposed to lithium.[11] In this study, most children scored lower on the Block patterns subtest of the WISC-III-NL, compared to norm scores. No other differences were reported. Another study compared Intelligence Quotient (IQ) scores of 20 children exposed to lithium in utero and maternal mood disorder, eight children exposed to maternal mood disorder but without exposure to lithium, and 11 children with no exposure to maternal mood disorder or lithium.[9] No differences in IQ were found. In earlier work in the same cohort, we compared 56 lithium-exposed children to 43 children from mothers with a bipolar spectrum disorder but without lithium exposure[10] using validated neuropsychological tests (NEPSY-II-NL and SON-R 6–40), to assess IQ and six different neuropsychological domains (i.e., attention and executive functioning, social perception, memory and learning, sensorimotor, visuospatial processing and language). Lithium-exposed children made more mistakes on the NEPSY Auditory Attention and Visuomotor Precision subtests, but in corrected statistical models, this did not result in a significant association. Overall, we found no statistically significant association between intrauterine lithium exposure and IQ or neuropsychological functioning.

There is, however, room for concern since preclinical studies have found effects of intrauterine lithium exposure on neurodevelopment in rodents and zebrafish.[12] One of these studies reported reduced brain weight in lithium-exposed mice offspring.[13] No studies to date have explored the effect of intrauterine lithium exposure on brain structure in human offspring. Brain imaging studies in adults have consistently shown an association between lithium treatment initiated in adulthood and increased global gray matter volume.[14] Additionally, studies of adults with bipolar disorder have shown a normalizing effect of lithium use on white matter microstructure.[15,16] These findings suggest a neuroprotective or normalizing effect of lithium on brain structure in individuals with bipolar disorder. Within this backdrop, it was the aim of the current study to investigate the influence of intrauterine lithium exposure on structural brain development in children of women with bipolar disorder. The current study is exploratory since this is the first study to investigate the association between intrauterine lithium exposure and structural brain measures in children.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

The children were recruited from a cohort, designed to investigate the influence of lithium exposure during pregnancy on behavior, cognition, and brain development. Participants were recruited from three Dutch medical centers, specialized in perinatal psychiatry (Leiden University Medical Center, Erasmus Medical Center Rotterdam, OLVG Amsterdam). A structured screening of electronic medical files (obstetric and psychiatric) was performed for all women who attended one of the perinatal mental health centers, and gave birth between 2003 and 2011. The screening and inclusion process are depicted in the diagram in Appendix S1. Offspring of these women were recruited into the lithium-exposed group if the mother used lithium during pregnancy. Offspring were recruited into the non-lithium-exposed group if the mother did not use lithium during pregnancy, but did have a comparable psychiatric diagnosis during or shortly after pregnancy (i.e., bipolar I disorder, bipolar II disorder and mania/affective psychosis limited to the postpartum period). Children between the ages of 8 and 14 years were eligible for participation in this study. Children were excluded from study participation if they were exposed to antiepileptic drugs during pregnancy and if they had dental braces. Data collection took place at Erasmus Medical Center in Rotterdam during one research visit between February 2017 and April 2020. Written and verbal information concerning the study was provided to all participating children (from the age of 12 years) and their parents or caretakers, before inclusion. Written informed consent was obtained from both parents, and assent when applicable (> = 12 years), prior to participation in the study. During the research visit, children underwent a structural brain magnetic resonance imaging (MRI) scan including T_1-weighted and diffusion tensor imaging (DTI) sequences. The study was approved by the Institutional Review Board of the Erasmus University Medical Center (MEC-2016-288).

2.2 | Maternal lithium exposure and psychiatric history

Information on lithium exposure during pregnancy, including information on dose, duration of use, and lithium blood level, was

extracted from the mother's medical file. Maternal lithium use was cross-checked at inclusion into the study in a questionnaire filled out by the mother. Information on other medication use during pregnancy and maternal medical and psychiatric history were also extracted from the mother's medical file. The mother's psychiatric diagnosis during pregnancy was extracted from her medical file using the psychiatrist's clinical diagnosis according to the DSM-IV classification. At inclusion into the study, the mother's current psychiatric diagnosis, current psychiatric treatment, and the number of lifetime mood episodes were assessed by questionnaire.

2.3 | Offspring characteristics

Information on the demographics and health of the child, the family situation, and socioeconomic status was collected by questionnaire at inclusion into the study. Information on medical problems, including psychiatric diagnoses, were also collected by questionnaire. Additionally, specific for the MRI investigation, handedness was determined using the Edinburgh Handedness Inventory.[17] Intelligence Quotient (IQ) of the child was estimated using the Snijders-Oomen Nonverbal Intelligence Test, Revision (SON-R 6–40).[18] Information on gestational age at birth and birth weight was obtained from the mother's obstetric file.

2.4 | Magnetic resonance imaging

All children underwent an initial mock scanning session to become familiarized with the magnetic resonance environment.[19] MRI data were acquired on a 3 Tesla GE Discovery MR750w system using an eight-channel receive-only head coil (General Electric, Milwaukee, WI). Cushions were placed inside the head coil to support the participant's head and to reduce head motion. Participants had the option to watch a movie or listen to music during MRI scanning. All participating children wore an MRI-compatible headphone during scanning in order to reduce the scanner noise and to allow for communication with the MR operator. High resolution T_1-weighted images were acquired using a 3D coronal inversion recovery fast spoiled gradient recalled (IR-FSPGR, BRAVO) sequence with the following parameters: repetition time (TR) = 8.77 ms, echo time (TE) = 3.4 ms, inversion time = 600 ms, flip angle = 10°, field of view = 220 × 220 mm, matrix = 220 × 220, ARC imaging acceleration factor of 2, slice thickness = 1.0 mm, number of slices = 230, and an in-plane resolution of 1.0 mm^2. Diffusion weighted images were acquired using an axial spin echo, echo planar imaging sequence with the following parameters: TR = 12,500 ms, TE = 72.8 ms, flip angle = 90°, field of view = 240 × 240 mm, matrix = 120 × 120, slice thickness = 2.0 mm, number of slices = 65, ASSET acceleration factor = 2. A total of 3 volumes without diffusion weighting (b = 0 s/mm^2) and 35 volumes with diffusion weighting (b = 900 s/mm^2).

2.5 | Image processing

FreeSurfer image suite version 6.0 was used to perform automated cortical reconstruction and volumetric segmentation (http://surfer.nmr.mgh.harvard.edu/).[20] The steps in this automated reconstruction and segmentation included: removal of non-brain tissue (e.g., skull strip), voxel intensity normalization, initial tissue segmentation, cortical reconstruction, and automated anatomical labeling. The DTI data were processed in an automated manner with the FMRIB Software Library (FSL).[21] The brain was extracted from non-brain tissue using 'bet' and images were corrected for motion and eddy-current artifacts using 'eddy.' The resulting transformation matrices were used to rotate the gradient direction table to account for rotations applied to the data. After DTI data processing, the diffusion tensor was fitted at each voxel with FSL (DTI FIT package) (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT/UserGuide#DTIFIT). Voxel-wise scalar maps of fractional anisotropy (FA) and mean diffusivity (MD) were computed. FA is a scalar value between 0 and 1 that indicates the degree of directionality of water diffusion. MD is the rate of diffusion of water (hydrogen) averaged in all directions. To compare FA and MD images from multiple subjects, 'Tract-Based Spatial Statistics (TBSS)' by FSL was used (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/TBSS/UserGuide). The first three steps of TBSS were followed: (1) FA data were prepared into the right format, (2) nonlinear registration: every FA image was aligned to every other FA image within our study to create a study specific registration, (3) nonlinear transforms are brought into standard space (MNI152). TBSS was also applied to MD images. Diffusion weighted metrics were calculated by applying the FMRIB58_FA_1mm atlas with a threshold of FA > 0.3 as a mask to calculate mean FA and MD for each individual scan.

Quality of the T_1-weighted and DTI images was visually inspected in a systematic manner. T_1 quality after FreeSurfer processing was manually rated using a 4-item rating scale (clarity of folia in the cerebellum, presence of axial waves, blurring of the gray matter/white matter interface, subcortical blurring).[22] Each of the four items received a rating from 0 to 3, resulting in a maximum rating of 12 (0 = excellent, 12 = poor). A rating of 6 or lower was considered usable data, a rating between 6 and 9 was rated as questionable, and ratings >9 meant exclusion. In datasets with questionable quality ($N = 5$), control points were applied manually and FreeSurfer was re-run (FsTutorial/ControlPointsV6.0—Free Surfer Wiki (harvard.edu)) and quality was rated again afterwards (in 2 datasets quality was improved). Datasets in which quality improvement was questionable were double checked by a second researcher. One T_1 dataset of a non-exposed child was excluded due to unusable quality, and eight DTI datasets (6 lithium-exposed and two non-exposed) were excluded. This left 63 (30 lithium-exposed and 33 non-exposed) of T_1-weighted datasets with usable image quality (98%) and 56 (24 lithium-exposed and 32 non-exposed) of the DTI datasets with usable image quality (89%). Three T_1 scans were rated as questionable quality (two lithium-exposed and one non-exposed). All scans were examined by a clinical radiologist for incidental findings.

2.6 | Brain morphology outcome measures

We were interested in the association between prenatal lithium exposure and brain structure. As per study protocol, our outcomes were brain volume measures: total brain volume, cortical and subcortical gray matter, cortical white matter, lateral ventricles, cerebellum, hippocampus and the amygdala, and global cortical thickness, total cortical surface area, and global FA and MD. Since we had no specific hypotheses based on laterality of brain measures, the anatomical subregions from left and right hemispheres were combined.

2.7 | Statistical analyses

All analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 24, IBM). Demographic and clinical characteristics are reported in a descriptive manner in accordance with the STROBE guidelines.[23] No *p*-values are reported with the demographic and clinical characteristics as we deem this more fitting for hypotheses testing. In our primary analyses, separate linear regression models were defined with prenatal lithium exposure as a dichotomous independent variable and structural brain outcomes as dependent variables. Assumptions for linear regression were checked. Analyses were adjusted for age, sex, and intracranial volume (ICV). The models evaluating total brain volume, global cortical thickness, total cortical surface area, global FA and MD as dependent variables were not corrected for ICV. In previous papers, the use of lithium during pregnancy was associated with a higher rate of preterm birth and lower gestational age at birth.[5,8] A potential effect of intrauterine exposure to lithium on brain structure may, therefore, be mediated by preterm birth (i.e., preterm birth may be on the causal pathway). Hence, we decided to explore the role of preterm birth as a potential mediator in the association between intrauterine lithium exposure and brain morphology outcomes. Notably, maternal mood episodes during pregnancy also may influence brain development of the child. We performed sensitivity analyses excluding the children of whom the mother experienced an episode during pregnancy, in order to assess whether our results were driven by the episode during pregnancy. The unstandardized and standardized regression coefficients with their corresponding 95% confidence intervals (CI) and p-values are reported. Since we performed primary analyses on 12 structural brain outcomes, the chance of a Type-I error was increased. To control for Type-I errors, we applied a false discovery rate (FDR) correction. Notably, because of the small sample size, the risk of a Type-II error was increased after FDR correction. Since the aim of the study was to explore potential adverse effects of intrauterine lithium exposure on brain structure, we chose to present both the *p*-values before and after FDR correction. FDR corrected *p*-values <0.05 were considered statistically significant. In sensitivity analyses, we repeated the analyses described above after excluding the three T1 scans with questionable image quality.

2.8 | Exploratory analyses

Subcortical structures other than the amygdala and hippocampus were not initially included as outcome measures in our protocol. In exploratory analyses, associations between intrauterine lithium exposure and volumes of the thalamus, putamen, globus pallidus and caudate nucleus were examined for future hypothesis testing. Associations were tested using the same statistical approach as described above, including corrections for multiple testing for the four test performed within the exploratory analyses. Additionally, differences in volume of the subcortical structures (hippocampus, amygdala, thalamus, putamen, globus pallidus and caudate nucleus) between the left and right hemispheres were explored.

2.9 | Comparison to the general population

Since we compared lithium-exposed and non-lithium-exposed offspring of mothers with bipolar spectrum disorders, we did not know how our study data would compare to that of the general population. In order to make this comparison, we used summary data from the Generation R study, a prospective population-based study conducted in Rotterdam with delivery dates from 2002 until 2006.[24] Brain MRI data of the Generation R study were collected between March 2013 and November 2015 on the same scanner (3 Tesla GE Discovery MR750w system) as the current study. Image acquisition and analyses of volumetric brain outcomes within the Generation R study were performed in the same way as in the current study.[22] Quality assessment of Generation R MRI data was performed both visually and automatically.[25] Only data of scans with usable image quality were included. A comparison of lithium-exposed and non-lithium-exposed children with data from the Generation R study was performed using separate linear regression analyses with cortical gray matter, subcortical gray matter, and cortical white matter as dependent variables. Dummy variables were created for the independent variable (lithium exposure and bipolar offspring without lithium exposure) using the Generation R population as the reference group. These analyses were adjusted for age, sex and intracranial volume and multiple testing by FDR correction (for the six tests performed to compare to the general population). While we performed multiple testing correction, given the importance of the question and the potential ramifications of a false negative finding, we present both *p*-values before and after FDR correction.

3 | RESULTS

In total, 63 children with usable structural imaging data participated in this study. Within this cohort, there were 13 sibling pairs (of which 3 twin pairs). Of these, six pairs were lithium-exposed (of which 3 twin pairs), four pairs were non-lithium-exposed, and three sibling pairs consisted of one lithium-exposed and one non-lithium-exposed

child. Table 1 shows the demographic characteristics of the lithium-exposed, non-lithium-exposed, and Generation R groups. Table 2 shows the clinical characteristics of the lithium-exposed and non-lithium-exposed groups.

TABLE 1 Demographic characteristics of the study sample

	Lithium-exposed	Non-lithium-exposed	Generation R
N	30	33	3243
Age at MRI in years, mean (*SD*)	10.0 (2.1)	11.1 (2.3)	10.1 (0.6)
Sex, % female	42.4	63.3	50.2
Country of birth both parents Netherlands, %	80.0	84.8	64.1
ICV (cm^3)	1478	1533	1511

Abbreviation: ICV, intracranial volume.

TABLE 2 Clinical characteristics of the study sample

	Lithium-exposed	Non-lithium-exposed
N	30	33
Child characteristics		
Psychiatric disorder, *N* (%)[a]	5 (16.7)	4 (12.1)
Use of psychotropic medication, *N* (%)[b]	2 (6.7)	1 (3.0)
Neurological disorder, *N* (%)[c]	3 (9.1)	1 (3.0)
Birth weight in grams, mean (*SD*)	3131 (792)	3614 (424)
Gestational age at birth in weeks, mean (*SD*)	37.1 (3.9)	40.0 (1.7)
Premature birth (<37 wk), *N* (%)	9 (31.0)	1 (3.2)
IQ, mean (*SD*)	101.0 (12.4)	100.0 (12.0)
Right handedness, *N* (%)	29 (96.7)	28 (84.8)
Pregnancy characteristics		
Average maternal daily lithium dosage in mg, mean (*SD*)	922 (246)	
Period of lithium use, *N* (%)		
1st trimester only	1 (3.4)	
1st + 2nd trimester	1 (3.4)	
2nd + 3rd trimester	2 (6.9)	
Whole pregnancy	25 (86.2)	
Lithium level weighted average (mmol/l), mean (*SD*)		
Whole pregnancy	0.54 (0.13)	
1st trimester	0.52 (0.12)	
2nd trimester	0.54 (0.18)	
3rd trimester	0.54 (0.15)	
Use of any other psychiatric medication, *N* (%)[d]	8 (26.7)	5 (15.2)
Smoking, *N* (%)	3 (10.0)	4 (12.1)
Use of alcohol, *N* (%)	0 (0.0)	4 (12.1)
Use of recreational drugs, *N* (%)[e]	1 (3.3)	0 (0.0)
Folate use, *N* (%)	25 (89.3)	28 (84.8)
Maternal characteristics		
Main diagnosis, *N* (%)		
Bipolar I disorder	25 (83.3)	18 (54.5)
Bipolar II disorder	5 (16.7)	0 (0.0)
Postpartum mania/affective psychosis[c]	0 (0.0)	14 (42.4)
Major depressive disorder (MDD)	0 (0.0)	1 (3.0)
Number of lifetime episodes, median (IQR)	4.5 (4)	2.0 (4)
Episode during pregnancy, *N* (%)	7 (28.0)	2 (6.3)
Mean age of onset mood disorder, mean (*SD*)	22.9 (5.5)	30.2 (4.6)
Household income in euro's per month, *N* (%)		
< 2400	11 (37.9)	7 (23.3)
> 2400	18 (62.1)	23 (76.7)
Higher education, *N* (%)	14 (46.7)	21 (63.6)
Paternal characteristics		
Lifetime psychiatric disorder, *N* (%)	9 (30.0)	8 (24.2)
Higher education, *N* (%)	18 (60.0)	22 (68.8)

Note: In case of missingness valid percentages and means are presented.

[a]Lithium-exposed: ADD/ADHD ($n = 2$), Autism spectrum disorder ($n = 2$), Gilles de la Tourette ($n = 1$), Non-lithium-exposed: ADD/ADHD ($n = 4$).

[b]Lithium-exposed: methylphenidate ($n = 1$), lamotrigine and levetiracetam for epilepsy ($n = 1$), Non-lithium-exposed: methylphenidate and aripiprazole ($n = 1$).

[c]Lithium-exposed: epilepsy ($n = 1$), one time epileptic insult ($n = 1$), low muscle tension and hypermobility ($n = 1$), Non-lithium-exposed: brain damage after fall from window at 4 weeks of age ($n = 1$).

[d]Lithium-exposed: antipsychotic medication and TCA ($n = 1$), TCA ($n = 2$), SSRI ($n = 1$), antipsychotic medication and benzodiazepine ($n = 1$), mirtazapine ($n = 2$), venlafaxine and antipsychotic medication ($n = 1$), Non-lithium-exposed: antipsychotic medication, SSRI and benzodiazepine (n = 2), SSRI and benzodiazepine ($n = 1$), antipsychotic medication and benzodiazepine ($n = 1$), benzodiazepine ($n = 1$).

[e]Lithium-exposed: one mother used cannabis during pregnancy.

3.1 | Lithium use

Different formulations of lithium were used during pregnancy. In 12 pregnancies, mothers used lithium carbonate (Camcolit® $n = 7$, Priadel® $n = 3$, lithium carbonate [other brands] $n = 2$). Lithium citrate, also known as Litarex®, was used in 14 pregnancies. In four pregnancies, the lithium formulation was unknown. Lithium citrate dosages (Litarex 564 mg = 6 mmol lithium) were multiplied by 0.395

to calculate lithium carbonate dosage equivalents (400 mg = 8 mmol lithium), in order to compare between individuals in the lithium-exposed group (mean: 922 mg/day, *SD*: 246).

3.2 | Magnetic resonance imaging

No serious clinically relevant abnormalities were reported by the clinical radiologist. In Table 3, the means and standard deviations of the brain MRI outcomes and results of the multivariate linear regression analyses are provided. Linear regression analyses showed a non-significant negative association of intrauterine exposure to lithium with subcortical gray matter volume (unstandardized β = −1.6, 95% CI: −3.1, −0.1, *p*-value = 0.04, *p*-value after FDR correction = 0.48). In sensitivity analyses removing the three T_1-weighted datasets with questionable quality, the association between prenatal lithium exposure and subcortical gray matter volume was not significant (unstandardized β = −1.3, 95% CI: −2.9, 2.9, p-value = 0.11). In sensitivity analyses, removing the datasets of children of whom the mother experienced an episode during pregnancy, the results did not change, that is, there was a statistically significant association between lithium use during pregnancy and subcortical volume (unstandardized β = −2.4, 95% CI: −4.0, −0.7, standardized β = −0.22, *p*-value = 0.005) but not with any of the other brain outcomes. The initial association between intrauterine exposure to lithium and subcortical gray matter volume was not mediated by preterm birth, since in our dataset, preterm birth was not associated with subcortical gray matter volume (unstandardized β = −0.7, 95% CI: −4.6, 3.1, p-value = 0.71). No associations were observed with the other brain structures examined. Also, no associations were found with global FA or MD.

3.3 | Exploratory analyses

In post-hoc analyses, a non-significant association between intrauterine lithium exposure and putamen volume (unstandardized β = −0.7, 95% CI: −1.3, −0.1, *p*-value = 0.02, *p*-value after FDR correction = 0.08) was found. There were no associations between intrauterine lithium exposure and thalamus (unstandardized β = −0.2, 95% CI: −0.6, 0.2, *p*-value = 0.34, *p*-value after FDR correction = 0.45), globus pallidus (unstandardized β = −0.08, 95% CI: −0.3, 0.1, *p*-value = 0.45, *p*-value after FDR correction = 0.45), and caudate nucleus volumes (unstandardized β = −0.4, 95% CI: −0.8, 0.04, *p*-value = 0.08, *p*-value after FDR correction = 0.16). Explorative analyses assessing left and right subcortical structures individually showed similar results to the combined measures. Lithium use during pregnancy was associated with both left (unstandardized β = −0.34, 95% CI: −0.67, −0.02, *p*-value = 0.04, p-value after FDR correction = 0.24) and right (unstandardized β = −0.37, 95% CI: −0.66, −0.08, *p*-value = 0.01, p-value after FDR correction = 0.12) putamen volume prior to FDR correction, but not after FDR correction and no association was found with any of the other subcortical structures. The results of these analyses are displayed in the table in Appendix S2.

TABLE 3 Outcomes of the MRI analyses in lithium-exposed and non-lithium-exposed offspring

	Lithium-exposed	Non-lithium-exposed	Regression coefficient[a]			
	Mean (*SD*)	Mean (*SD*)	Unstandardized β (95% CI)	Standardized β	*p*-value	*p*-value after FRD correction
Total Brain (cm^3)	1178.9 (102.6)	1232.7 (107.0)	−25.7 (−76.6, 25.1)	−0.12	0.32	0.77
Cortical GM (cm^3)	575.8 (51.1)	598.1 (55.7)	−14.6 (−32.1, 2.9)	−0.14	0.10	0.40
Subcortical GM (cm^3)	58.1 (5.7)	61.3 (4.4)	−1.6 (−3.1, −0.1)	−0.15	0.04	0.48
Cortical WM (cm^3)	400.0 (46.6)	426.8 (49.7)	−7.1 (−20.1, 6.0)	−0.07	0.28	0.84
Lateral Ventricles (cm^3)	13.3 (6.2)	12.4 (4.4)	1.1 (−1.7, 3.9)	0.10	0.45	0.77
Cerebellum (cm^3)	145.5 (13.7)	147.2 (11.4)	1.5 (−3.9, 6.9)	0.06	0.58	0.87
Hippocampus (cm^3)	7.9 (0.8)	8.2 (0.8)	−0.02 (−0.29, 0.26)	−0.01	0.89	0.89
Amygdala (cm^3)	3.3 (0.3)	3.5 (0.3)	−0.02 (−0.16, 0.12)	−0.03	0.79	0.86
Total cortical surface area (cm^2)	1810.7 (159.1)	1882.7 (176.2)	−2.0 (−9.7, 5.8)	−0.06	0.61	0.81
Global cortical thickness (mm)	2.7 (0.1)	2.7 (0.1)	−0.04 (−0.09, 0.01)	−0.21	0.08	0.48
Global FA	0.393 (0.011)	0.396 (0.015)	−0.001 (−0.008, 0.006)	−0.05	0.73	0.88
Global MD (mm^2/s)	0.00086 (0.00002)	0.00086 (0.00003)	$-5.51\,e^{-6}$ (0.00, 0.00)	−0.11	0.43	0.86

Abbreviations: FA, fractional anisotropy; GM, gray matter; MD, mean diffusivity; WM, white matter.

[a]Corrected for age, sex and ICV (total brain volume, cortical thickness, cortical surface area, FA and MD are not corrected for ICV).

3.4 | Comparison to the general population

The results of the regression analyses for comparison of lithium-exposed and non-lithium-exposed children to the Generation R population are presented in Table 4. Subcortical gray matter volume and cortical white matter volume were significantly reduced in lithium-exposed children compared to children from the Generation R cohort (unstandardized β = −1.4, 95% CI: −2.4, −0.5, *p*-value = 0.004, *p*-value after FDR correction = 0.008 and unstandardized β = −14.3, 95% CI: −22.3, −6.2, *p*-value <0.001, *p*-value after FDR correction = 0.006 respectively). These associations remained significant after removing the three datasets with questionable quality (unstandardized β = −1.3, 95% CI: −2.3, −0.3, *p*-value = 0.01 and unstandardized β = −15.6, 95% CI: −24.0, −7.3, *p*-value <0.001, respectively). Cortical gray matter volume did not differ between lithium-exposed children and the Generation R cohort. Cortical gray matter volume was significantly increased in non-lithium-exposed offspring compared to the Generation R cohort (unstandardized β = 15.4, 95% CI: 6.5, 24.2, *p*-value <0.001, *p*-value after FDR correction = 0.003), while cortical white matter volume was reduced (unstandardized β = −8.4, 95% CI: −16.2, −0.7, *p*-value = 0.03, *p*-value after FDR correction = 0.045), and subcortical gray matter volume showed no difference.

4 | DISCUSSION

This is the first cohort study that investigated the influence of intrauterine lithium exposure on brain structure in children. In our primary analyses, no statistically significant associations were found between intrauterine lithium exposure and structural brain outcome or global white matter integrity after FDR correction for multiple testing. Interestingly, without FDR correcting, there was an initial association between lithium exposure and reduced subcortical gray matter volume. Notably, when excluding three cases with questionable T_1-weighted imaging data, a negative association remained but the effect was smaller and non-significant. This could be due to a power problem or the influence of image quality on these results. The latter explanation seems less likely as the exclusion of the three scans with questionable imaging quality did not influence the results in comparison with the general population and these cases were no outliers for subcortical volume. We found no statistically significant association between lithium exposure and the amygdala or hippocampus volumes. Exploratory analyses did show non-significant reduced putamen volume in lithium-exposed children compared to non-lithium-exposed children. Since the exploratory analyses were conducted post-hoc, they should be interpreted with caution. Compared to the general population, children with intrauterine lithium exposure showed significantly reduced subcortical gray matter volume and cortical white matter volume. Interestingly, there was no difference in subcortical gray matter volume between non-lithium-exposed children from mothers with bipolar spectrum disorder and

TABLE 4 Outcomes of the linear regression analyses for comparison with the normal population

	Regression coefficient lithium-exposed vs. Generation R[a]				Regression coefficient non-lithium-exposed vs. Generation R[a]			
	Unstandardized β (95% CI)	Standardized β	*p*-value	*p*-value after FDR correction	Unstandardized β (95% CI)	Standardized β	*p*-value	*p*-value after FDR correction
Cortical GM (cm^3)	4.0 (−5.1, 13.2)	0.01	0.40	0.48	15.4 (6.5, 24.2)	0.03	<0.001	**0.003**[b]
Subcortical GM (cm^3)	−1.4 (−2.4, −0.5)	−0.03	0.004	**0.008**[b]	0.3 (−0.7, 1.2)	0.01	0.56	0.56
Cortical WM (cm^3)	−14.3 (−22.3, −6.2)	−0.03	**<0.001**	**0.006**[b]	−8.4 (−16.2, −0.7)	−0.02	0.03	**0.045**[b]

[a] Corrected for age and sex and ICV.

[b] *p*-value after FDR correction < 0.05.

the general population, suggesting a more specific effect of lithium exposure on subcortical gray matter.

In adult imaging studies, lithium use was associated with increased global brain volumes and white matter integrity. We did not find this in our study. In contrast, our results point toward a possible negative association between lithium exposure and subcortical brain volume. This may be explained by the fact that we investigated intrauterine lithium exposure in children aged 8–14 years old. The majority of these children did not have a psychiatric disorder at the time of inclusion. A meta-analysis showed that lithium use is associated with increased gray matter volume in adults with bipolar disorder, compared to non-lithium using adults with bipolar disorder, but not when compared to healthy controls, suggesting a normalizing or neuroprotective effect of lithium on the brain.[14] Also, this putative neuroprotective mechanisms, as seen in adults, cannot be directly translated to the fetal brain during prenatal development. Prenatal neurodevelopment involves a highly complex orchestrated cascade of events, in which lithium could interact. Thus, the possible negative association between prenatal exposure and subcortical brain volume may reflect the influence of lithium on fetal development through pathways that are different from that in adults. Although lithium's mechanism of action is not yet fully unraveled, research has shown that lithium has influence on glycogen synthase kinase 3β (GSK3β) and brain-derived neurotrophic factor (BDNF).[26] GSK3β has been reported to regulate gene expression, embryonic development, and neuronal survival, among other processes, through various downstream pathways.[26] BDNF plays an important role in fetal metabolic programming.[27] In a previous study on fetal development after lithium exposure, we found head circumference to be larger at 20 weeks gestational age.[8] In this study, fetal weight was also increased, for which the observed increase of head circumference likely reflects increased fetal growth and cannot be related specifically to the brain.

Notably, the influence of confounding by indication cannot be ruled out, that is, the indication for which lithium is prescribed (maternal bipolar disorder) may also have an effect on brain structure of the offspring through genetic predisposition or familial environment. However, structural MRI studies in offspring of parents with bipolar disorder show inconsistent results[28,29] and do not take maternal medication use into account. We compared lithium-exposed offspring of mothers with bipolar disorder with non-lithium-exposed offspring of mothers with a comparable psychiatric disorder, in an attempt to minimize the influence of confounding by indication. However, disease severity appears to be greater in mothers of lithium-exposed offspring, as reflected by the younger age at onset of the disease and a higher number of lifetime episodes.

4.1 | Strengths

To our knowledge, this is the first study investigating the association of intrauterine exposure to lithium and brain structure in children. Whether lithium use during pregnancy influences neurodevelopment is an important clinical question, especially since brain development continues into early adulthood and thus subtle differences could be 'unmasked' later in development. This study adds to a growing knowledge of all potential influences of intrauterine lithium exposure on the development of the child. In this study, lithium exposure was assessed with high certainty, due to the available information from the maternal medical files. This also enabled us to report detailed clinical characteristics of the children, their mothers, and the pregnancies. Quality of MRI T_1-weighted and DTI data were high considering this concerns a group of children between the ages of 8 and 14. Regarding the T_1-weighted and DTI data, 98% and 89% were of good quality, respectively. Within our data-collection procedures, we spent time and effort on preparing children for the MRI session. They all underwent a mock MRI session and we took the time to explain procedures and make the child feel as comfortable as possible. We believe this positively influenced both the quality of our MRI data and the experience of the child. We were able to compare our data to that of the general population. This is another strength of our study, especially because in our study, we used the same MRI scanner as the Generation R study and we used the same MRI sequence and processing methods.

4.2 | Limitations

MRI imaging is challenging in children, and intrauterine lithium exposure is a rare event. Despite the considerable efforts of the research team and cooperation between three healthcare centers specialized in perinatal psychiatry working in close collaboration with local obstetrical care units, our sample size is not large. Our study is likely underpowered to detect smaller differences in brain structure between lithium-exposed and non-lithium-exposed children. The non-significant finding of lower subcortical gray matter volume could thus be either confirmed or refuted with larger sample sizes. To investigate whether this trend represents true structural brain differences associated with intrauterine lithium exposure, a much larger study population is required. For example, based on our findings for gray matter volume and a required power of 80% and alpha of 0.05, a total sample size of 168 children is required. We propose either meta-analyses or large-scale data-sharing initiatives to perform mega-analyses across different research centers. This would be an approach to further investigate this question. Due to our small sample size, we were not able to correct for several potential confounding factors, including family-specific factors (our study included 13 sibling pairs), maternal disease severity and parental education or social status. Likewise, we did not correct for the potential influence of IQ, although the groups were very well matched and previous investigations did not show an association between intrauterine lithium exposure and IQ of the child.[9,10] Additionally, while our sample and the Generation R sample was collected on the same MRI scanner, the two studies did have different study designs and data were collected at different times. Even though harmonization occurred between the two studies (both in acquisition and processing), the datasets may be influenced by differences in data-collection, for

example, in the recruitment or guidance of the children. Hence, unmeasured confounding cannot be ruled out.

In summary, we found no statistically significant associations between intrauterine lithium exposure and structural brain MRI outcome measures in our primary analyses. However, our results do point toward a possible effect of intrauterine lithium exposure on subcortical brain volume. Given that this is a rare population to recruit and to study, future, likely multi-site studies with larger datasets are required to validate and extend our initial findings.

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CONFLICT OF INTEREST

The authors have nothing to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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