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The effect of prenatal lithium exposure on the neuropsychological development of the child

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Abstract

Objectives: Lithium is an effective treatment for bipolar disorder, also during pregnancy to prevent the recurrence of episodes in the perinatal period. Little is known about the neuropsychological development of lithium-exposed offspring. The current study was designed to investigate neuropsychological functioning in lithium-exposed children with the aim to provide further knowledge on the long-term effects of lithium use during pregnancy.

Methods: Participants were offspring of women with a diagnosis of bipolar spectrum disorder, aged 6–14 years. In total, 99 children participated in the study, 56 were exposed to lithium *in utero* and 43 were not exposed to lithium. Neuropsychological tests were administered, including the Snijders-Oomen Nonverbal Intelligence Test and the NEPSY-II-NL assessment. Linear and negative binomial regression models were used to investigate the association between prenatal lithium exposure and neuropsychological functioning. In secondary analyses, the association between lithium blood level during pregnancy and neuropsychological functioning was assessed. Additionally, norm scores and percentiles for task outcomes were calculated.

Results: Lithium use during pregnancy was associated with the total number of mistakes made on the Auditory Attention task, but not statistically significant after full adjustment for potential confounding factors. No association between prenatal lithium exposure and IQ was found. Also, no relationship between lithium blood level during pregnancy and neuropsychological functioning was found after adjustment for potential confounders. Task outcomes in both groups were comparable to the general population.

Conclusion: In this study, we found no evidence for significantly altered neuropsychological functioning of lithium-exposed children at the age of 6–14 years, when compared to non-lithium-exposed controls.

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KEYWORDS
bipolar disorder, cognition, fetal exposure, intelligence quotient, lithium, neuropsychological development, offspring, pregnancy

1 | INTRODUCTION

Bipolar disorder is a severe psychiatric disorder characterised by episodes of depression and (hypo)mania. Lithium is the most effective maintenance treatment and is also well established during the acute phase of the disease.[1] As the onset of bipolar disorder is often in early adulthood, lithium is frequently prescribed to women of childbearing age and may be continued during pregnancy. An important reason to continue lithium treatment during pregnancy is that it reduces the risk of a recurrent mood episode during both pregnancy and the postpartum period.[2,3] However, lithium crosses the placenta freely, resulting in fetal serum levels equalling that of the mother.[4] For well-informed balanced decision-making, more information on the potential fetal impact is needed.

Most research has focused on the teratogenicity of lithium, investigating the incidence of congenital malformations in lithium-exposed infants. Recently, two large studies have confirmed the results of previous smaller studies and reported that lithium use during pregnancy was associated with an increased risk of congenital malformations, including cardiac malformations, but this effect was smaller than previously estimated.[5,6] Some other studies have reported an increased risk of miscarriage, preterm birth, increased birth weight and neonatal admissions.[5,7–9]

Much less is known about the development of the child after birth. In a previously published systematic review and meta-analysis, we investigated long-term neurodevelopmental effects of prenatal exposure to lithium in both clinical and preclinical studies.[10] Pre-clinical studies suggested a detrimental effect of prenatal lithium exposure on motor activity, developmental milestones and reflexes, spatial memory and brain weight. Four clinical studies found normal neurodevelopment in general in lithium-exposed children. The first study compared 60 lithium-exposed children with 57 non-exposed siblings.[11] Based on the mothers' retrospective assessment of their children's developmental milestones, assessed by questionnaire, no differences were found. A second study prospectively compared developmental milestones between 22 lithium-exposed children and non-exposed children, assessed by phone interview.[12] Also no differences were found in this study. Van der Lugt et al. (2012) performed an observational cohort study, including 15 lithium-exposed children, using standardised validated tests to assess neurological, cognitive and behavioural outcomes. Outcomes were compared to norm scores from the general population; there was no matched non-exposed control group. In this study, most lithium-exposed children scored lower on the Block patterns subtests of the WISC-III-NL, compared to norm scores. No other differences were found.[13] The fourth study systematically evaluated in a small cohort whether maternal mood disorders and lithium exposure during pregnancy influenced cognition of children aged 4–5 years. They compared 20 children exposed to lithium and maternal major mood disorder, 8 children exposed to maternal mood disorder but not to lithium, and 11 children not exposed to mood disorder or lithium. No differences in intelligence quotients (IQ) were found between groups.[14] These studies are of great importance to the field. However, sample size and methodological limitations hamper the interpretation of the results.

In this largest prospective cohort study thus far, validated and systematic measurements controlled for maternal disease severity were used to investigated the effect of lithium exposure *in utero* on the neuropsychological functioning of children aged 6–14 years. The aim of the study was to provide further knowledge on the long-term effects of lithium use during pregnancy that may enable women with bipolar disorder to make more well-informed decisions regarding their treatment during pregnancy.

2 | PATIENTS AND METHODS

2.1 | Study design and participants

The current study is a clinical cohort study designed to investigate the influence of fetal lithium exposure on long-term neuropsychological development of the child. Participants were recruited from three Dutch medical centres that provide specialised healthcare for perinatal psychiatry (Erasmus Medical Center Rotterdam, Leiden University Medical Center, Onze Lieve Vrouwe Gasthuis Amsterdam). A structured screening was performed of the electronic medical files for all women who consulted one of the perinatal psychiatry centres and gave birth to a living child between 2003 and 2011. The screening and inclusion process is depicted in the diagram in Appendix 1. The offspring of these women were selected for the lithium-exposed group, if lithium was used during pregnancy. Offspring were selected for the disease-matched unexposed group if the mother did not use lithium during pregnancy but did have a diagnosis of bipolar spectrum disorder (bipolar I, bipolar II and mania/affective psychosis limited to the postpartum period). Mothers and their offspring aged 6–14 years were invited to participate during a single research visit. If the mother was unable to accompany the child, the father was invited instead. Oral and written study information was provided to all parents and their offspring (from the age of 12 years) before inclusion, and all provided signed, informed consent forms regarding participation in the study. During the research visit, two subtests from the Snijders-Oomen Nonverbal Intelligence Test, Revision (SON-R 6-40) were administered, followed by a selection of subtests from the NEPSY-II-NL. The SON-R 6-40 took about 30–45 min to administer and

the NEPSY-II-NL about 60 min. There was a break between the two tests. If indicated, an additional short break could be added in between the SON-R 6-40 Mosaics and Categories subtests. Data collection took place from February 2017 until March 2020. This 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 dose, duration of use and lithium blood level, were extracted from the mother's medical file. Information on maternal medical history, other medication use and the psychiatric diagnosis during pregnancy were also extracted from the mother's medical file. The mother's current psychiatric diagnosis and status of psychiatric treatment and the number of maternal lifetime episodes were assessed by questionnaire at inclusion in the study.

2.3 | Offspring characteristics

Information on the child's demographics, health, family situation and socioeconomic status was collected by questionnaire at inclusion in the study. Information on gestational age at birth and birth weight was extracted from the mother's obstetric file.

2.4 | Outcome assessment

2.4.1 | IQ

The Snijders-Oomen Nonverbal Intelligence Test, Revision (SON-R 6-40), is a nonverbal intelligence test for children and adults aged 2.5–40 years. The SON-R 6-40 has been validated and correlates highly ($r = 0.55–0.83$) with several other intelligence tests (WISC, WAIS, WNV and NIO) and has a high reliability with Cronbach's $\alpha = 0.95$.[15,16] The test consists of four subtests and we used two subtests: Mosaics and Categories. In the Mosaics subtest, the subject has to copy a spatial figure from an example picture, by placing red and white square tiles in a frame. The test consists of two series of 13 items. In the Categories subtest, three images are shown on the left page and five images on the right page. The subject needs to recognise the common feature of the left images and select two images from the right page that match them. The tests consists of three series of 12 items. The raw scores on the Categories and Mosaics subtests were taken together to compute an IQ-score, using the SON-R 6-40 computer program. The IQ test was performed in both the offspring and their biological parent. The offspring IQ was an outcome variable and the IQ of the parent was collected as a covariate in order to correct for the association between parental and offspring IQ.

2.4.2 | Neuropsychological assessment

Neuropsychological development of the offspring was examined using a selection of subtests from the NEPSY-II-NL assessment. The NEPSY-II-NL is an official and validated Dutch translation and adaptation of the North American NEPSY-II.[17] Acceptable to good reliability and validity have been reported for the NEPSY-II.[18] It consists of 34 subtests in six different cognitive domains: attention and executive functioning, language, memory and learning, sensorimotor, social perception and visuospatial processing. A selection of subtests can be used and gives valid subscores. To limit the time constraint on our participating children, we selected nine subtests covering all six cognitive domains. The selected subtests and corresponding outcome values were as follows: Auditory Attention and Response Set (total number mistakes, i.e. a combined measure of commission, omission and inhibition mistakes), Affect Recognition (total score), Memory for Faces (total score), Memory for Faces delayed (total score), Narrative Memory (total score for free and cued recall combined), Geometric Puzzles (total score), Inhibition (total number of mistakes and total completion time in seconds), Visuomotor Precision (total number of mistakes and total completion time in seconds) and Word Production (total number of correct words in semantic subtest). Rules of the NEPSY-II manual were closely followed.[19] It took about 60 min to administer this selection of subtests. In Appendix 2, a full description of the NEPSY subtests is provided. For the Inhibition and Visuomotor precision subtest, the number of mistakes and total time were inverse Z-transformed (using the mean of all subjects combined) and the average of both outcomes was calculated per subject. This created a 'combined mistakes and time' variable for which high scores represented high performance, that is, low number of mistakes and a low completion time.

2.5 | Covariates

Selected covariates were sex and age of the offspring, gestational age at birth, maternal smoking and alcohol use during pregnancy, maternal folic acid use, maternal use of psychotropic medications other than lithium during pregnancy, maternal education, number of maternal lifetime mood episodes, parental IQ and household income. Since gestational age at birth was included as a covariate in our analyses, birth weight and premature birth were not included to avoid collinearity.

2.6 | Statistical analyses

Descriptive statistics and statistical analyses were performed using the Statistical Package for the Social Sciences (version 24, IBM). In our primary analyses, separate multivariate regression models were used to investigate the association between prenatal lithium exposure and neuropsychological functioning. The association between prenatal lithium exposure and IQ was investigated using multivariate

linear regression models. The association between prenatal lithium exposure and NEPSY outcome was investigated using multivariate linear regression models if the outcomes followed a normal distribution (Affect Recognition, Memory for Faces, Narrative Memory, Geometric puzzles, Inhibition total time, Visuomotor precision total time) or multivariate Negative Binomial regression models if the outcome was count data and followed a Negative Binomial distribution (Auditory Attention, Response Set, Inhibition total mistakes, Visuomotor precision total mistakes, Word production). A square root transformation was used to normalise the Visuomotor precision total completion time outcome. Linear regression models were used to investigate the association between prenatal lithium exposure and the 'combined mistakes and time' outcomes.

In the first step of our analyses, we defined simple models with prenatal lithium exposure as a dichotomous independent variable. IQ and NEPSY subtest scores were used as dependent variables and age and sex were added as covariates in the NEPSY analyses for Model I. In Model II, we added the maternal number of lifetime episodes as a covariate to the model in an attempt to eliminate the influence of confounding by indication to our results. This is because a potential association between prenatal lithium exposure and neuropsychological outcome might be confounded by the disease severity of the mother. In this second step, IQ of the parent was also added to the model with IQ of the child as dependent variable. For Model III, we fully adjusted the model and added the following covariates: maternal number of lifetime episodes, gestational age at birth, household income, maternal education level (except for the IQ model since parental IQ was already included), folic acid use during pregnancy, smoking and alcohol use during pregnancy and the use of other psychotropic medication during pregnancy. In a previous paper, we found that maternal bipolar disorder and lithium use during pregnancy were associated with lower gestational age at birth, possibly partly due to a higher rate of induced labour,[7] leading to the hypothesis that gestational age at birth could be a mediating factor in the relationship between lithium exposure during pregnancy and neuropsychological development. Therefore, the role of gestational age at birth as a mediator in the association between lithium use and IQ and NEPSY scores was explored. All continuous covariates were mean centred to improve interpretation. Since there were very few missing values for the covariates (2%), the missing values were imputed with the population mean.

The unexposed group included some offspring ($n = 18$) of which the mother was diagnosed with mania or affective psychosis in the postpartum period, which might be a less severe bipolar spectrum disorder.[20] Therefore, sensitivity analyses were performed excluding these offspring from the analyses, in order to investigate whether the results of our analyses were influenced by the imbalance in maternal diagnosis between the exposed and unexposed groups. Sensitivity analyses were also performed limiting the analyses to one child (the first) per family in order to explore the influence of genetic predisposition and lifestyle factors within families.

In our primary analyses, we chose negative binominal regression models because they are conservative in handling outliers. However, all of our outcome values included in this study were true test outcomes. Hence, we performed sensitivity analyses using Poisson models to study the effect of lithium use during pregnancy on neuropsychological test outcome with a more sensitive statistical approach.

In our secondary analyses, we explored whether there was a dose–response relationship by investigating the association between lithium blood levels during pregnancy and IQ, and NEPSY subtest outcomes. For this aim, regression models as described above were repeated with the independent variable being the average weighted lithium blood level during pregnancy. The average weighted lithium blood levels were calculated as follows: (1) each registered lithium blood level was multiplied by the number of days between that measurement and the previous measurement, (2) the last known lithium level was also multiplied with the number of days between this measurement and the date of delivery, and (3) a cumulative lithium level was calculated and divided by the total number of days of pregnancy.

Additionally, in order to explore how our exposed and unexposed children compared to the general population, we calculated percentile and norm scores for all outcomes using the SON-R 6-40 computer program for IQ[15] and the psychometric norms provided in the NEPSY-II manual.[18] For NEPSY-II percentiles, calculations were not exact but calculated into categories. Therefore, we report the percentage of children with a percentile of 50 or lower, which in the general population would be approximately 50%. For normally distributed data NEPSY-II provided norm scores instead of percentiles, a norm score of 10 (SD = 3) is considered average.

Since we performed analyses on 15 neuropsychological outcomes, the chance of a Type-I error was increased. To control for Type-I error, we applied a false discovery rate (FDR) correction.[21] 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 investigate the potential adverse effect of prenatal lithium exposure on neurodevelopment, we would rather be on the safe side and not dismiss any potential effect. Therefore, the models original p-values are presented and test outcomes were considered statistically significant if the original p-value was <0.05. Additionally, test outcomes that remained significant after FDR correction were marked.

3 | RESULTS

3.1 | Descriptive characteristics

Table 1 shows the child, maternal and paternal characteristics of all subjects that participated in this study.

A total of 99 children from 67 different families participated in the study. The number of participating children per family varied from one to three children (the latter being the case for two families). Three twin pairs participated in the study, and all were lithium exposed. For all covariates, there were 2% missing values.

TABLE 1 Demographic and clinical characteristics of the participants

	Exposed to lithium	Not-exposed to lithium
N	56	43
Child characteristics		
Age (years), mean (SD)	9.0 (2.2)	10.6 (2.4)
Sex, % female	60.7	48.8
Country of birth both parents Netherlands, %	78.6	86.0
Psychiatric disorder[a], *N* (%)	11 (19.6%)	5 (11.6%)
Use of psychotropic medication[b], *N* (%)	3 (5.4%)	1 (2.3%)
Learning disability, *N* (%)	12 (22.2%)	5 (11.6%)
Birth weight (g), mean (SD)	3290 (729)	3541 (509)
Premature birth (<37 week), *N* (%)	14 (26.4%)	3 (7.9%)
Gestational age at birth in weeks, mean (SD)	37.6 (3.4)	39.6 (1.9)
Pregnancy characteristics		
Average maternal lithium dosage (mg), mean (SD)	926 (257)	
Period of lithium use (*N*)		
1st trimester only	2	
1st + 2nd trimester	1	
2nd + 3rd trimester	4	
1st + 2nd + 3rd trimester	48	
Unknown	1	
Lithium level weighted average (mmol/L), mean (SD)		
Whole pregnancy	0.53 (0.12)	
1st trimester	0.47 (0.12)	
2nd trimester	0.51 (0.15)	
3rd trimester	0.57 (0.17)	
Use of any other psychiatric medication, N (%)[c]	17 (30.4%)	5 (11.6%)
Antidepressants	14 (25%)	3 (7.0%)
Antipsychotics	8 (14.3%)	3 (7.0%)
Benzodiazepines	1 (1.8%)	5 (11.6%)
Use of alcohol, *N* (%)	1 (1.9%)	6 (14%)
Use of recreational drugs, *N* (%)	1 (1.8%)	0 (0%)
Smoking, *N* (%)	4 (7.1%)	4 (9.3%)
Folate use, *N* (%)	49 (92.5%)	37 (90.2%)
Maternal characteristics		
Main diagnosis, *N* (%)		
Bipolar I disorder	45 (80.4%)	23 (53.5%)
Bipolar II disorder	8 (14.3%)	1 (2.3%)
Postpartum mania/ affective psychosis[d]	0 (0.0%)	18 (41.9%)
Schizoaffective disorder	1 (1.8%)	0 (0.0%)
Major depressive disorder (MDD)	2 (3.6%)	1 (2.3%)
Time of diagnosis, *N* (%)		
Before pregnancy	56 (100%)	20 (46.5%)
During pregnancy	0 (0%)	1 (2.3%)
After pregnancy	0 (0%)	22 (51.2%)
Number of lifetime episodes, median (IQR)	5.5 (3–8)	2 (1–5)
Episode during pregnancy, *N* (%)	10 (20.8%)	2 (4.8%)
Mean age of onset mood disorder, mean (SD)	23 (6.0)	30 (4.4)
Household income in Euro's per month, *N* (%)		
<2400	14 (25.9%)	10 (25.6%)
>2400	40 (74.1%)	29 (74.4%)
Higher education, *N* (%)	33 (58.9%)	26 (60.5%)
Paternal characteristics		
Lifetime psychiatric disorder, *N* (%)	14 (25.9%)	11 (25.6%)
Higher education, *N* (%)	34 (63%)	25 (62.5%)

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

[a] Exposed group: ADHD/ADD *N* = 3, Autism Spectrum Disorder (ASD) *N* = 5, Tourette's syndrome *N* = 1, Developmental Coordination Disorder *N* = 1, other behavioural disorder *N* = 1. Non-exposed group: ADHD/ADD *N* = 2, ASD *N* = 1, ADHD and ASD *N* = 1, Tourette's syndrome *N* = 1.

[b] Exposed group: methylphenidate *N* = 2, lamotrigine *N* = 1. Non-exposed group: methylphenidate *N* = 1.

[c] Use of any other psychotropic medication than lithium at some point during pregnancy, also subdivided by medication group. Some women used more than one additional type of medication.

[d] These mothers have not experienced episodes outside of the postpartum period.

3.2 | Lithium use

Different types and compounds of lithium were used during pregnancy. In 24 pregnancies, mothers used lithium carbonate (Camcolit® *n* = 13, Priadel® *n* = 5, lithium carbonate [other brands] *n* = 6). Lithium citrate, also known as Litarex®, was used in 19 pregnancies. In 13 pregnancies, the type of lithium medication 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 calculate the average lithium dosage in the lithium-exposed group of 926 mg/day. For 34 children, information on the maternal lithium blood level during the whole pregnancy was available. On average, there were 6.5 serum level measurements per pregnancy with a range of 1–22 measurements. There was no correlation between the number of

serum level measurements and the average weighted lithium level (data not shown).

3.3 | Neuropsychological tests

IQ tests were performed in 96 children (54 exposed and 42 non-exposed). NEPSY tests were performed in 99 children (56 exposed and 43 non-exposed). The distribution of IQ outcome of the offspring is presented in Figure 1. The mean IQ was 100.4 in the lithium-exposed group and 101.0 in the non-exposed group. Also presented in Figure 1 is the distribution of number of mistakes made on the Auditory Attention NEPSY subtest. The distribution of all NEPSY subtest outcomes is presented in Appendix 3. Visual inspection of the violin plots showed a comparable distribution shape in the lithium-exposed and non-exposed groups for IQ. The distribution shapes of Auditory Attention, Response Set, Inhibition and Visuomotor Precision (number of mistakes) show that in the lithium-exposed group more children have a relatively high number of mistakes, when compared to the non-exposed group. Additionally, more lithium-exposed children have lower scores on the Geometric Puzzles and Affect recognition.

In Table 2, the results of the multivariate regression analyses are presented. An association between prenatal lithium exposure and the number of total mistakes made on the Auditory Attention subtest was found after correction for age, sex and maternal number of lifetime episodes (Incidence Rate Ratio (IRR) = 2.09, 95% CI: 1.30, 3.38). This association was no longer statistically significant in the fully adjusted analysis. In the sensitivity analysis excluding offspring from mothers with mania or affective psychosis limited to the postpartum period, no association between lithium use during pregnancy and Auditory Attention total mistakes was found. Sensitivity analyses with Poisson regression models showed an association between lithium use during pregnancy and Auditory Attention total mistakes and additionally with Visuomotor Precision total mistakes (fully adjusted model: IRR = 1.26, 95% CI: 1.07, 3.49). Other associations between prenatal lithium exposure and neuropsychological subtest outcomes were not found.

3.4 | Dose–response

The results of the secondary analyses on the association between lithium blood level during pregnancy and neuropsychological test outcomes are presented in Table 3. Weighted lithium blood levels were associated with offspring IQ after adjustment for parental IQ and maternal number of lifetime episodes (β = −0.35, 95% CI: −81.57, −0.43) but no longer statistically significant in the fully adjusted model. No other associations between lithium blood level during pregnancy and neuropsychological test outcomes were found.

3.5 | Percentile and norm scores

In the lithium-exposed group and the non-exposed group, the mean percentiles for IQ were 49.3 and 50.6, respectively. For the NEPSY subtest outcomes, the percentages of lithium-exposed offspring with a percentile of 50 or lower and the mean norm scores are depicted in Figure 2. As shown in Figure 2, most norm and percentile values lie within the average or above average range, except for Affect Recognition and Visuomotor Precision (mistakes) in the lithium-exposed group.

4 | DISCUSSION

In this clinical cohort study, the influence of prenatal exposure to lithium on the neuropsychological functioning of offspring was investigated. Multiple neuropsychological domains were investigated with the aim to provide knowledge of the effects of prenatal lithium

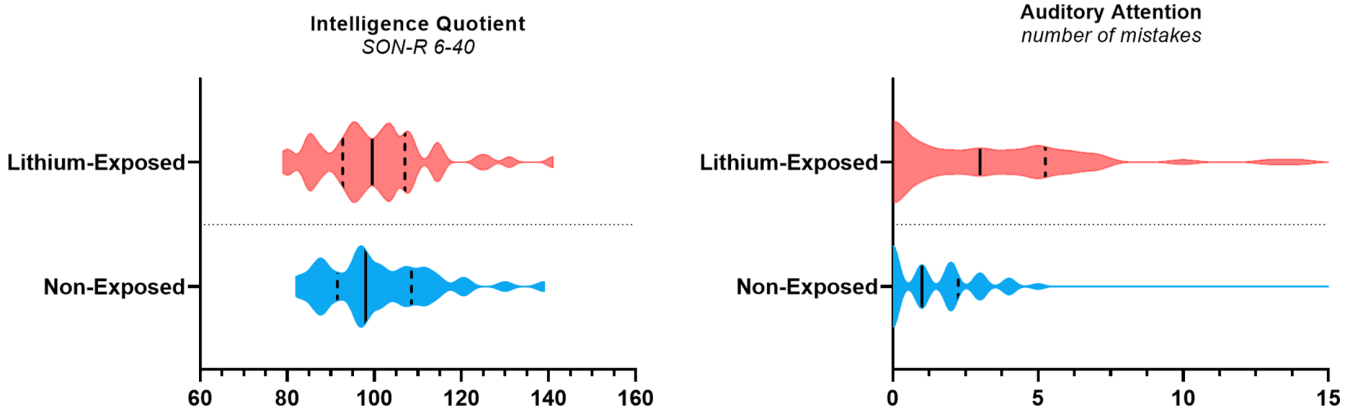

FIGURE 1 Distribution of IQ and Auditory Attention total mistakes in lithium-exposed and non-exposed offspring. Solid lines represent median and striped lines represent interquartile range. Violin plot: a kernel density estimation of the distribution shape of the IQ and Auditory Attention data. Distribution shapes are presented for the non-exposed and lithium-exposed groups separately. Wide sections of the violin plot represent a higher probability that offspring within this group will take on the given value while narrow sections represent a lower probability

TABLE 2 Associations between prenatal lithium exposure and neuropsychological test outcome[a]

	Model I[b]		Model II[c]		Model III[d]	
Outcome	**Coefficient (95% CI)**	***p*-value**	**Coefficient (95% CI)**	***p*-value**	**Coefficient (95% CI)**	***p*-value**
SON-IQ (L)	−0.03 (−5.82, 4.52)	0.80	−0.02 (−5.57, 4.78)	0.88	0.06 (−4.35, 7.52)	0.60
Auditory Attention, total mistakes (NB)	1.99 (1.25, 3.12)	0.003**	2.09 (1.30, 3.38)	0.002**	1.76 (0.96, 3.21)	0.07
Response Set, total mistakes (NB)	1.08 (0.66, 1.79)	0.75	1.12 (0,68, 1.86)	0.65	1.02 (0.58, 1.78)	0.95
Affect Recognition, total score (L)	−0.06 (−2.49, 1.24)	0.51	−0.04 (−2.31, 1.48)	0.67	−0.05 (−2.58, 1.50)	0.60
Memory for Faces, total score (L)	0.003 (−1.08, 1.11)	0.98	−0.04 (−1.30, 0.89)	0.71	−0.04 (−1.40, 1.03)	0.76
Memory for Faces Delayed, total score (L)	−0. 04 (−1.47, 0.97)	0.68	−0.09 (−1.72, 0.71)	0.41	−0.07 (−1.73, 0.96)	0.57
Narrative Memory, total free and cued recall (L)	0.02 (−1.69, 2.14)	0.81	0.03 (−1.56, 2.33)	0.70	0.05 (−1.58, 2.74)	0.59
Geometric Puzzles, total score (L)	−0.07 (−2.41, 0.96)	0.40	−0.09 (−2.56, 0.88)	0.33	−0.06 (−2.47, 1.27)	0.53
Inhibition mistakes (NB)	0.86 (0.55, 1.34)	0.50	0.85 (0.54, 1.35)	0.49	0.85 (0.52, 1.40)	0.53
Inhibition time (L)	0.09 (−13.10, 31.54)	0.41	0.06 (−15.74, 29.54)	0.55	0.03 (−21.77, 27.54)	0.82
Inhibition combined mistakes and time (L)	−0.01 (−0.36, 0.32)	0.90	0.00 (−0.34, 0.34)	0.99	0.02 (−0.35, 0.41)	0.89
Visuomotor Precision time (L)	−0.02 (−1.01, 0.82)	0.84	−0.02 (−1.04, 0.83)	0.83	−0.07 (−1.37, 0.71)	0.53
Visuomotor Precision mistakes (NB)	1.22 (0.77, 1.94)	0.39	1.21 (0.75, 1.96)	0.42	1.10 (0.65, 1.85)	0.73
Visuomotor Precision combined mistakes and time (L)	−0.09 (−0.32, 0.10)	0.30	−0.09 (−0.32, 0.10)	0.30	−0.04 (−0.28, 0.18)	0.68
Semantic word Production, total correct words (NB)	0.96 (0.63, 1.48)	0.86	0.96 (0.62, 1.49)	0.87	0.97 (0.61, 1.57)	0.92

[a] Results from multivariate regression models. Coefficients: for linear regression models (L) the standardised beta and for Negative Binomial regression models (NB) the exponent of the beta (incident rate ratio) are reported. Original p-values (before FDR correction) are presented.

[b] Adjusted for: age and sex in the models on NEPSY subtest outcomes.

[c] Adjusted for: age, sex (NEPSY models), IQ parent (IQ model) and maternal number of lifetime episodes.

[d] Additionally adjusted for: gestational age at birth, household income, maternal education level, folic acid use during pregnancy, smoking and alcohol use during pregnancy, other psychotropic medication used during pregnancy.

* Statistically significant with an original *p*-value < 0.05; ** Statistically significant after Benjamini–Hochberg correction.

exposure on neuropsychological functioning. Lithium-exposed offspring did not significantly differ from non-exposed offspring in IQ and neurodevelopmental NEPSY tasks, after correction for potential confounding variables. Additionally, we did not find a relationship between lithium blood level during pregnancy and neuropsychological test outcomes. When compared to the norm scores of both the SON-R 6-40 and NEPSY-II NL subtests, both the lithium-exposed and non-exposed groups did not show meaningful deviations from scores expected in the normal population.

Although the fully adjusted analyses did not reveal any statistically significant associations between lithium use during pregnancy and neuropsychological test outcomes, there are some results that need further elaboration. The association with Auditory Attention total mistakes was present after adjustment for age and sex of the offspring and maternal lifetime number of episodes, but no longer statistically significant after correction for potential confounders and in a sensitivity analysis excluding offspring of mothers with mania or affective psychosis limited to the postpartum period. Additionally, using the conservative negative binominal models, no association with Visuomotor Precision total mistakes was found while with Poisson models this association was present, and did not disappear after correction for confounding factors or in the sensitivity analyses. Notably, when visually inspecting the violin plots, we saw that lithium-exposed children make more mistakes on several NEPSY subtests. While these performances could be outliers driving our results, we want to emphasise that all values were true test outcome values. It is important to conclude that by using conservative statistical models and after correction for confounders, we do not find a statistically significant effect of prenatal lithium exposure on neuropsychological functioning of the child. Additionally, it is also important to consider the possibility of a small effect in some of the children (as depicted by our true outliers) that could not be detected in our study due to lack of statistical power. It remains difficult to interpret the minor differences that we found between groups. It is likely that mothers from the lithium group had more psychiatric symptoms in the years after delivery. This more stressful postnatal environment also has the potential to influence neuropsychological functioning. Low scores in the Auditory Attention subtest are associated with problems in selective and sustained attention. The Auditory Attention subtest and especially the Response Set subtest are sensitive for ADHD. Also children with autism, language and calculation disorders tend to have lower scores on both tasks. Notably, we did not find an association between prenatal lithium use and outcome on the Response Set task. Low scores for Auditory Attention and normal scores for Response Set may imply that the child is more alert or motivated in a more challenging task than in a more monotonous task. Problems in the Visuomotor Precision subtest are

TABLE 3 Associations between weighted lithium levels during pregnancy and neuropsychological test outcome*

	Model I		Model II[a]		Model III[b]	
Outcome	**Coefficient (95% CI)**	***p*-value**	**Coefficient (95% CI)**	***p*-value**	**Coefficient (95% CI)**	***p*-value**
SON-IQ (L)	−0.35 (−81.61, 0.23)	0.051	−0.35 (−81.57, −0.43)	0.048*	−0.18 (−71.84,29.70)	0.40
Auditory Attention, total mistakes (NB)	0.15 (0.004, 6.29)	0.32	0.14 (0.003, 6.21)	0.31	0.30 (0.003, 27.36)	0.60
Response Set, total mistakes (NB)	15.06 (0.32, 706,82)	0.17	13.52 (0.27, 672.50)	0.19	3.03 (0.02, 493.24)	0.67
Affect Recognition, total score (L)	0.14 (−7.69, 23.37)	0.31	0.13 (−8.01, 23.28)	0.33	0.12 (−14.27, 28.38)	0.50
Memory for Faces, total score (L)	0.16 (−4.38, 11.84)	0.36	0.18 (−3.79, 11.91)	0.30	0.27 (−4.89, 17.10)	0.26
Memory for Faces Delayed, total score (L)	0.09 (−7.74, 12.29)	0.65	0.10 (−7.09, 12.42)	0.58	0.08 (−10.61, 14.83)	0.73
Narrative Memory, total free and cued recall (L)	−0.06 (−17.60, 11.20)	0.65	−0.06 (−17.88, 11.49)	0.66	−0.09 (−25.21, 15.98)	0.65
Geometric Puzzles, total score (L)	0.13 (−5.55, 18.23)	0.29	0.14 (−5.47, 18.57)	0.27	0.18 (−7.48, 24.51)	0.28
Inhibition mistakes (NB)	2.80 (0.10, 82.31)	0.55	2.57 (0.08, 79.53)	0.59	5.42 (0.08, 350.69)	0.43
Inhibition time (L)	0.25 (−54.94, 287.88)	0.18	0.25 (−56.22, 292.44)	0.18	0.01 (−213.15, 221,15)	0.97
Inhibition combined mistakes and time (L)	−0.26 (−3.85, 0.54)	0.14	−0.26 (−3.86, 0.60)	0.15	−0.17 (−3.82, 1.63)	0.41
Visuomotor Precision time (L)	0.05 (−5.70, 7.54)	0.78	0.05 (−5.84, 7.66)	0.78	−0.18 (−11.45, 5.08)	0.43
Visuomotor Precision mistakes (NB)	0.81 (0.02, 32.25)	0.91	0.82 (0.02, 33.06)	0.92	1.79 (0.02, 137.03)	0.79
Visuomotor Precision combined mistakes and time (L)	0.03 (−1.58, 1.89)	0.86	0.03 (−1.60, 1.93)	0.85	0.28 (−0.57, 3.61)	0.15
Semantic word Production, total correct words (NB)	0.80 (0.04, 16.27)	0.89	0.79 (0.04, 16.29)	0.88	0.68 (0.01, 35.04)	0.85

[a] Results from multivariate regression models. Coefficients: for linear regression models (L) the standardised beta and for negative binomial regression models (NB) the exponent of the beta (incident rate ratio) are reported. Original p-values (before FDR correction) are presented. Data derived from 34 children.

[b] Adjusted for: age and sex in the models on NEPSY subtest outcomes.

[c] Adjusted for: age, sex (NEPSY models), IQ parent (IQ model) and maternal number of lifetime episodes.

[d] Additionally adjusted for: gestational age at birth, household income, maternal education level, folic acid use during pregnancy, smoking and alcohol use during pregnancy, other psychotropic medication used during pregnancy.

*Statistically significant with a p-value < 0.05, not statistically significant after Benjamini–Hochberg correction.

usually associated with problems in coordination of fine motor hand movements, or in the speed of hand movements. However, in this task, the number of mistakes and the time to finish are related. Personal style of the child can be of influence; hyperactive or impulsive children may try to finish the task quickly, thereby sacrificing accuracy. To address this matter, we created a 'combined mistakes and time' variable. We found no association with time to finish the task or with the combined variable. This suggests that combined visuomotor precision is not impaired and that a high number of mistakes is often compensated with a low completion time. Importantly, none of the lithium-exposed children had any clinical motor problems (data from questionnaires, not shown). Interestingly, children within the lithium-exposed group did appear to have a higher percentage of psychiatric disorders (19.6% vs. 11.6%) and learning disabilities (22.2% vs. 11.6%). Since this was outside the scope of this study, no statistical tests were performed to analyse these differences. Overall, we found no evidence for significant alterations in neuropsychological functioning after prenatal lithium exposure for children aged 6–14 years.

The findings of this study are consistent with existing literature from previous clinical studies. Forsberg et al. did not find a difference in full scale intelligence quotient (FSIQ), verbal intelligence quotient (VIQ) and performance intelligence quotient (PIQ) between lithium-exposed and non-exposed children, using the Wechsler Preschool and Primary Scale of Intelligence 3rd edition.[14] Children exposed to major mood disorder during pregnancy, with or without lithium exposure, had significantly lower scores on the processing speed quotient (PSQ). Van der Lugt et al. found no abnormalities in Verbal Intelligence Quotient, Performance Intelligence Quotient and Total Intelligence Quotient (Wechsler Preschool and Primary Scale of Intelligence or the Wechsler Intelligence Scale for Children), by comparing outcomes of lithium-exposed children with norm scores.[13] For two children aged between 16 and 30 months, no abnormalities were found in the Bayley Scales of Infant Development. The authors note, however, that many children had (non-significant) lower scores on the performance tests, especially on the subtest block patterns. The block patterns subtest mainly measures spatial visualisation ability and also requires visuomotor coordination. Two other clinical studies did not find an effect of lithium on development, but they did not use systematic tests.[11,12] To our understanding, no other study has used the NEPSY-II NL or a comparable test battery to systematically assess different domains of neuropsychological functioning in addition to IQ in lithium-exposed children. We investigated the cognitive domains attention and executive functioning, language, memory and learning, sensorimotor, social perception and visuospatial

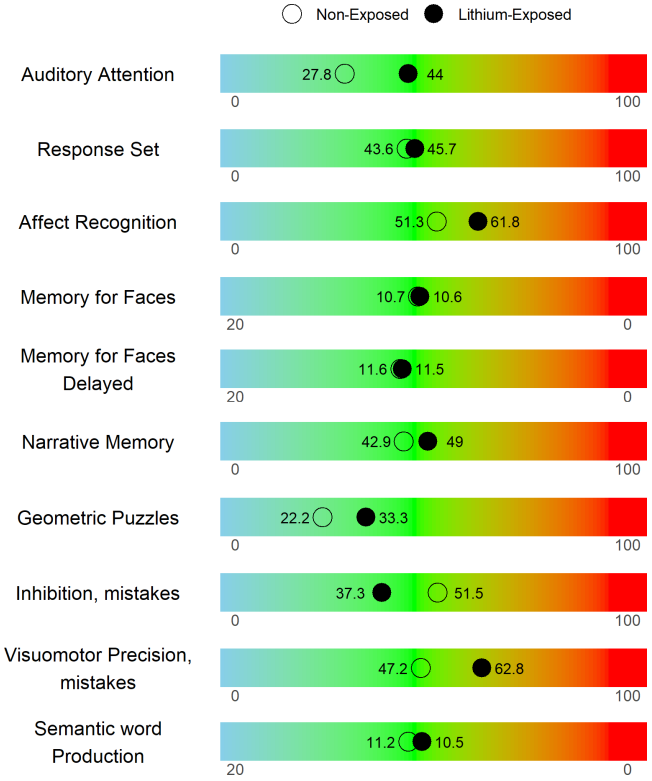

FIGURE 2 NEPSY-II-NL percentile and norm scores for the lithium-exposed and non-exposed groups. The black circle represents the lithium-exposed group and the open circle represents the non-exposed group. The percentage of offspring with a percentile <50 is presented on a scale from 0 to 100%. The mean norm scores are presented on a scale from 20 to 0. A colour range is used to depict how norms and percentages relate to the normal population (green = average/expected, blue = above average/better than expected, red = below average/worse than expected)

processing. Some preclinical studies have suggested detrimental effects of gestational lithium exposure in rodents and zebrafish on locomotor activity, developmental milestones and reflexes, spatial memory and brain weight.[22–26] However, these preclinical studies had substantial methodological limitations and may not be directly translatable to the clinical practice.

Lithium serum level during pregnancy did not affect neuropsychological outcome in our study. An effect of lithium blood level on IQ was found after correction for parental IQ and maternal lifetime number of episodes, but not present after correction for multiple potential confounders. Importantly, lithium has a small therapeutic range that is usually closely monitored during pregnancy. As a result of the small range, a possible effect of serum level may not become apparent in our relatively small subsample. It should also be noted that serum lithium levels during pregnancy were only available in 61% of lithium-exposed pregnancies and that we found wide confidence intervals with our model estimates. Hence, the results of these analyses should be interpreted with caution as they were likely underpowered.

The current study has several strengths and limitations. First, this is the largest prospective cohort study on this topic thus far. Another strength of this study is the use of validated tests for the assessment of IQ and neuropsychological functioning. Although we did not study every aspect of neuropsychological functioning, we did provide information on IQ and six different cognitive domains. Because we recruited our participants via specialised centres for perinatal psychiatry, detailed information during pregnancy was available and this made it possible to define the exposure with large certainty and correct for the most relevant confounding factors. Also, by including a non-exposed control group in which the maternal psychiatric diagnosis was matched to the exposed group, we addressed the issue of confounding by indication in the best way possible for a cohort study. Severity of disease is likely to be higher for women that choose to continue lithium treatment during pregnancy. This also follows from the higher number of lifetime mood episodes and the younger age of onset in the lithium-exposed group in our study. The non-exposed group contained a larger group of women that were diagnosed with postpartum psychosis only, which is generally considered to have a better prognosis than bipolar disorder.[20] We addressed this issue by performing a sensitivity analysis and by correcting for maternal lifetime number of mood episodes. The association between lithium use during pregnancy and Auditory Attention total mistakes was present after correction for maternal lifetime number of episodes. For all the other tests, no significant association was found. The latter could be seen as an argument for the safety of lithium on eventual neuropsychological functioning and IQ of the offspring or even a neuroprotective effect of lithium. This is because one would expect that maternal disease severity would negatively impact neuropsychological development of the child.[27] Thanks to the collaboration between Erasmus MC, Leiden University Medical Center and Onze Lieve Vrouwe Gasthuis we were able to include a large number of participants in this study. This enabled us to study neuropsychological functioning with more power.

Limitations of the current study are the fact that lithium serum levels were not available for all women and that the analyses on the association between lithium blood level and neuropsychological function were, as a consequence, underpowered. Also, most children had Dutch parents, limiting the ethnic variety in our sample. Neuropsychological functioning is a result of many factors such as genetic make-up, brain development, parental education, parenting strategies and life events. Since it would be relevant to find out if prenatal lithium exposure does affect brain structure in the offspring, brain MRI studies might provide further elucidation of this question.

Knowledge of long-term consequences of maternal lithium use during pregnancy for the offspring has so far been limited, but is essential for women with bipolar disorder to make informed decisions regarding their treatment during the perinatal period. Our findings reveal no evidence for significantly altered neuropsychological functioning for children exposed to lithium *in utero*. Several smaller differences in neuropsychological functioning may need further investigation. Since the collection of data in this specific group of children is challenging and sample sizes are generally small, we propose data sharing as a mean to create more power. Overall, the current and previous studies on this topic point towards a clinical neurodevelopment within the normal range for lithium-exposed offspring.

When counselling women with bipolar disorder on treatment options in the perinatal period, this information should preferably be integrated in the knowledge of all potential consequences of maternal lithium use during pregnancy.

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CONFLICT OF INTEREST

None.

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 may be found in the online version of the article at the publisher's website.

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