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Neurodevelopment in school-aged children after intrauterine exposure to antipsychotics

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Abstract

Objective: Antipsychotics are increasingly prescribed in pregnancy, yet little is known about potential long-term developmental effects on children. In this study, we investigated the effect of prenatal antipsychotic exposure on neurodevelopmental functioning in school-aged children.

Methods: We performed a cross-sectional neurodevelopmental assessment of 91 children aged 6–14 years whose mothers had severe mental illness and were either exposed or unexposed to antipsychotic medication during pregnancy. Neurodevelopmental outcomes were assessed using validated neurodevelopmental assessment instruments to examine the child's IQ and global cognitive functioning, and the presence of any psychiatric disorders and/or learning problems in the child was assessed by parental report.

Results: No statistically significant associations were found between antipsychotic exposure during pregnancy and either adverse neurodevelopmental outcomes (IQ, neuropsychological function), likelihood of psychiatric diagnosis, or learning problems based on parental report. Analyses were likely limited in power to detect subtler differences in neurodevelopmental functioning because of small sample size and heterogeneity of the sample.

Conclusions: In this exploratory cohort study, intrauterine exposure to antipsychotics was not associated with any adverse effect on IQ or neurodevelopmental functioning in a cohort of school-aged children (6–14 years).

KEYWORDS

antipsychotics, IQ, neurodevelopment, offspring, pregnancy

1 | INTRODUCTION

Antipsychotic medications are widely prescribed for a range of illnesses including schizophrenia, bipolar disorder, depression, and obsessive compulsive disorder (OCD).[1–3] Since many of these disorders have their onset in adolescence, antipsychotic medication may also be prescribed to women of childbearing age. The number of pregnant women exposed to antipsychotics has increased over time.[4–6] In the USA, reports indicate that the prevalence of antipsychotic use in pregnancy increased from 0.3–0.4% to 0.8–1.3%[4,5] over the first decade of the 21st century. Antipsychotics cross the placenta, and in some cases, the fetus is exposed to a higher concentration than the mother.[7] Antipsychotics block dopamine D2 receptors, and dopamine influences the proliferation and differentiation of neural progenitor cell in the developing fetus.[8,9] It is therefore possible that in utero exposure to antipsychotics could influence neural development and might have lasting developmental effects.

Antipsychotic exposure has been associated with obstetric and neonatal complications, such as gestational diabetes, preterm birth, low birth weight, and neonatal withdrawal symptoms.[10–12] The known pervasive adverse fetal effects of exposure to severe maternal mental illness in itself[13–15] make the results difficult to interpret. At present very limited data exist on long-term outcomes associated with intrauterine exposure to antipsychotics.[16–18] Infant studies have found some evidence of early neuromotor problems, but less is known about long-term neurodevelopmental functioning of prenatally exposed children. Only one study has investigated the effect of antipsychotic exposure on IQ.[19] Slone et al. compared 2141 children exposed to phenothiazines and 26,217 unexposed controls as part of a multisite prospective cohort study (Collaborative Perinatal Project) and found no differences in IQ scores at 4 years of age. Three recent studies[17,18,20] used population-based datasets to examine psychiatric diagnoses in mid-childhood through early adulthood for children of mothers who either continued or discontinued antipsychotics for pregnancy, and none of these studies found a significant association. Wang et al. and Hálfdánarson et al. were both able to do sibling-discordant analyses, and neither found any increase in diagnoses of autism spectrum disorder (ASD) or attention-deficit/hyperactivity disorder (ADHD) with intrauterine antipsychotic exposure.[17,20] Momen et al. compared individuals whose mothers continued antipsychotics in pregnancy ($n = 2035$) to those whose mothers discontinued prior to pregnancy ($n = 6976$), and also examined paternal antipsychotic use to distinguish direct pharmacological effects from other environmental and genetic factors.[18] This study found no increase in diagnoses of emotional or psychiatric disorders with intrauterine antipsychotic exposure. When sex specific analyses were performed, a modestly elevated risk of psychiatric disorders for boys was found. These studies greatly advanced the field but were register based, which means that mental health outcomes were based on ICD diagnoses made during hospital visits. More detailed information on cognitive functioning and mental health outcomes was not available.

Significant outcomes

- No adverse effects on IQ or neurodevelopmental functioning were observed in association with intrauterine antipsychotic exposure in a cohort of school-aged children.
- Prevalence of learning problems and psychiatric disorders did not differ between antipsychotic-exposed and unexposed children.

Limitations

- Small differences in neurodevelopmental functioning may not have been detected because of small sample size and heterogeneity of the sample.
- Confounding by indication may influence any observed associations between intrauterine exposure to psychotropic medication and child development.

1.1 | Aims of the Study

The present study aimed to investigate the influence of intrauterine exposure to both typical and atypical antipsychotics on neurodevelopmental functioning of school-aged children. This clinical cohort study is to our knowledge the first study to report detailed in-person neurodevelopmental assessments in school-aged children (aged 6–14 years) who were exposed to antipsychotics in utero.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

The current investigation was part of a cohort study designed to investigate neurodevelopmental functioning of children of mothers with SMI who were exposed or unexposed to lithium or antipsychotic medication in utero.[21] Patients were recruited from three centers in the

Netherlands, all expert centers in perinatal psychiatry with referrals from a wide catchment area (Erasmus Medical Center in Rotterdam, Leiden University Medical Center and Onze Lieve Vrouwe Gasthuis in Amsterdam). Women who had been treated in one of these centers during their pregnancies were invited to participate with their children. The Institutional Review Board of the Erasmus University Medical Center approved the study and all participants and their mothers signed informed consent (MEC 2016-288). For the current analyses, children aged 6 to 14 years who were prenatally exposed to one or more antipsychotics (including both typical and atypical antipsychotics) at any time during pregnancy were compared with children not exposed to any antipsychotic medication. Exposure to other psychotropic medication during pregnancy was not an exclusion criterion for either group. All children were offspring of mothers with severe mental illness. Information on the mother's medical history, psychiatric diagnosis, pregnancy characteristics, and medication exposure during pregnancy, including dose and duration, was extracted from the mother's medical file. Birth weight and gestational age at delivery were also obtained from the mother's obstetric file. Mothers filled in a questionnaire covering educational level of the parents, socioeconomic status, and general health of the child and existence of learning problems or a psychiatric disorder in the child. Neurodevelopmental testing took place during a single research visit. The assessments were conducted by trained PhD students and research assistants, who were not blinded to medication exposure.

2.2 | Neurodevelopmental outcome assessment

Two subtests (Categories and Mosaics) from the Snijders-Oomen Nonverbal Intelligence Test Revision (SON-R 6-40)[22] were performed to compute an IQ-score, using the SON-R 6-40 computer program. The SON-R 6-40 is a non-verbal intelligence test for children and adults aged 2.5 to 40 years that has been validated and correlates well ($r = 0.55–0.83$) with several other intelligence tests (WISC, WAIS, WNV, NIO).[22,23] Additionally, neurodevelopment was assessed by administering nine subtests from the NEPSY-II-NL assessment. The NEPSY-II-NL is a validated Dutch adaptation of the North-American NEPSY-II, for which acceptable to good reliability and validity have been reported.[24] The NEPSY-II-NL covers six different cognitive domains: attention and executive functioning, social perception, memory and learning, sensorimotor, visuospatial processing and language.[24,25] In order to limit the time burden for participating children, we selected nine out of 34 subtests. We selected subtests that matched the age group of our participants and covered all six cognitive domains. The administered subtests and corresponding outcome measures for each domain were as follows. For the attention and executive functioning domain, Auditory Attention (score of correct responses), Response Set (score of correct responses), and Inhibition (total number of mistakes and total response time) were administered. For Auditory Attention and Response Set a high number of correct responses to auditory cues is considered a good score. For Inhibition, a short response time and a low number of mistakes reflect good functioning. For the social perception domain, Affect Recognition (total score) was administered. A high number of correctly recognized emotions reflects good functioning. For the memory and learning domain, Memory for Faces (total score), Memory for Faces delayed (total score) and Narrative Memory (total score for free and cued recall combined) were administered. For the Memory for Faces tasks, a high number of correctly memorized faces reflects good functioning. For Narrative Memory, a high score on free and cued recall reflects good functioning. For the visuospatial processing domain, Geometric Puzzles (total score) was administered. A high number of correctly solved puzzles reflects good functioning. For the sensorimotor domain, Visuomotor Precision (total completion time and total number of mistakes) was administered. A short completion time and low number of mistakes reflects good functioning. For the language domain, Semantic Word Production (number of correct words) was administered. A high number of generated words reflects good functioning. A detailed description of the selected subtests may be found in our previously published paper.[21] Presence of learning problems and/or psychiatric disorders was assessed by parental report, worded as follows: “Has your child been diagnosed with a psychiatric disorder? If so, which diagnosis did he/she receive?” and “Does your child have learning problems? If so, has he/she been formally diagnosed?”

2.3 | Statistical analyses

Distribution of data was visually inspected. Separate multivariable linear regression models were used to investigate the association between antipsychotic exposure and NEPSY and SON outcomes for variables that were normally distributed (IQ, Affect Recognition, Memory for Faces, Memory for Faces Delayed, Narrative Memory, Geometric puzzles, Inhibition total time, Visuomotor precision total time). For count outcome variables that were

not normally distributed (Auditory Attention, Response Set, Inhibition total mistakes, Visuomotor precision total mistakes, Word production), multivariable Negative Binomial regression models were used. For NEPSY outcomes, the models were adjusted for sex and age of the child. For linear regression models the unstandardized beta, confidence interval, and *p*-value are reported. For negative binomial regression models the exponent of the beta (incidence rate ratio [IRR]), confidence intervals, and *p*-values are reported. *P*-values smaller than 0.05 were considered statistically significant. The unexposed sample included nine children whose mothers received a psychiatric diagnosis in the postpartum period, meaning that the pregnancy itself may not have been influenced by the psychiatric disorder. In order to minimize the influence of the timing of maternal psychiatric diagnosis on our outcome, we performed sensitivity analyses excluding these children. We also performed a sensitivity analysis in which we limited inclusion to only the first-born child per family, in order to exclude the potential influence of lifestyle factors or genetic predisposition. In separate sensitivity analyses, the influences of maternal educational level and prematurity were investigated by adding these to the model. As secondary analyses, unadjusted logistic regression models were used to investigate whether the prevalence of learning problems and psychiatric disorders was associated with antipsychotic exposure.

3 | RESULTS

Table 1 shows the characteristics of the participants included in this study. In total, 91 children from 63 separate families were included. 22 families with two children each, and three families with three children each participated. Two twin pairs were included. Several differences between the groups were observed. The non-exposed group included nine children whose mothers were first diagnosed with a psychiatric illness in the postpartum period, whereas mothers in the exposed group had all received psychiatric diagnoses before pregnancy. The maternal diagnoses of schizophrenia and schizoaffective disorder only occurred in the antipsychotic-exposed group. Furthermore, the group not exposed to antipsychotics had a higher percentage of children exposed to lithium, whereas the antipsychotic-exposed group had a higher rate of co-treatment with antidepressants. Lastly, the educational level of both parents was higher in the group not exposed to antipsychotics. Maternal antipsychotic use is described in Table 2, including information on dosage and duration.

TABLE 1 Characteristics of the study sample.[a]

	SMI + antipsychotics	SMI + no antipsychotics
N	17	74
Child characteristics		
Age (years), mean (SD)	10.0 (2.0)	10.0 (2.7)
Sex, % female	41.2	54.1
Birth weight (g), mean (SD)	3069 (714)	3344 (750)
Premature birth (<37 week), *N* (%)	3 (17.6%)	15 (20.8%)
Gestational age at birth in weeks, mean (SD)	37.9 (2.9)	38.1 (3.4)
Pregnancy characteristics		
Use of any other psychiatric medication, *N* (%)	15 (88%)	53 (72%)
Antidepressants	11 (65%)	14 (19%)
Lithium	6 (35%)	48 (65%)
Benzodiazepines	7 (41%)	1 (1%)
Maternal characteristics		
Main diagnosis, *N* (%)		
Bipolar I disorder	7 (41.2%)	59 (79.7%)
Bipolar II disorder	0 (0%)	9 (12.2%)
Schizoaffective disorder	1 (5.9%)	0 (0%)
Borderline personality disorder	4 (23.5%)	5 (6.8%)
Schizophrenia	4 (23.5%)	0 (0%)
OCD	1 (5.9%)	0 (0%)
Psychotic disorder NOS	0 (0%)	1 (1.4%)
Higher education, *N* (%)	3 (17.6%)	47 (63.5%)
Time of diagnosis, *N* (%)		
Before pregnancy	17 (100%)	65 (87.8%)
During pregnancy	0 (0.0%)	0 (0.0%)
After pregnancy	0 (0.0%)	9 (12.2%)
Paternal characteristics		
Lifetime psychiatric disorder, *N* (%)	4 (28.6%)	18 (25.4%)
Higher education, *N* (%)	3 (21.4%)	48 (68.6%)

Abbreviation: SMI, severe mental illness.
[a]In case of missing data valid percentages and means are presented.

The distribution of IQ scores is presented in a violin plot in Figure 1. The distribution of NEPSY outcomes is presented in violin plots in Figure A1. As can be seen in these plots, the distributions of IQ scores for the two groups are similar, whereas for some NEPSY outcomes, spread and shape of the distribution differ between groups. Descriptives for the SON-IQ and NEPSY outcomes and the prevalence of psychiatric disorders and

TABLE 2 Information on antipsychotic use during pregnancy per child ($N = 17$)

Child	Type	Specification	Duration of use in pregnancy
1	Atypical & typical	Quetiapine 200 mg + haloperidol 2 mg	Whole pregnancy
2	Atypical	Quetiapine 600 mg	Whole pregnancy
3	Typical	Haloperidol 7,5 mg	Whole pregnancy
4	Typical	Haloperidol 3 mg (for 2 weeks), pipamperon 20 mg (for 3 weeks), pipamperon as needed 20 mg (18 weeks)	2nd + 3rd trimester
5	Typical	Flupentixol 1,5 mg (10 weeks), Haloperidol 2 mg (20 weeks)	Whole pregnancy
6	Typical	Pipamperone 60 mg (1st trimester) + 20 mg (2nd + 3rd trimester)	Whole pregnancy
7	Atypical	Olanzapine 5 mg	Whole pregnancy
8	Atypical	Olanzapine 5 mg (28 weeks) + 2,5 mg (12 weeks)	Whole pregnancy
9	Typical	Haloperidol 1 mg	Whole pregnancy
10	Typical	Flupentixol	2nd + 3rd trimester
11	Typical	Penfluridole 2×/week 10 mg	Whole pregnancy
12	Typical	Haloperidol 2 mg	Whole pregnancy
13	Atypical	Quetiapine 25 mg	1st + 2nd trimester
14	Typical	Haloperidol 2 mg	2nd trimester
15	Atypical & typical	Haloperidol 2 mg	Whole pregnancy
16	Typical	Bromperidol 20 mg	Whole pregnancy
17	Atypical	Olanzapine 10 mg	Whole pregnancy

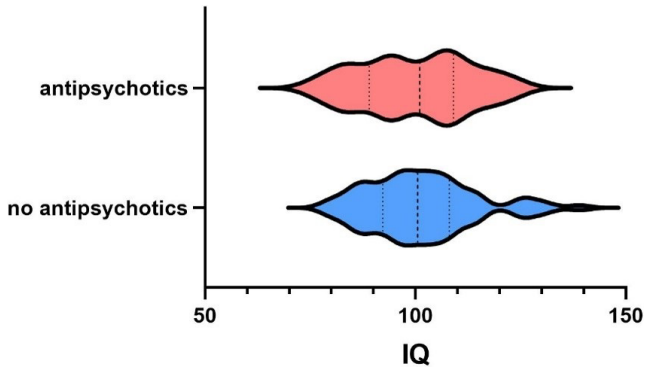

FIGURE 1 Distribution of IQ scores for antipsychotic-exposed and non-exposed children. Striped lines represent median and dotted lines represent interquartile range. A violin plot shows a kernel density estimation of the distribution shape of the data. Wide sections represent a higher probability that children within this group will take on the given value while narrow sections represent a lower probability.

learning problems are shown in in Tables A1 and A2 in Appendix 1. In Table A1, outcomes are presented for the antipsychotics and the no-antipsychotics group. Table A2 shows three groups, in which the no-antipsychotics group is subdivided into subgroups with and without exposure to adjunctive psychotropic medication.

Linear regression analysis revealed no association between prenatal antipsychotic exposure and IQ of the child (*ß*: −1.48, 95% CI [−8.42, 5.46] *p*-value: 0.67). No association between prenatal antipsychotic exposure and outcome on any of the NEPSY subtests was observed: Auditory Attention (IRR: 0.99, 95% CI [0.57, 1.72], *p*-value: 0.97), Response Set (IRR: 1.03, 95% CI [0.58, 1.84], *p*-value 0.91), Affect Recognition (*ß*: 1.14, 95% CI [−1.25, 3.53], *p*-value 0.35), Memory for faces (*ß*: −0.39, 95% CI [−1.76, 0.98], *p*-value: 0.58), Memory for faces delayed (*ß*: −1.07, 95% CI [−2.68, 0.53], *p*-value: 0.19), Narrative memory (*ß*: 0.51, 95% CI [−2.24, 3.26], *p*-value 0.71), Geometric puzzles (*ß*: 0.07, 95% CI [−2.02, 2.15], *p*-value: 0.95), Inhibition total mistakes (IRR: 0.68, 95% CI [0.39, 1.18], *p*-value: 0.17), Inhibition summed time (*ß* -0.76, 95% CI [−31.29, 29.77], *p*-value: 0.96) Visuomotor precision total time (*ß*: -8.47, 95% CI [−33.09, 16.14], *p*-value 0.50), Visuomotor precision total mistakes (IRR: 1.08, 95% CI [0.61, 1.90], *p*-value: 0.80), Semantic Word Production (IRR: 1.08, 95% CI [0.63, 1.85], *p*-value: 0.78). In sensitivity analyses excluding children with a maternal psychiatric diagnosis after pregnancy, no associations between antipsychotic exposure and IQ or NEPSY outcomes were found. Likewise, no associations were found when limiting the analyses to only the firstborn child per

family. In addition, neither incorporating educational level of the mother nor prematurity into the model altered the results.

Learning problems were reported for 6.3% of children in the antipsychotics group and 20.8% in the no-antipsychotics group. Psychiatric diagnoses were reported for 17.6% of children in the antipsychotics group and 21.6% in the no-antipsychotics group. No statistically significant association between antipsychotic exposure and learning problems (OR: 0.26, 95% CI [0.03, 2.11], $p = 0.21$) or psychiatric diagnoses (OR: 0.78, 95% CI [0.20, 3.04], $p = 0.72$) was observed.

4 | DISCUSSION

This is the first study to use detailed neurodevelopmental assessments to examine the cognitive and psychiatric functioning of school-aged children who were exposed to typical or atypical antipsychotics in utero. We found no association between antipsychotic exposure and adverse neurodevelopmental outcomes (IQ and neurocognitive domains). Neither did we find an association between antipsychotic exposure and frequency of learning problems or psychiatric disorders in the child. The analyses were, however, limited in power and potential smaller differences may not have been detected because of small sample size and heterogeneity of the sample.

An important strength of the study was the use of detailed and validated neurodevelopmental assessments to examine neurodevelopmental functioning. Previous studies in this area have relied on diagnoses in the medical record. Other strengths of this study were participation only by offspring of women with severe mental disorders, thereby minimizing the potential confounding effect of maternal mental illness on our results, and the availability of detailed information regarding exposure to antipsychotic medication during pregnancy and health outcomes of mother and child.

The main limitations of this study were the heterogeneity of the sample and the small sample size, which also prevented us from stratifying by subclass of antipsychotic medication. This is important because typical and atypical antipsychotics have distinct pharmacological and side-effect profiles, and it is possible that any developmental effects could be subclass-specific.[26] Also, sex specific analyses were not possible given the small sample size, but should be considered in future studies.[18]

Given the small sample size, we were unable to perform extensive adjustments for confounding factors. As can be seen in Table 1, there were differences between groups with respect to maternal diagnosis. For example, only the antipsychotic-exposed group included women with schizophrenia or schizoaffective disorder. Furthermore, for nine subjects in the unexposed group the mother's initial psychiatric diagnosis occurred after pregnancy, with a first lifetime psychiatric episode in the postpartum period, which may represent less severe illness than disease onset before or during pregnancy. Additionally, educational attainment for both parents was notably higher in the no-antipsychotics group than in the antipsychotics group. Together, this all raises concern for confounding by indication, with maternal diagnostic, severity, and educational indicators all potentially predisposing towards better outcomes in the no-antipsychotics group. In this light, it is remarkable that we did not find differences between the groups.

Another limitation of our study was that the investigators who conducted the neurodevelopmental assessments were not blinded to exposure status because of practical reasons. In addition, the overall cohort contained a large proportion of siblings, which may have introduced bias caused by genetic and lifestyle factors within families. We addressed this matter by performing a sensitivity analysis including only the firstborn child for each family.

Another potential confounder is the high rate of prematurity in both groups (17.6% and 20.8%), which is substantially higher than the 5.3%–5.6% for singleton pregnancies in the general Dutch population.[27] It is known that the risk of prematurity is greater in women with severe mental illness.[13,14] Furthermore, a substantial number of women used lithium, which has been associated with prematurity in multiple studies.[28,29] Premature birth may negatively influence intelligence and neurodevelopmental outcomes.[30,31] We therefore performed a sensitivity analysis, adding prematurity as a covariate, and found no change in the outcome.

Overall, the choice to continue antipsychotic medication during pregnancy is an individual decision, which is usually made by the patient, the partner, and health care providers. Given that most patients with antipsychotic treatment have severe mental illness, the decision to continue medication is mainly driven by the risk of relapse during pregnancy or right after delivery. Psychiatric relapse impairs the life functioning of the pregnant woman and her family, and has been demonstrated to be harmful for her offspring as well.[13,32–36] This relapse risk should be weighed against all potential adverse effects of antipsychotic medication on the child.

The current study adds to a small literature on the long-term neurodevelopmental effects of prenatal antipsychotic exposure on the child. Additional studies with both long-term follow-up and larger sample sizes are needed. Our sample size is small but our results are valuable considering the limited literature on this topic. Since

data collection in this specific group of subjects is challenging, we suggest data sharing and the use of multiple smaller studies in a meta-analysis to estimate a pooled effect.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

PEER REVIEW

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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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APPENDIX 1: Neurodevelopmental outcomes

TABLE A1 Neurodevelopmental outcomes for two groups

	SMI[a] + antipsychotics	SMI + no antipsychotics
N	17	74
With learning problems (%)[b]	6.3	20.5
With psychiatric disorder (%)	17.6	21.6
IQ (mean + SD)	99.9 (13.3)	101.4 (12.9)
NEPSY tasks[c]		
Attention and executive functioning		
Auditory attention, total score (med + IQR)	29.0 (3)	29.0 (3)
Response set, total score (med + IQR)	29.0 (7)	32.0 (5)
Inhibition, total mistakes (med + IQR)	14.0 (14)	11.0 (9)
Inhibition, summed time in seconds (mean + SD)	236.1 (27.9)	237.4 (63.7)
Social perception		
Affect recognition, total score (mean + SD)	26.5 (4.7)	25.2 (5.8)
Memory and learning		
Memory for faces, total score (mean + SD)	10.5 (2.9)	10.9 (2.6)
Memory for faces delayed, total score (mean + SD)	9.7 (4.4)	10.7 (2.8)
Narrative memory, total score (mean + SD)	22.4 (5.6)	21.7 (6.4)
Visuospatial processing		
Geometric puzzles, total score (mean + SD)	29.1 (4.0)	28.9 (5.2)
Sensorimotor		
Visuomotor precision, total time in seconds (mean + SD)	115.7 (50.1)	126.2 (49.0)
Visuomotor precision, total mistakes (med + IQR)	9.0 (10)	6.0 (13)
Language		
Semantic word production, total score (med + IQR)	31.0 (19)	32.0 (15)

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

[a]SMI, severe mental illness.

[b]Reported learning problems for non-antipsychotics group: (suspicions of) dyslexia ($n = 7$), dyscalculia ($n = 1$), dyscalculia and dyslexia ($n = 1$), language problems ($n = 3$), concentration problems ($n = 2$), unspecified ($n = 1$); for antipsychotics group: unspecified ($n = 1$). Reported psychiatric diagnoses in children for non-antipsychotics group: AD(H)D ($n = 4$), PDD-NOS ($n = 3$), ASS ($n = 4$), Tourette syndrome ($n = 2$), PTSD ($n = 1$), other ($n = 2$); for antipsychotics group: AD(H)D ($n = 1$), PDD-NOS ($n = 2$).

[c]Mean and standard deviation (SD) for normally distributed data; median (med) and interquartile range (IQR) for variables that were not normally distributed.

TABLE A2 Neurodevelopmental outcomes for three groups

	SMI[a] + antipsychotics	SMI + other psychotropics	SMI no psychotropic medication
N	17	53	21
With learning problems (%)[b]	6.3	21.2	19.0
With psychiatric disorder (%)	17.6	24.5	14.3
IQ (mean + SD)	99.9 (13.3)	101.1 (12.0)	102.1 (15.1)
NEPSY tasks[c]			
Attention and executive functioning			
Auditory attention, total score (med + IQR)	29.0 (3)	29.0 (4)	29.5 (3)
Response set, total score (med + IQR)	29.0 (7)	32.0 (5)	33.0 (6)
Inhibition, total mistakes (med + IQR)	14.0 (14)	11.0 (9)	12.0 (9)
Inhibition, summed time in seconds (mean + SD)	236.1 (27.9)	246.3 (67.7)	212.5 (43.4)
Social perception			
Affect recognition, total score (mean + SD)	26.5 (4.7)	26.5 (4.6)	25.4 (5.8)
Memory and learning			
Memory for faces, total score (mean + SD)	10.5 (2.9)	10.9 (2.8)	10.9 (2.0)
Memory for faces delayed, total score (mean + SD)	9.7 (4.4)	10.7 (3.0)	10.9 (2.3)
Narrative memory, total score (mean + SD)	22.4 (5.6)	21.5 (5.8)	22.2 (8.1)
Visuospatial processing			
Geometric puzzles, total score (mean + SD)	29.1 (4.0)	28.5 (5.4)	30.0 (4.5)
Sensorimotor			
Visuomotor precision, total time in seconds (mean + SD)	115.7 (50.1)	130.8 (50.8)	114.2 (42.7)
Visuomotor precision, total mistakes (med + IQR)	9.0 (10)	7.0 (15)	3.5 (13)
Language			
Semantic word production, total score (med + IQR)	31.0 (19)	33.0 (14)	30.5 (17)

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

[a]SMI, severe mental illness.

[b]Reported learning problems for antipsychotics group: unspecified ($n = 1$); for other psychotropics group: (suspicions of) dyslexia ($n = 5$), dyscalculia ($n = 1$), dyscalculia and dyslexia ($n = 1$), language problems ($n = 2$), concentration problems ($n = 1$), unspecified ($n = 1$); for no psychotropics group: (suspicions of) dyslexia ($n = 2$), language problems ($n = 1$), concentration problems ($n = 1$). Reported psychiatric diagnoses in children for antipsychotics group: AD(H)D ($n = 1$), PDD-NOS ($N = 2$); for other psychotropics group: AD(H)D ($n = 3$), PDD-NOS ($n = 2$), ASS ($n = 4$), Tourette syndrome ($n = 1$), PTSD ($n = 1$), other ($n = 2$); for no antipsychotics group: AD(H)D ($n = 1$), PDD-NOS ($n = 1$), Tourette syndrome ($N = 1$).

[c]Mean and standard deviation (SD) for normally distributed data; median (med) and interquartile range (IQR) for variables that were not normally distributed.

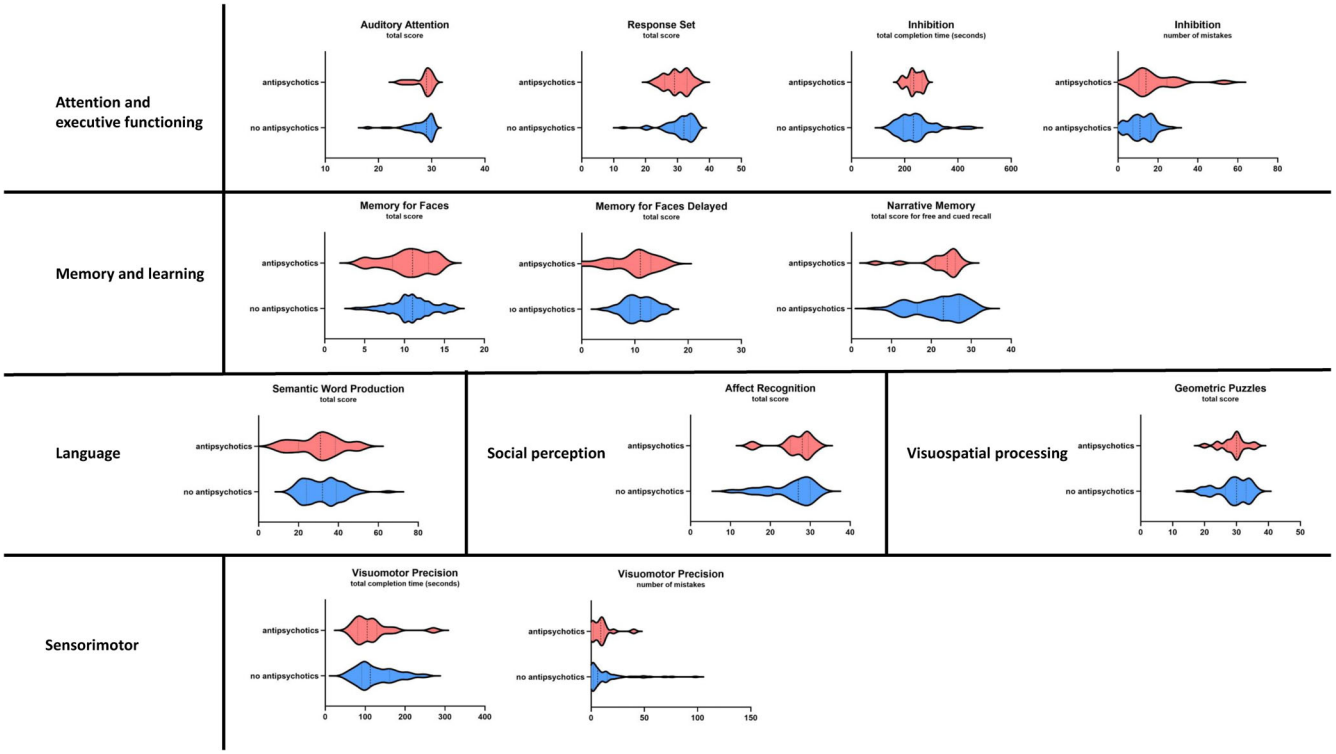

FIGURE A1 Distribution of NEPSY-II-NL subtest scores for antipsychoticexposed and non-exposed children. Striped lines represent median and dotted lines represent interquartile range. A violin plot shows a kernel density estimation of the distribution shape of the data. Wide sections represent a higher probability that children within this group will take on the given value while narrow sections represent a lower probability.