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Maternal serotonin transporter genotype and offsprings' clinical and cognitive measures of ADHD and ASD

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ABSTRACT

Serotonin (5-HT) is an important factor for prenatal neurodevelopment whereby its neurotrophic actions can be regulated through maternal-fetal interactions. We explored if maternal 5-HTTLPR genotype is associated with clinical and cognitive measures of attention-deficit/hyperactivity disorder (ADHD) and comorbid autism spectrum disorder (ASD) in typically-developing and ADHD-diagnosed offspring, beyond classical inheritance and environmental- and comorbidity-mediators/confounders. Family-based variance decomposition analyses were performed incorporating 6–31 year-old offsprings' as well as parental genotypes of 462 ADHD and control families from the NeuroIMAGE cohort. Dependent measures were offsprings' ADHD symptom- and ASD trait-scores and cognitive measures including executive functioning (including response inhibition and cognitive flexibility), sustained attention, reward processing, motor control, and emotion recognition. Offsprings' stereotyped behavior was predicted by an interaction between maternal 5-HTTLPR genotype and offsprings' sex. Furthermore, offspring of mothers with low-expressing genotypes demonstrated larger reward-related reductions in reaction time. While specifically adult male offspring of these mothers reported a faster reversal learning with less errors, specifically young female offspring of these mothers were more accurate in identifying happy faces. Adult offspring from the mothers with low-expressing 5-HTTLPR genotypes were also slower in identifying happy faces. However, this association seemed to be mediated by offsprings' high anxiety levels. In sum, we found some support for a role of the maternal 5-HT system in modulating fetal brain development and behavior. Offsprings' cognitive measures might be more sensitive to small alterations within the maternal 5-HT system than their ADHD and ASD clinical phenotypes. Further studies are needed to specify the association between maternal genotype and risk for neurodevelopmental disorders.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorders (ASD) are common neurodevelopmental disorders that are clinically heterogeneous and have been associated with serotonin (5-HT) dysregulation (Banerjee and Nandagopal, 2015; Garbarino et al., 2019; Muller et al., 2016b; Murphy et al., 2004). Both disorders have an onset in childhood and boys are disproportionally affected (Christensen et al., 2016; Weyandt, 2007). While ADHD is characterized by inappropriate levels of inattention and/or hyperactivity and impulsivity, ASD is characterized by social and communication deficits, stereotyped behaviors, and sensory abnormalities (American Psychiatric Association, 2013). Such symptoms are considered continuous traits in the general population (Larsson et al., 2012; Spiker et al., 2002). Problems within the domains of executive functioning (i.e. cognitive flexibility), sustained attention, motor control, reward processing, and emotion recognition are common features in both disorders (Kopp et al., 2010; Luman et al., 2010; Oerlemans et al., 2014; Rommelse et al., 2011; van Dongen et al., 2015). Deficits in response inhibition, another form of executive functioning, seem to be mainly explained by ADHD (Craig et al., 2016).

5-HT not only plays a role as neurotransmitter throughout life (e.g. involved in mood regulation and cognition), but also acts as neurotrophic factor during embryonic development (Gaspar et al., 2003; Kepser and Homberg, 2015; Whitaker-Axmitia, 2001). In early gestation, 5-HT influences neurogenesis, neural migration, and circuit maturation of, amongst others, the prefrontal-limbic and thalamocortical circuitries (Hanswijk et al., 2020). Functional alterations within these circuitries have been associated with ADHD and ASD (Banerjee and Nandagopal, 2015; Schauder et al., 2015; Velasquez et al., 2017). Given the critical role of 5-HT in the maturation of these circuitries, perturbed 5-HT signaling throughout early gestation may contribute to the pathophysiology of neurodevelopmental disorders.

Converging evidence from rodent and human studies indicates a placenta-derived source of 5-HT (i.e. placental 5-HT synthesis and/or 5-HT from maternal platelets), providing 5-HT to the embryo in early gestation (Bonnin et al., 2011; Kliman et al., 2018). Indeed, functional genetic variation within the maternal 5-HT system has been suggested to affect embryonic brain 5-HT content (Muller et al., 2016a). This can in turn alter 5-HT-neurotrophic related brain development and influence the potential risk for neurodevelopmental disorders (Hanswijk et al., 2020). Two variants that may affect the embryo are the 5-HT transporter (5-HTT)-linked polymorphic region (5-HTTLPR: S vs L allele) and the single nucleotide polymorphism (SNP) within the 5-HTTLPR (rs25531: L allele A to G substitution) (Hu et al., 2006; Lesch et al., 1996). The L_AL_A genotype results in the highest 5-HTT mRNA expression and function and thus the lowest 5-HT-availability. This genotype differs significantly from other genotypes (SS, SL_G, L_GL_G, and L_AL_G) with regard to 5-HTT mRNA expression, except for the SL_A genotype (Hu et al., 2006). Earlier studies showed an association between maternal 5-HTTLPR L-allele and child's somatosensory cortex morphology, motor control, and ASD symptoms (Kistner-Griffin et al., 2011; van der Knaap et al., 2014). Offspring 5-HTTLPR genotype has been considered as one of the potential candidates in the development of ADHD and ASD as well (see Supplementary Materials Table 1 for an overview of the studies investigating 5-HTTLPRs' candidacy). Notably, genetic heterogeneity might partly be explained by child's age. ADHD in children has been suggested to be associated with an overrepresentation of the 5-HTTLPR L-allele (meta-analyses Faraone et al., 2005; Gizer et al., 2009), while adult ADHD seems to be marginally associated with an overrepresentation of the 5-HTTLPR S-allele (meta-analyses Landaas et al., 2010). In support, Kiive and Harro (2013) reported an association between 5-HTTLPR L-allele with both inattentive and hyperactive symptoms at the age of 15 while no associations were found at the age of 25.

The association between maternal 5-HTTLPR genotype and off-springs' neurodevelopmental disorders may be mediated by environmental factors. For instance, 5-HTTLPR S-allele carrying mothers exhibited less positive parenting in response to disruptive child behavior (ADHD together with oppositional defiant disorder symptoms) (Morgan et al., 2018). Given the complex gene-environment interplay of 5-HTT genotypes within families, it is difficult to disentangle effects of offspring genotypes from effects of within-family parental genotypes and the associated environment. The present exploratory study was thus designed to test whether maternal 5-HTTLPR genotype is associated with clinical measures of ADHD, comorbid ASD traits, and associated cognitive problems in typically-developing offspring and offspring with ADHD. Each clinical and cognitive domain was assessed separately. To control for potential effects of the transmission of risk-alleles we used a family-based variance decomposition analysis incorporating children's as well as parents' genotypes. To investigate potential environmental mediating effects, we contrasted the effects of paternal genotypes (i.e. external environment alone) with those of maternal genotypes (i.e. including the intrauterine environment). In addition, we investigated mediating/confounding effects of specific environmental factors including, amongst others, prenatal smoking, maternal positive expressed emotion (PEE), offsprings' psychoactive medication intake, and offsprings' comorbidity with anxiety disorder. We hypothesized that there is an association between maternal 5-HTTLPR genotype and clinical and cognitive measures of ADHD and comorbid ASD in typically-developing and ADHD-diagnosed offspring, beyond classical inheritance and environmental- and comorbidity-mediators/confounders. Especially an association between maternal high-expressing 5-HTTLPR genotypes (i.e. L_AL_A and SL_A) and offspring higher ASD trait severity was expected (mostly in females).

2. Material and methods

2.1. Participants

Participants were part of the NeuroIMAGE study, which is the Dutch follow-up study of the International Multicenter ADHD Genetics (IMAGE) study (Müller et al., 2011a, 2011b). Families with at least two children of whom at least one diagnosed with ADHD (combined type) were recruited from outpatient psychiatric or pediatric clinics. Control families were recruited from schools in the same region. All participants were of European Caucasian descent, had an IQ above 70, and no diagnosis of autistic disorder or Asperger disorder, epilepsy, general learning difficulties, brain disorders, and known genetic disorders. Participants were asked to withhold use of their psychoactive medication for 48 h before measurements. An in-depth description of participants' consent, recruitment, and general testing procedures has been published in the method and design paper of the NeuroIMAGE project (von Rhein et al., 2015b).

2.2. ADHD and ASD phenotypes

2.2.1. ADHD symptoms

For the NeuroIMAGE study, ADHD diagnosis was made in accordance with the DSM-IV-TR criteria (American Psychiatric Association, 2000). The diagnostic procedures are extensively explained elsewhere (e.g. O'Dwyer et al., 2014; van Rooij et al., 2015; von Rhein et al., 2015b). In short, all participants (parents and their children ≥6 years) were assessed using a semi-structured diagnostic interview (Dutch translation of the Schedule for Affective Disorders and Schizophrenia for School-Age Children [K-SADS]; Kaufman et al., 1997) as well as the Conners' ADHD questionnaires Conners' Parent Rating Scale – Revised: Long version (CPRS-R:L) combined with either a teacher-rating (Conners' Teacher Rating Scale – Revised: Long version (CTRS-R:L) applied for children <18 years or a self-report Conners' Adult ADHD Rating Scales – Self-Report: Long version (CAARS-S:L) applied for children ≥18 years or a report filled in by the partner of the participating parent (CAARS-O:SV); Conners et al., 1998a, 1998b). Symptom counts from the

K-SADS as well as the Conners' questionnaires were combined to provide a continuous score for ADHD symptomatology (score 0–18) and symptom specific scores considering inattentive or hyperactive-impulsive ADHD symptoms (score 0–9).

2.2.2. ASD traits

Even though a clinical diagnosis of DSM-IV defined autistic disorder or Asperger disorder had been an exclusion criterion for the IMAGE study, an earlier study reported elevated ASD traits in children with ADHD within this cohort (O'Dwyer et al., 2014). To obtain scores of the continuous distribution of ASD traits, children were assessed using the Children's Social and Behavioral Questionnaire (CSBQ) completed by parents. The CSBQ contains items which either refer to core DSM-IV-TR criteria for autism (American Psychiatric Association, 2000) or refer to more subtle ASD traits (Hartman et al., 2006). An aggregate score of four subscales was used to investigate ASD specific symptoms: 1) reduced contact and social interest, 2) difficulties in understanding of social information, 3) fear of and resistance to change, and 4) stereotyped behavior (respective total score of 24, 14, 6, 16 leading to an aggregate score of 0–60).

2.3. ADHD- & ASD-related cognition

2.3.1. Executive functioning and sustained attention domains measured using the stop signal task

Executive functioning and sustained attention were measured using a version of the stop signal task (Logan et al., 1984). The applied version is extensively described elsewhere (van Rooij et al., 2015). In short, in two practice and four test blocks, each consisting of 60 trials, children were presented a screen with a go-signal, to which they needed to respond by a left or right button press, unless the go-signal was shortly after followed by a stop-signal (stop-trial, 25% of trials). During these stop-trials the children were asked to withhold their response. A dynamic delay time between the go- and stop-signal was used leading to a successful inhibition rate of approximately 50% of the stop-trials. This created the possibility to estimate the latency of the stop-process in milliseconds based on the mean response time and stop-signal delay, known as the Stop-Signal Reaction Time (SSRT). The SSRT assesses response inhibition which is a form of executive functioning. Secondary performance measures, mainly related to attentional processes, were the total number of errors on go-trials and the intra-individual coefficient of variation of responses on go trials.

2.3.2. Executive functioning domain measured using the reversal learning task

Reversal learning is another executive functioning task as it measures cognitive flexibility and is tested as described earlier (Vanes et al., 2014). In short, children were presented a total of four stimuli, one at a time in a randomized order. They were instructed to react to some of the four stimuli with the goal to find out which stimuli required a response and which did not. They were also informed that the response-required-stimuli could unexpectedly change. After learning which two stimuli required a response, the response-required-stimuli were reversed without warning. During both the discrimination learning and reversal learning phase, testing was completed when 9 correct responses were given within 10 consecutive trials or after a total of 120 trials. After every trial, a feedback screen showed if the given response was correct or incorrect. Performance measures were 1) the number of trials until the test was completed and 2) the total number of errors. Thirty-two participants did not succeed in learning the new response-required-stimuli within the 120 trials.

2.3.3. Reward processing domain measured using the monetary incentive delay task

The monetary incentive delay task investigates deficits in reward processing and is described in earlier studies using the NeuroIMAGE

cohort (e.g. van Dongen et al., 2015; von Rhein et al., 2015a). In short, children were instructed to respond as quickly and accurately as possible to a target by pressing a button. A target-preceding cue indicated whether a button press within a given time window was rewarded or not, with a ratio of 50%. Rewards consisted of a maximum of €5. A dynamic time window in which responses were considered correct was used leading to an expected hit rate of 33%. At the end of a trial a feedback screen showed the outcome of the trial. In the current study we focused on the behavioral performance measures; i.e. the difference between the rewarded and neutral conditions in participants' reaction time in millisecond and their coefficients of variation.

2.3.4. Motor control domain measured using tracking & pursuit tasks

Visuomotor control problems were investigated using computerized subtests of the Amsterdam Neuropsychological Tasks (ANT; De Sonneville, 1999). Both tasks, tracking and pursuit, are fully described elsewhere (Rommelse et al., 2007). In short, motor control without continuous adaptation was investigated using the tracking task. In this task, children were instructed to trace an invisible midline (radius 8 cm) between an outer (radius 8.5 cm) and inner circle (radius 7.5 cm) as quickly and precisely as possible. Performance measures were precision (i.e. mean distance to the midline in millimeter) and stability (i.e. standard deviation of the distance). Motor control under continuous adaptation was investigated using the pursuit task. In this task, children were instructed to 'catch', and thus follow, a randomly moving target (asterisk) as precisely as possible. The same performance measures were used as in tracking.

2.3.5. Emotion recognition domain measured using the identification of facial emotions task

Emotion recognition problems were tested using the identification of facial emotions task; according to previously described procedures (De Sonneville, 1999; Oerlemans et al., 2014). In short, photographs of a human face with a distinct affective emotion (i.e. fear, angry, or happy) were presented to children via a computer screen. Children were instructed to judge (yes or no) whether the presented photograph depicted the target emotion. For each emotion the child needed to perform 40 trials of which 50% were the target emotion. Performance measures were the speed (i.e. mean reaction time in millisecond for correct responses for each of the three emotions separately) and accuracy (percentage of errors for each of the three emotions separately). In this analysis, we only used fear, angry, and happy affective emotional faces, as the other variables, sadness and disgust, were only completed by a few participants.

2.4. 5-HTTLPR genotyping

DNA extraction and 5-HTTLPR genotyping (including rs25531) is described in the Supplementary Materials Methods. For the analyses, we grouped maternal, paternal, and offsprings' 5-HTTLPR genotypes in: low 5-HTT mRNA expressing genotypes (SS, $S L_G$, $L_G L_G$, & $L_A L_G$) and high 5-HTT mRNA expressing genotypes ($L_A L_A$ & $S L_A$). Parental genotype frequencies did not deviate from the Hardy–Weinberg equilibrium, neither did offspring genotypes. Notably, even though 5-HTTLPR $S L_A$ genotype does not differ from the $L_A L_A$ genotype in mRNA expression, in some publications the $S L_A$ genotype is grouped in the low 5-HTT mRNA expressing genotype group. To create the opportunity to compare our studies we briefly state our results obtained by the use of such classification (i.e. $L_A L_A$ versus the rest). These results are described in the Supplementary Materials Results.

2.5. Potential environmental confounders

To validate a role of the intrauterine environment, we investigated if significant findings were confounded by environmental factors, which involve socioeconomic status (SES), prenatal smoking, maternal PEE,

maternal ADHD symptom severity, offsprings' psychoactive medication intake, and offsprings' perceived stress. We also explored whether findings were confounded by comorbidity of oppositional defiant disorder, conduct disorder, and anxiety disorder in the offspring.

2.5.1. Parental SES

Parental SES (total score 0–17) was based on averaged parental education level (van der Meer et al., 2017).

2.5.2. Prenatal smoking

Prenatal exposure to maternal smoking (exposed versus not exposed) was retrospectively assessed through the Prechtl optimality scale questionnaire (Nijmeijer et al., 2010; van der Meer et al., 2017).

2.5.3. Maternal caregiving behavior: Maternal PEE

Assessment of maternal expressed emotion, encompassing criticism and warmth towards their children, has been described in earlier studies (Richards et al., 2015; Sonuga-Barke et al., 2008; Sonuga-Barke et al., 2009). In short, Camberwell Family Interview Codings were used while evaluating parental responses throughout a one-hour clinical assessment. Warmth was assessed by the tone of voice, spontaneity, sympathy, and/or empathy towards the child. Mothers were divided over four groups, with zero meaning a great deal of expressed warmth and three meaning only a little expressed warmth. Criticism was assessed by statements, which criticized or found fault with the child based on tone of voice and critical phases. Mothers were divided over five groups, with zero meaning no expressed criticism and four meaning a lot of expressed criticism. For each mother, scores of expressed warmth and criticism were combined into one factor, i.e. PEE (score 0–7; higher values represent lower PEE).

2.5.4. Offsprings' psychoactive medication intake

Children's psychoactive medication use (present, past, or never exposed) was measured by pharmacist prescription data and self-report questionnaire (Groenman et al., 2019).

2.5.5. Offsprings' perceived stress

Assessment of offsprings' perceived stress has been described in earlier papers (van der Meer et al., 2014, 2015). In these earlier papers, a composite score of two questionnaires was used. The current study focused on one of these questionnaires as these earlier studies reported similar outcomes when using the composite score of two questionnaires and using each questionnaire separately. In short, children filled in the Stressful Live Events (SLE) questionnaire (Bosch et al., 2012; Oldehinkel et al., 2008). The SLE contained eleven items to explore whether children have been exposed to specific major stressful events in the past five years, such as death or serious illness of a loved one, physical or sexual abuse, or failure at something important to them (aggregate score of 0–11). Questionnaires were excluded when less than half of the questions were filled in.

2.5.6. Oppositional defiant and conduct disorders' phenotypes

Symptoms concerning oppositional defiant disorder and conduct disorder in children were assessed during the K-SADS semi-structured diagnostic interview (both phenotypes have a total score of 0–8).

2.5.7. Anxiety disorder phenotype

An earlier study showed that in this cohort ADHD neurocognitive dysfunctions were especially associated with self-reported anxiety (Bloemsma et al., 2013). Hence, this phenotype was included as potential environmental mediator. As described in Bloemsma et al. (2013) we asked the children to complete the Multidimensional Anxiety Scale for Children (MASC; March et al., 1997). An aggregate score from all four subscales was used to investigate anxiety symptoms: 1) physical symptoms, 2) harm avoidance, 3) social anxiety, and 4) separation/panic (aggregate score of 0–117).

2.6. Statistical analyses

To investigate the association between maternal 5-HTTLPR genotype and ADHD- and ASD-related phenotypes, and associated cognitive problems in typically-developing offspring (including the unaffected siblings of ADHD-diagnosed participants) and offspring with ADHD, we performed multiple analyses using the variance component method employed by the Sequential Oligogenic Linkage Analysis Routines (SOLAR) software package (http://www.nitrc.org/projects/se_linux; Almasy and Blangero, 1998, Kochunov et al., 2014). Importantly, SOLAR analyses family-based quantitative data by partitioning the observed covariance into maternal, paternal, and offspring genetic components and thus correcting for family-relatedness (i.e. siblings and the correlation between parental and offsprings' genotype). In these analyses, we included parental 5-HTTLPR genotype and offsprings' sex, age group (child <18 years versus adult ≥18 years), and 5-HTTLPR genotype as independent variables, together with the kinship matrix, and explored interaction effects between parental gene variance and offsprings' sex and/or age group. Factors were tested simultaneously to explore unique effects mutually adjusting for each other. Effects that did not reach nominal significance ($p \le 0.1$) were dropped from the model, using the standard "screen" option in SOLAR (for more details see the Supplementary Materials Methods). Given multiple testing, we conducted the False Discovery Rate (FDR)-method for all studied domains. That is, ADHD symptoms, ASD traits, executive functioning (including response inhibition and cognitive flexibility), sustained attention, reward processing, motor control, and emotion recognition. For all domains we considered results to be significant at $p \le 5\%$ FDR and marginal significant at $p \le 10\%$ FDR. Post hoc tests were performed to further investigate the interactions ($p \le 0.05$ and marginal significant at $p \le 0.1$).

2.6.1. Sensitivity analyses

We investigated if significant findings of the maternal 5-HTTLPR genotype were confounded by environmental factors. Firstly, we investigated potential mediating effects of specific environmental factors including parental SES, prenatal smoking, maternal PEE, and maternal ADHD symptom severity. Secondly, we studied whether offsprings' psychoactive medication intake and perceived stress could be potential environmental confounders. Thirdly, we explored whether findings were confounded by comorbidity with oppositional defiant disorder, conduct disorder, and anxiety disorder in the offspring. To be considered as a potential confounder, an environmental factor or comorbidity had to be significantly ($p \le 0.05$) associated with maternal 5-HTTLPR genotype. If so, the potential confounder(s) was/were included as covariate in the main and post hoc models to test if the confounder(s) could drive the effect of maternal 5-HTTLPR genotype on offspring clinical and cognitive measures of ADHD and ASD (sensitivity model $p \le 0.05$).

3. Results

3.1. Demographic characteristics

1009 children from 462 families were included in the current study (see Supplementary Materials Methods). Table 1 displays the demographics of the families included. No significant differences were found between maternal and paternal 5-HTTLPR expressing genetic groups when testing offsprings' sex, age group, and IQ. Furthermore, maternal 5-HTTLPR genetic groups did not differ on the potential (mediating) environmental confounders (i.e. parental SES, prenatal smoking, maternal PEE and ADHD symptom severity, and offsprings' psychoactive medication intake and perceived stress). Therefore, effects of the maternal 5-HTTLPR genotype are unlikely to be confounded by these factors. Regarding comorbidity, offspring from mothers with low-expressing 5-HTTLPR genotypes displayed lower anxiety levels in

Table 1

Participant demographics and descriptive statistics. Maternal and paternal group comparisons in offsprings' sex, age group, IQ, and symptom severity regarding ADHD, ASD, oppositional defiant disorder, conduct disorder, and anxiety disorder, and group comparisons concerning parental SES, prenatal smoking, maternal PEE and ADHD, and offsprings' psychoactive medication use and perceived stress. While all included offspring's were genotyped, this was not the case for parents; 946 mothers (93.8%) and 802 fathers (79.5%) were genotyped.

Risk factor	n	Sex, %males	Age group, %children	Estimated IQ[a], M (SD)	ADHD symptom levels, M (SD)	ASD trait levels, M (SD)	ODD symptom levels, M (SD)	CD symptom levels, M (SD)	Anxiety symptom levels, M (SD)	SES, M (SD)	Prenatal smoking, %yes	Maternal PEE, M (SD)	Maternal ADHD, M (SD)	Offsprings' psychoactive medication use, %Never used	Offsprings' perceived stress, M (SD)
%data complete		*100*	*100*	90.4	*100*	72.8	96.7	96.6	64.3	97.0	*61.8*	45.6	98.4	84.4	94.8
All participants	1009	56.0	61.8	100.16 (15.99)	6.60 (6.27)	10.50 (10.01)	0.98 (1.99)	0.19 (0.84)	39.42 (15.38)	11.80 (2.47)	19.6	3.13 (1.50)	2.02 (3.90)	55.2	2.12 (1.56)
Maternal 5-HTTLPR															
Low expression	259	56.8	63.7	98.34 (15.92)	7.14 (6.27)	10.94 (10.41)	1.01 (1.95)	0.20 (0.91)	37.79* (16.16)	11.57 (2.44)	20.3	3.24 (1.52)	1.96 (3.92)	53.8	2.25 (1.70)
High expression	687	56.0	62.2	100.05 (16.07)	6.58 (6.27)	10.74 (9.98)	1.00 (2.02)	0.18 (0.80)	40.10 (15.15)	11.81 (2.46)	19.6	3.10 (1.50)	2.16 (3.99)	54.2	2.09 (1.52)
Paternal 5-HTTLPR															
Low expression	288	55.2	61.5	101.06 (16.00)	6.44 (6.01)	9.23** (10.17)	0.95 (2.00)	0.23 (0.96)	39.81 (14.71)	–	–	–	–	–	–
High expression	514	57.0	62.5	101.22 (16.13)	7.09 (6.36)	11.19 (10.09)	1.00 (1.99)	0.18 (0.82)	38.99 (15.59)	–	–	–	–	–	–

Low versus high expression genotype groups *: p-value ≤ 0.05; **: p-value ≤ 0.01; the age group "children" ranges from 6 to 18 years old, while the group "adults" ranges from 18 to 31 years old; 5-HTTLPR: serotonin transporter-linked polymorphic region; ADHD: attention-deficit/hyperactivity disorder; ASD: autism spectrum disorders; CD: conduct disorder; M: mean; ODD: oppositional defiant disorder; PEE: positive expressed emotion; SD: standard deviation; SES: socioeconomic status.

Italics is used to show that the first data row is about the completion of the whole dataset while the other rows are focusing on specific sub groups as shown in the title row, e.g. %males of all participants and %smoking of all (yes, no, unkown) participants.

[a] Estimated IQ was based on two subtests of the Wechsler intelligence scale for Children (WisC) or Wechsler adult intelligence scale (Wais-iii).

comparison to offspring from mothers with high-expressing genotypes ($U(N_{\text{low 5-HTT expression}}$ = 174, $N_{\text{high 5-HTT expression}}$ = 435) = 41.715, z = 1.97, p = 0.05). This effect is mostly seen in females (maternal 5-HTTLPR low expressing genotypes: males mean ± SD 36.06 ± 16.70, females 40.24 ± 15.14; maternal 5-HTTLPR high expressing genotypes: males mean ± SD 37.55 ± 15.19, females 43.58 ± 14.41). All other factors were evenly distributed over the genotype groups. Consequently, sensitivity analyses were performed including offsprings' anxiety levels as covariate in the model. Of note, offspring from fathers with low-expressing 5-HTTLPR genotypes displayed lower ASD trait levels than offspring from fathers with high-expressing genotypes ($U(N_{\text{low 5-HTT expression}}$ = 201, $N_{\text{high 5-HTT expression}}$ = 387) = 44.488, z = 2.87, p = 0.004). This effect is again mostly seen in females (paternal 5-HTTLPR low expressing genotypes: males mean ± SD 11.96 ± 11.55, females 5.80 ± 6.73; paternal 5-HTTLPR high expressing genotypes: males mean ± SD 13.36 ± 10.08, females 8.15 ± 9.31).

Solar analyses showed that offsprings' sex and age group predict some of the ADHD- and ASD-related phenotypes and associated cognitive problems (see Supplementary Materials Table 2–8). Male offspring reported a significantly higher inattention score (p = 0.002) and a higher score regarding the ASD subdomain "reduced contact and social interest" (p = 0.003) than female offspring. In support, similar trends were found regarding offsprings' total ASD (p = 0.03), total ADHD (p = 0.04), and hyperactive-impulsive scores (p = 0.07). Furthermore, male offspring were significantly slower and made more errors when completing the reversal learning task (trials p = 0.02, errors p = 0.03). Regarding offsprings' age group, adult offspring made less errors and completed the reversal learning task significantly faster (trials p = 0.001, errors p = 0.002), reported smaller reward-related reductions in reaction time and coefficient of variation (reaction time p = 0.04, coefficient of variation p = 0.05), and marginally smaller intra-individual coefficient of variation of responses on go trials in the stop signal task (p = 0.05) in comparison to offspring younger than 18 years old. Adult offspring also reported an increased motor stability and, when tested under continuous adaptation, also an increased precision (tracking stability p = 0.004, pursuit stability p < 0.0001, pursuit precision p < 0.0001) than offspring younger than 18 years old. Similarly, adult offspring recognized angry faces marginally faster and fearful faces marginally more accurate in the "identification of facial emotions task"

(angry faces speed p = 0.01, fearful faces accuracy p = 0.03).

3.2. Association of maternal 5-HTTLPR genotype with offsprings' clinical measures of ADHD

5-HTTLPR genotype of the main predictor, the mother, was not associated with clinical ADHD measurements of the offspring, nor were the 5-HTTLPR genotypes of the father and child (see Supplementary Materials Table 2). There was also no interaction between parental 5-HTTLPR genotype and offsprings' sex and/or age group.

3.3. Association of maternal 5-HTTLPR genotype with offsprings' clinical measures of ASD

Stereotyped behavior of the offspring was predicted by a combination of paternal 5-HTTLPR genotype (p = 0.05, r^2 = 0.01) and the interaction between maternal 5-HTTLPR genotype and offsprings' sex (p = 0.02, r^2 = 0.07) (see Supplementary Materials Table 3). As the interaction between maternal 5-HTTLPR genotype and offsprings' sex was marginally significant, a sensitivity test was performed with offsprings' anxiety levels as covariate. In this test, a strong significant interaction between the maternal 5-HTTLPR genotype and offsprings' sex was found (p < 0.0001) with a low to medium proportion of variance explained (r^2 = 0.06). This suggests that the main findings are robust. Paternal 5-HTTLPR genotype and offsprings' anxiety levels were not associated with offsprings' stereotyped behavior. To explore the findings of the main and sensitivity analyses further, post hoc analyses were performed to investigate the maternal genotype interaction with offsprings' sex. Results revealed a tendency towards an association between maternal 5-HTTLPR genotype and stereotyped behavior in only female offspring. That is, female offspring from mothers with low-expressing 5-HTTLPR genotypes reported marginally higher stereotypic scores than female offspring from mothers with high-expressing genotypes (p = 0.08, r^2 < 0.01). The sensitivity analysis regarding offsprings' anxiety confirmed the robustness of this finding (p = 0.07, r^2 < 0.01) (Fig. 1).

Maternal, paternal, and offspring 5-HTTLPR genotypes were not associated with total ASD trait score and the three ASD subdomains: "reduced contact and social interest", "difficulties in understanding of social information", and "fear of and resistance to change". No
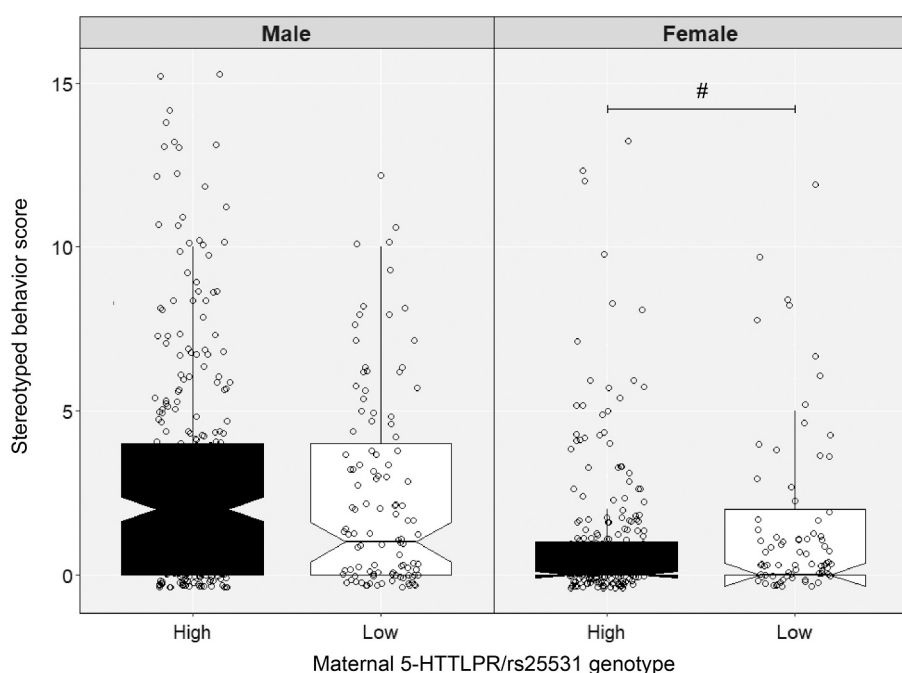

Fig. 1. Association of stereotyped behavior with maternal 5-HTTLPR/rs25531 genotype. Maternal 5-HTTLPR genotype tended to be associated with offspring stereotyped behavior in females (with anxiety p = 0.07). Maternal high-expressing 5-HTTLPR genotypes include $L_A L_A$ and $L_A S$ (black box), while maternal low-expressing 5-HTTLPR genotypes include SS, $L_G S$, $L_G L_G$, and $L_A L_G$ (white box). The box indicates the interquartile range and the whiskers show 95% confidence interval. #: post hoc test p-value ≤0.1.

interactions were found between parental 5-HTTLPR genotype and offsprings' sex and/or age group.

3.4. Association of maternal 5-HTTLPR genotype with offsprings' cognitive measures related to ADHD and/or ASD

3.4.1. Association of maternal 5-HTTLPR genotype with offsprings' executive functioning

Offspring executive functioning was studied via measuring offsprings' response inhibition (i.e. SSRT), the main performance measure of the stop signal task, and via measuring offsprings' cognitive flexibility through two performance measures of the reversal learning task (i.e. "the number of trials until the test was completed" and "the total number of errors"). Offsprings' response inhibition was not predicted by the main predictor, maternal 5-HTTLPR genotype, nor by any of the other main/interactive factors (see Supplementary Materials Table 4). On the contrary, both performance measures of the reversal learning task were marginally significantly predicted by the maternal 5-HTTLPR genotype interaction with offsprings' age group (trials $p = 0.07$, errors $p = 0.05$) and by offsprings' genotype (trials $p = 0.09$, errors $p = 0.04$). The maternal genotype interaction with offsprings' sex and age group was included in the prediction model as well, but did not survive FDR-correction (trials $p = 0.1$, errors $p = 0.06$). More than half of the proportion of variance explained depended on the maternal 5-HTTLPR interactions (trials: total $r^2 = 0.015$ vs. maternal $r^2 = 0.007$; errors: total $r^2 = 0.014$ vs. maternal $r^2 = 0.006$). Sensitivity testing, concerning offsprings' anxiety levels, partly supported the main analysis. Meaning, while maternal genotype interaction with offsprings' age group was only marginally associated with the number of trials the participant needed to learn the task ($p = 0.08$), maternal 5-HTTLPR interaction with offsprings' sex and age group significantly predicted both performance measures (trials $p = 0.02$, $r^2 = 0.004$; errors $p = 0.02$, $r^2 = 0.006$). The sensitivity analyses, therefore, point towards the maternal 5-HTTLPR interaction with offsprings' sex and age group as predictive factor instead of the maternal genotype interaction with offsprings' age group. Offsprings' 5-HTTLPR genotype as well as anxiety levels were not associated with either performance measures. Post hoc analyses were performed to further explore the maternal 5-HTTLPR genotype interaction with offsprings' sex and age group. A robust significant association was found between the maternal 5-HTTLPR genotype and errors made, and number of trials needed, in adult male offspring (trials: without the sensitivity covariate offsprings' anxiety $p = 0.03$ and with anxiety $p = 0.02$, both $r^2 = 0.03$; errors: without offsprings' anxiety $p = 0.05$ and with anxiety $p = 0.01$, both $r^2 = 0.09$). As shown in Fig. 2, adult male offspring from mothers with low-expressing 5-HTTLPR genotypes made less errors and needed less trials to complete the reversal learning task.

3.4.2. Association of maternal 5-HTTLPR genotype with offsprings' sustained attention

Both offspring performance measures of the stop signal task featuring attentive processes (i.e. "number of errors on go-trials" and "intra-individual coefficient of variation") were not predicted by the main predictor, maternal 5-HTTLPR genotype, by the father and offspring 5-HTTLPR genotype, nor by an interaction between maternal genotype and offsprings' sex and/or age group (see Supplementary Materials Table 5). Notably, an interaction between paternal 5-HTTLPR genotype and offsprings' sex and age group significantly predicted the number of errors made by the offspring ($p = 0.02$). Post hoc analyses indicated that girls from fathers with low-expressing 5-HTTLPR genotypes reported marginally lower numbers of errors ($p = 0.06$, $r^2 = 0.031$), while adult female offspring from similar fathers (i.e. with low-expressing 5-HTTLPR genotypes) reported marginal high numbers of errors ($p = 0.1$, $r^2 = 0.049$) (Supplementary Materials Fig. 1).

3.4.3. Association of maternal 5-HTTLPR genotype with offsprings' reward processing

Deficits in reward processing were investigated using the "monetary incentive delay task". While the performance measure "offsprings' difference in coefficient of variation between the rewarded and neutral trials" was not associated with any of the main/interactive factors, "offsprings' difference in reaction time between the rewarded and neutral trials" was significantly predicted by maternal 5-HTTLPR genotype (see Supplementary Materials Table 6). More specifically, offspring from mothers with low-expressing 5-HTTLPR genotypes demonstrated greater differences in reaction times between neutral and rewarded conditions in comparison to differences observed in offspring from mothers with high-expressing genotypes ($p = 0.01$, $r^2 = 0.03$) (Fig. 3A). A sensitivity analysis including offsprings' anxiety levels as covariate confirmed this association ($p = 0.03$, $r^2 = 0.03$).
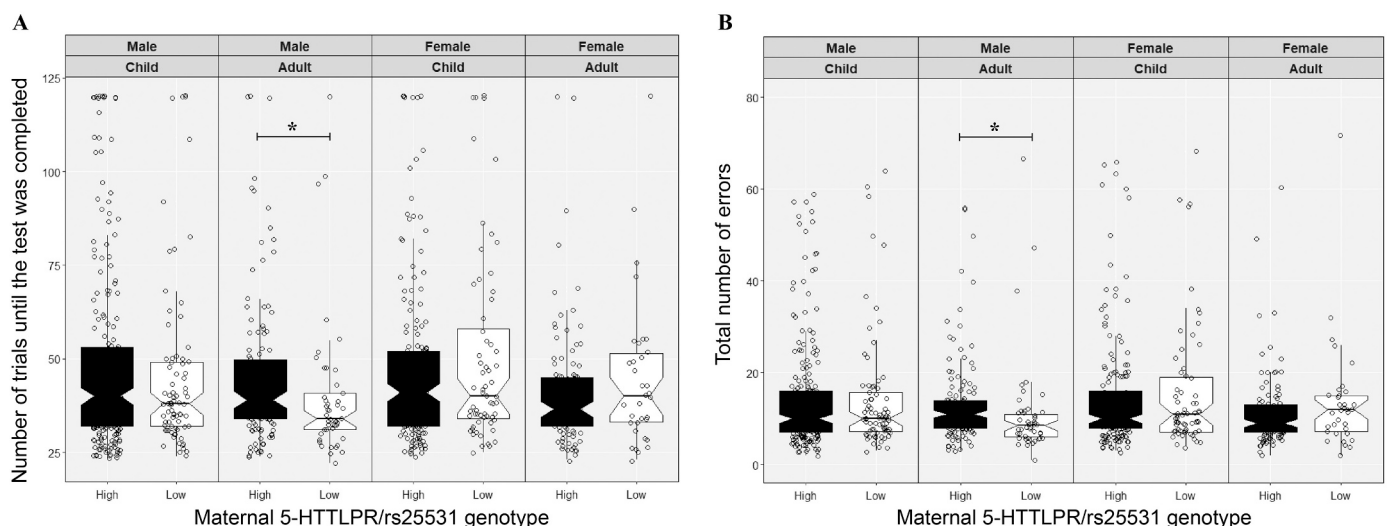

Fig. 2. Maternal 5-HTTLPR/rs25531 genotype is associated with deficits in cognitive flexibility. A) Adult male offspring from mothers with low-expressing 5-HTTLPR genotypes completed the reversal learning task faster and B) with less errors in comparison to adult male offspring from mothers with high-expressing genotypes, independent of offsprings' anxiety levels (with anxiety trials $p = 0.02$, errors $p = 0.01$). Maternal high-expressing 5-HTTLPR genotypes include L_AL_A and L_AS (black box), while maternal low-expressing 5-HTTLPR genotypes include SS, L_GS, L_GL_G, and L_AL_G (white box). The box indicates the interquartile range and the whiskers show 95% confidence interval. *: sensitivity and post hoc tests p-value ≤ 0.05.

3.4.4. Association of maternal 5-HTTLPR genotype with offsprings' motor control

Offsprings' visuomotor control stability and precision were tested with and without continuous adaptation, using the tracking and pursuit tasks, respectively. 5-HTTLPR genotype of the main predictor, the mother, was not associated with variations in visuomotor control, nor were the genotypes of the father and child. Parental genotype did not interact with offsprings' sex and/or age group (see Supplementary Materials Table 7).

3.4.5. Association of maternal 5-HTTLPR genotype with offsprings' emotion recognition

Offsprings' accuracy and speed in recognizing happy faces during the "identification of facial emotions task" might be dependent on the maternal 5-HTTLPR genotype (see Supplementary Materials Table 8). Offsprings' accuracy in recognizing happy faces was significantly predicted by the maternal 5-HTTLPR genotype interaction with offsprings' sex ($p = 0.006$). The maternal genotype interaction with the sex and age

group of the offspring was included in the prediction model as well, but did nog survive FDR-correction ($p = 0.02$). Together these factors predicted offsprings' accuracy in recognizing happy faces with a low proportion of variance explained ($r^2 = 0.02$). When including offsprings' anxiety levels as sensitivity covariate, both maternal genotype interactions became significant (maternal 5-HTTLPR genotype x offsprings' sex $p = 0.008$ and maternal 5-HTTLPR genotype x offsprings' sex x offsprings' age group $p = 0.005$, $r^2 = 0.02$). This shows the robustness of the association between the variable "offsprings' accuracy in recognizing happy faces" and the maternal genotype by offsprings' sex interaction. In addition, this sensitivity analysis indicated a potential stronger association with the maternal genotype by offsprings' sex by age group interaction than the maternal genotype by offsprings' sex interaction. Offsprings' anxiety levels did not significantly predict offsprings' accuracy in recognizing happy faces. Exploring the findings of the sensitivity analysis further, post hoc analyses were performed investigating maternal genotype interaction with offsprings' sex and age group. Results showed that girls from mothers with low-expressing 5-
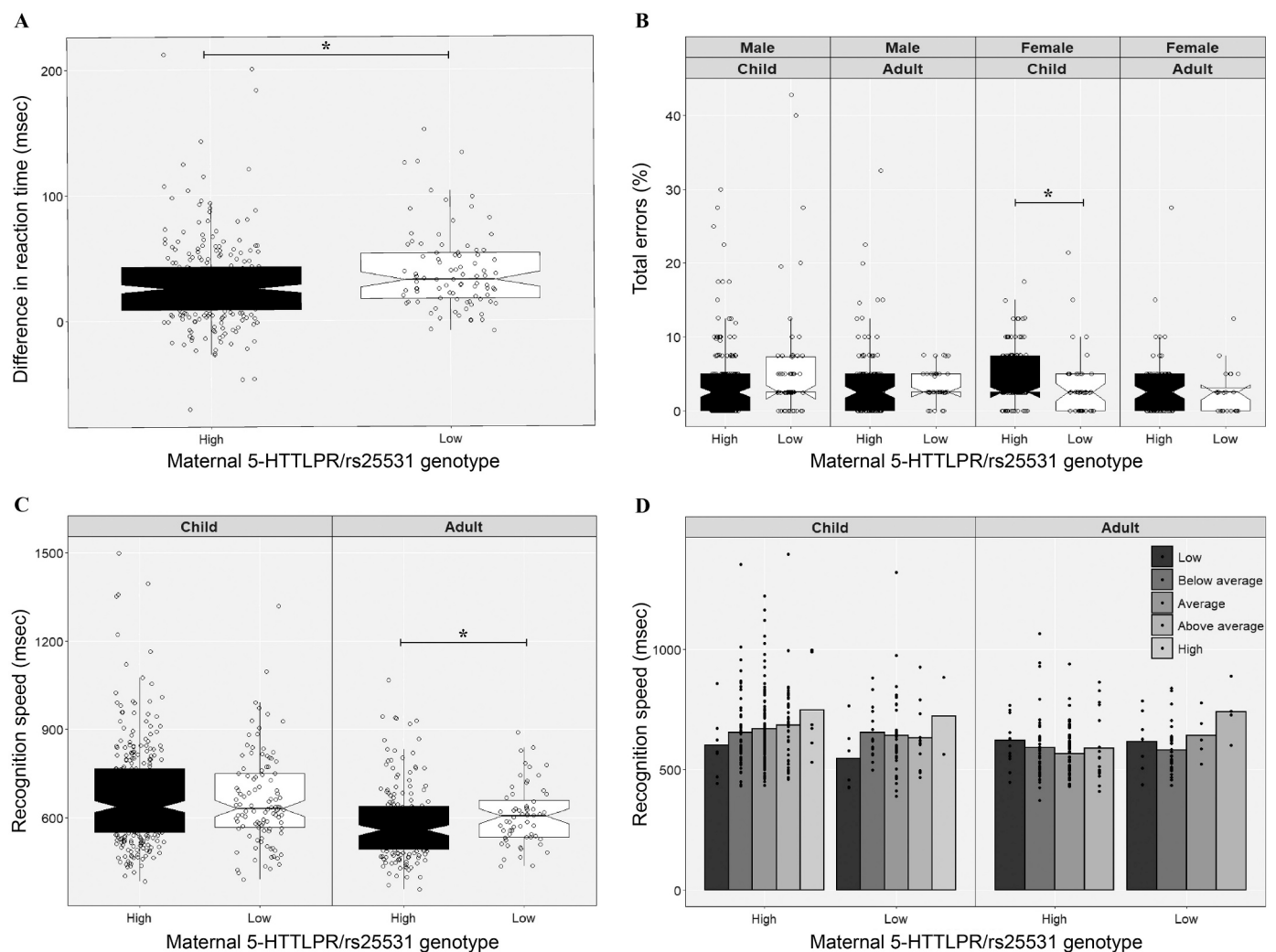

Fig. 3. Maternal 5-HTTLPR/rs25531 genotype is associated with deficits in reward processing and recognizing happy faces. A) Offspring from mothers with low-expressing 5-HTTLPR genotypes responded more dissimilarly to a rewarded target versus a neutral target than offspring from mothers with high-expressing genotypes. Including offsprings' anxiety levels as covariate did not influence this association (with anxiety $p = 0.03$). B) Girls from mothers with low-expressing 5-HTTLPR genotypes showed an increased accuracy when recognizing happy faces in comparison to girls from mothers with high-expressing genotypes, mostly independent of offsprings' anxiety levels (with anxiety $p = 0.04$). C) Adult offspring from mothers with low-expressing 5-HTTLPR genotypes recognized happy faces at a slower rate in comparison to adult offspring from mothers with high-expressing genotypes (without anxiety $p = 0.05$). D) However, this effect disappeared when adding the sensitivity covariate offsprings' anxiety levels. Maternal high-expressing 5-HTTLPR genotypes include L_AL_A and L_AS (black box), while maternal low-expressing 5-HTTLPR genotypes include SS, L_GS, L_GL_G, and L_AL_G (white box).The box indicates the interquartile range and the whiskers show 95% confidence interval. *: sensitivity and post hoc tests *p*-value ≤ 0.05; %: percentage; msec: millisecond.

HTTLPR genotypes reported an increased accuracy in recognizing happy faces in comparison to girls from mothers with high-expressing genotypes ($p = 0.03$, $r^2 = 0.03$). This outcome was supported by the sensitivity analysis regarding offsprings' anxiety ($p = 0.04$, $r^2 = 0.03$) (Fig. 3B). Offsprings' recognition speed was marginally predicted by the interaction between the maternal 5-HTTLPR genotype and offsprings' age group ($p = 0.01$, $r^2 = 0.06$). Sensitivity analysis, including offsprings' anxiety levels as covariate, supported this main finding as the offsprings' recognition speed of happy faces was significantly predicted by the maternal genotype-offsprings' age-interaction ($p < 0.0001$, $r^2 = 0.05$). Offsprings' anxiety score significantly predicted offsprings' recognition speed of happy faces as well ($p = 0.03$, $r^2 = 0.01$). Post hoc analyses revealed that adult offspring from mothers with low-expressing 5-HTTLPR genotypes reported slower recognition times in comparison to adult offspring from mothers with high-expressing genotypes ($p = 0.05$, $r^2 = 0.01$) (Fig. 3C). However, sensitivity analysis refuted this finding as this association disappeared when including the sensitivity covariate offsprings' anxiety levels (Fig. 3D). Offsprings' accuracy and speed in recognizing angry and fearful faces were not associated with their own 5-HTTLPR genotype or that of their mothers and fathers.

4. Discussion

Using a well-characterized sample of parents and their 6- to 31-year-old male and female offspring with and without ADHD, we explored whether maternal 5-HTTLPR genotype would be associated with offsprings' clinical measures of ADHD and comorbid ASD traits and associated cognitive problems beyond classical inheritance and environmental- and comorbidity-mediating/confounding effects. While we found only a single association with offsprings' ASD traits, we found some associations with cognitive measures that are related to ADHD and ASD. More specifically, we found some indications suggesting that offspring from mothers with low-expressing 5-HTTLPR genotypes demonstrate marginally higher stereotypic scores (specifically females), report larger reward-related reductions in reaction time, are more rapid and accurate in reversing their behavior (specifically adult males), and are more accurate in identifying happy faces (specifically young females) than offspring from mothers with high-expressing genotypes. As offspring from mothers with low-expressing 5-HTTLPR genotypes (i.e. SS, L_GS, L_GL_G, L_AL_G) demonstrated lower anxiety levels in comparison to offspring from mothers with high-expressing genotypes (i.e. L_AL_A, L_AS), offsprings' anxiety was taken into account as potential mediator. Indeed, the observed slower identification of happy faces in adult offspring from mothers with low-expressing 5-HTTLPR genotypes seemed to be mediated by offsprings' high anxiety levels. No maternal genotype associations were found when investigating recognition of angry and fearful emotions, motor control, response inhibition, and sustained attention. Notably, most of the associations found had a small proportion of explained variance, and thus clinical relevance is probably low. Overall, these findings illustrate that offsprings' sex, age, and anxiety levels influence maternal 5-HTTLPR genotype effects on offsprings' clinical and cognitive measures of ADHD and ASD. Furthermore, these data may suggest that offsprings' cognitive measures are more sensitive to small alterations within the maternal 5-HT system than their ADHD and ASD clinical phenotypes.

Our findings regarding offsprings' ADHD phenotypes are consistent with earlier research showing that maternal 5-HTTLPR genotype did not affect auditory attention and response set behaviors (van der Knaap et al., 2014). However, we were not able to replicate the findings of an altered fine motor precision in a visuomotor task without continuous adaptation reported by these authors (van der Knaap et al., 2014). Even though we found no associations with ADHD symptoms, maternal 5-HTTLPR genotype was related to reward-related reductions similar to reward-related reductions seen in participants with ADHD versus controls (von Rhein et al., 2015a). Noteworthy, the study of Von Rhein et al. (2015a) used a strongly overlapping sample from the NeuroIMAGE

cohort. Importantly, rare mutations resulting in an impaired maternal 5-HT production, instead of the common 5-HTTLPR polymorphism were associated with ADHD symptoms in adult male offspring (Halmoy et al., 2010).

Our findings regarding offsprings' ASD phenotypes are not in line with an earlier study that demonstrated an association between presence of the maternal 5-HTTLPR L-allele and offspring ASD diagnosis (Kistner-Griffin et al., 2011). Interestingly, our association with stereotyped behavior and theirs with ASD diagnosis were both mostly seen in female offspring. Noteworthy, in our study increased stereotyped behavior was associated with low- instead of high-expressing 5-HTTLPR genotypes. Furthermore, the rate of stereotyped behavior in girls was very low with more than half of all females reporting a stereotyped behavior score of 0. In view of the hypothesis of Happe and Ronald (2008) that distinct genetic influences underlie different aspects of ASD, it might be expected that we only found an association with stereotyped behavior. Consistently, Montgomery et al. (2018) found an association between highly restricted and repetitive behavior in the offspring and low maternal whole blood 5-HT levels. Our reversal learning findings may support the maternal 5-HTTLPR L-allele induced risk for offsprings' ASD found by Kistner-Griffin et al. (2011). While ASD and ADHD are characterized by reductions in cognitive flexibility, our findings reported improvements in reversal learning of adult males from mothers with low-expressing 5-HTTLPR genotypes (see review Rommelse et al., 2011). Regarding the ASD social subdomain, our "happy face recognition" findings may suggest that the maternal 5-HTTLPR genotype might be able to have a small indirect effect. Slower and less accurate identification of emotional states have been seen in participants with ASD, especially in cases of ASD and ADHD comorbidity (Oerlemans et al., 2014). Our findings, therefore, suggest an association between maternal low-expressing 5-HTTLPR genotypes and girls' increased accuracy of recognizing happy faces. In contrast, adult offspring of these mothers with low-expressing 5-HTTLPR genotypes who reported high anxiety levels, demonstrated slower recognition times of happy faces. Consistently, an earlier IMAGE study reported an association between slower response speed to external cues and self-reported anxiety in ADHD participants (Bloemsma et al., 2013).

The difference in offsprings' total ASD trait scores found between the paternal 5-HTTLPR expressing groups (section 3.1), might be related to group differences in paternal PEE. That is, offspring from fathers with low-expressing 5-HTTLPR genotypes were exposed to lower paternal PEE scores, and thus exposed to more warmth and less criticism, than offspring from fathers with high-expressing genotypes ($p = 0.05$; data not shown). This might indicate a role for more positive paternal parenting to the reported lower total ASD trait scores in offspring from fathers with low-expressing 5-HTTLPR genotypes. In support, girls from fathers with low-expressing 5-HTTLPR genotypes showed a tendency towards lower inattentive behavior in the stop signal task (although adult females showed opposite effects). Including paternal PEE as sensitivity covariate diminished these associations, but did not function as predictor of offspring behavior itself (data not shown). No paternal 5-HTTLPR expressing group differences were found regarding SES, paternal ADHD, and offsprings' psychoactive medication intake and perceived stress (data not shown). Recent publications have suggested that a higher paternal age is associated with an increased risk for ASD, potentially via changes in sperm (Breuss et al., 2020; Oldereid et al., 2018). However, paternal and maternal age did not differ between the paternal as well as maternal 5-HTTLPR genotype groups (data not shown).

Our findings are in line with the idea that the maternal 5-HT system, potentially through neurotrophic mechanisms, contribute to offsprings' neurodevelopment and the aforementioned altered behavior. In typically-developing participants as well as participants with ASD, 5-HT platelet up-take and storage have been reported to be influenced by 5-HTTLPR genotypes (Anderson et al., 2002; Coutinho et al., 2004; Coutinho et al., 2007; Greenberg et al., 1999; Jaiswal et al., 2015).

Consequently, maternal 5-HTT mRNA related to low-expressing 5-HTTLPR genotypes might result in lower platelet 5-HT levels that may lead to lower placental and fetal forebrain 5-HT levels (Kliman et al., 2018). Notably, other studies reported a lack of a functional relationship between 5-HTTLPR and platelet 5-HT concentration (Betancur et al., 2002; Cross et al., 2008; Pivac et al., 2009). Other researchers have suggested a role for the maternal 5-HTT in placental metabolic and innate immune system pathways (Muller et al., 2016a). These pathways may indirectly alter placental 5-HT homeostasis and in turn, fetal forebrain 5-HT levels (Muller et al., 2016a). Future studies will be necessary to investigate through which of these proposed mechanisms (i.e. altered maternal platelet 5-HT content versus altered placental 5-HT synthesis) maternal 5-HTTLPR genotype influences fetal forebrain 5-HT levels and whether these mechanisms act in parallel. Furthermore, future studies should include 5-HT-related neurotrophic processes to test for causality to confirm our current exploratory associations.

When interpreting the discussed findings certain strengths and limitations need to be considered. An important strength is that multiple controls were implemented to adjust for potential transmission of 5-HTTLPR risk alleles and potential environmental and comorbidity mediators/confounders. Another strength is that we studied maternal 5-HTTLPR genotype influence on multiple clinical and cognitive ADHD- and ASD-related domains. Hereby we provide a comprehensive overview on if and how maternal 5-HTTLPR genotype plays a role in offspring's ADHD- and ASD-related behaviors. Of note, as each domain can independently be influenced by maternal 5-HTTLPR genotype the FDR-correction was performed for each domain separately. When performing an FDR-correction for all 25 subtests together, the variable "offsprings' accuracy in recognizing happy faces" was predicted by the maternal genotype by offsprings' sex interaction at an FDR of 20%. The variables stereotyped behavior, "offsprings' difference in reaction time between the rewarded and neutral trials", and "offsprings' speed in recognizing happy faces" were predicted by a main/interactive effect of the maternal 5-HTTLPR genotype at an FDR of 30%. A limitation of our study is that we investigated potential associations only from one common 5-HTTLPR polymorphism. Future studies, combining our 5-HTTLPR effects with (potential) effects of other genetic variants, may reveal the full consequence of maternal 5-HT genotype on offsprings' cognition and phenotypes characterizing ADHD and ASD (Bralten et al., 2013). Other limitations relate to the (Neuro)IMAGE inclusion/exclusion criteria. Participants were of European Caucasian descent, were typical-developing or diagnosed with the combined type of ADHD and were excluded when diagnosed with ASD. These study criteria may limit us in generalizing our findings to other communities; i.e. ethnicities, severe ASD cases, and inattentive and hyperactive/impulsive subtypes of ADHD. However, we believe that our findings are still of importance as in general ADHD and ASD symptoms have been considered to be continuous traits (Bralten et al., 2018; Larsson et al., 2012; Spiker et al., 2002). Notably, consistent with our findings, Kistner-Griffin et al. (2011) only found an association between offspring 5-HTTLPR genotype and ASD diagnosis in the Non-European ancestry cohort but not in the European ancestry cohort. While we controlled for multiple potentially mediating factors, we cannot preclude the influence of other potential factors such as prenatal stress (Hecht et al., 2016) and pregnancy and delivery complications (Brinksma et al., 2017). Inconsistent with earlier findings, maternal expressed emotion was similar between the two maternal genotype groups (Bakermans-Kranenburg and van Ijzendoorn, 2008; Cents et al., 2014; Mileva-Seitz et al., 2011; Morgan et al., 2018).

In sum, our findings are in line with the idea that effects due to the maternal 5-HTTLPR genotype are not explicitly driven by relatedness nor by environmental or comorbidity mediators/confounders. In line with the 5-HT neurotrophic hypothesis, maternal 5-HTT genotype (but not child 5-HTT genotype) seems to be associated with stereotyped behavior and with cognitive flexibility, reward processing, and emotion recognition that are cognitive measures related to neurodevelopmental disorders, such as ADHD and ASD. However, most of these associations are only visible in specific subgroups (i.e. offsprings' sex, age, anxiety levels). Overall, our exploratory study emphasizes the need for future studies on the relation between the maternal 5-HT genotype and cognitive and behavioral impairments in ADHD and ASD.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

An in-depth description of participants' consent, recruitment, and general testing procedures has been published in the method and design paper of the NeuroIMAGE project (von Rhein et al., 2015b).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2021.110354.

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