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ORIGINAL PAPER

Children's ADHD and Dysregulation Problems, DAT1 Genotype and Methylation, and their Interplay with Family Environment

Eleonora Marzilli[1] · Luca Cerniglia[2] · Renata Tambelli[1] · Silvia Cimino[1]

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Abstract

Background International literature has underlined the complex interplay between genetic and environmental variables in shaping children's emotional-behavioral functioning.

Objective This study aimed to explore the dynamic relationship between children's Dopamine Transporter (DAT1) genotype and methylation, and maternal and paternal affective environment, on children's Attention Deficit Hyperactivity Disorder (ADHD) problems and dysregulation problems.

Method In a community sample of 76 families with school-aged children, we assessed children's DAT1 genotype and methylation, their own ADHD problems and dysregulation profile (CBCL 6–18 DP), and maternal and paternal psychopathological risk, parenting stress, and marital adjustment. Hierarchical regressions were carried out to verify the possible moderation of children's genotype on the relationship between children's methylation and psychopathological risk, parental environment and children's methylation, and parental environment and children's psychopathological risk.

Results The levels of methylation at M1 CpG significantly predicted ADHD problems among children with 10/10 genotype, whereas high levels of methylation at M6 CpG predicted low ADHD problems for children with 9/x genotype. High levels of methylation at M3 CpG were associated with high scores of CBCL DP. DAT1 genotype moderated the relationship between maternal and paternal variables with children's methylation and psychopathological risk. The scores of maternal and paternal Dyadic Adjustment Scale showed indirect effects on children's methylation and psychopathological risk in relation to those exerted by risk factors.

Conclusion Our study has supported the emerging evidence on the complex nature of children's emotional-behavioral functioning and the associated risk and protective factors, with important implications for the planning of preventive programs.

Keywords DAT1 · Genotype · Methylation · ADHD · Dysregulation

✉ Eleonora Marzilli
Eleonora.marzilli@uniroma1.it

[1] Department of Dynamic and Clinical Psychology, Sapienza, Via degli Apuli 1, 00185 Rome, Italy

[2] Faculty of Psychology, International Telematic University Uninettuno, Corso Vittorio Emanuele II, 39, 00136 Rome, Italy

Introduction

A growing body of research has evidenced the importance to consider the complex interplay between genetic and environmental influences for a better understanding of the etiopathogenesis related to psychopathological risk among middle childhood (Li et al., 2017). Indeed, children's inherited genetic variations may confer an increased vulnerability and/or resiliency to emotional-behavioral difficulties both directly (Brikell et al., 2020) and indirectly (Hettema et al., 2015), especially through their interaction with family environmental exposures (Ahmadzadeh et al., 2019). Interestingly, individual genetic disposition and environmental exposure may also lead to epigenetic changes of DNA, which alter the gene expression and the resulting long-term effects on children's emotional-behavioral functioning (Barker et al., 2018; O'Donnell & Meaney, 2020). In particular, clinicians and researchers rooted in the Developmental Psychopathology theoretical framework have posited that genetic and epigenetic factors can mitigate or increase the impact of environmental influences in that sequence of events defined as "developmental cascades" (Cicchetti & Curtis, 2007), which refers to the effects of different levels of functioning or domains that mutually influence each other in shaping the course of ontogenesis and epigenesis (Masten & Cicchetti, 2010).

The Role of Dopamine Transporter Gene

The expression of genes involved in dopaminergic neurotransmission represents one of the main candidate genes studied in this field, due to the central role of dopamine (DA) in the regulation of mood (Radwan et al., 2019), cognition (Juarez et al., 2019), and reward-motivated behavior (Bromberg-Martin et al., 2010). Some regions that are primarily engaged in the brain's reward and emotional circuits (e.g., parietal and frontal lobes) are subject to numerous changes after the first 5 years of life (Mills et al., 2014). Furthermore, the key role played by DA in affiliation behaviors and exploration of the world in search of hedonic stimuli (Deyoung, 2013), further supported the importance of focusing attention on the possible dopaminergic dysregulation in studying psychopathological risk among middle-childhood. The availability of DA at the synaptic level is primarily regulated by the gene that encodes for its transporter, a protein known as dopamine active transporter (DAT), which reuptakes DA at the level of the pre-synaptic terminals (Tatsch & Poepperl, 2013). The three prime untranslated region (3'-UTR) of the DAT1 gene has a polymorphic 40 base pair variable number of tandem repetitions (VNTR) sequence, which can be repeated from 3 to 11 times (Vandenbergh et al., 1992). However, the 9- or 10-tandem repeats represent the most frequent polymorphisms (Faraone et al., 2014). Interestingly, some studies have suggested that genetic variations of the DAT1 can have a functional effect on the DAT1 expression (Wonodi et al., 2009), and a subsequent alteration of DA synaptic availability (Faraone et al., 2014). Coherently, genetic studies have found significant associations between children's DAT1 genotype and psychiatric disorders commonly related to a DA imbalance in the brain—especially Attention deficit hyperactivity disorder (ADHD) (Adriani et al., 2018; Mick et al., 2008; Tonelli et al., 2020). Regarding the specific children's DAT1 genotype associated with worse psychopathological outcomes, from the pioneering study by Cook et al. (1995) on a sample of ADHD children, a greater symptomatic severity in children carrying the 10/10 genotype has been reported in further studies (Adriani et al., 2018; Faraone et al., 2014; Grünblatt et al., 2019). Significant associations for other

psychiatric diagnoses were also found (Guo et al., 2007; Mick et al., 2008). However, other studies have evidenced higher psychopathological symptoms among children with at least one 9-repeat allele (Joyce et al., 2009; Li & Lee, 2013), showing that the current literature in this field is still inconsistent. The research on community samples of children is also increasing, showing significant associations with both internalizing and externalizing difficulties (e.g., withdrawal, effortful control, and aggressive behaviors; Davies et al., 2015; Hayden et al., 2013; Lahey et al., 2011), and phenomena of hyperactivity, impulsivity, and inattentiveness (Akutagava-Martins et al., 2016; Cornish et al., 2005). However, to our knowledge, no studies have examined the possible role played by school-aged children's DAT1 genotype on children's Dysregulation Profile (DP), an empirically based dysregulation profile characterized by the co-occurrence of internalizing and externalizing problems (Cianchetti, 2020), and associated with major psychopathology over time (Deutz et al., 2020).

DAT1 and Its Interplay with the Family Environment

The research in the field of gene-environment interaction (GxE) has suggested that children's DAT1 genotype may also affect the degree of individual's susceptibility to both positive and negative environmental exposure, evidencing an interactive effect mainly with the quality of maternal parenting (Hayden et al., 2013; Lahey et al., 2011; Li & Lee, 2013). Only a few studies have also focused on the quality of paternal parenting (Janssens et al., 2017), and parental psychopathological risk (Cimino et al., 2018, 2019). However, to date, no study has considered the possible associations with other contextual factors commonly associated with children's emotional-behavioral functioning [such as the stress perceived by parents in the relationship with their children (Cherry et al., 2019; Lin et al., 2017), and the quality of marital adjustment (Camisasca et al., 2019; Rollè et al., 2017), which may act as an additional risk factor or compensate for a biological-environmental risk profile. However, recent evidence has underlined that the influence of the family environment on children's development, may also be mediated by epigenetic mechanisms (Champagne & Curley, 2009; O'Donnell & Meaney, 2020). The methylation of DNA is the most studied in this context. It may represent a "dynamic signature" of genetic and environmental influences (Schiele & Domschke, 2018), a way through which family adversities can leave an endophenotypic mark (Overbeek et al., 2020). Indeed, although it is potentially heritable, it is influenced by both environmental exposures and individual genotype (Duman & Canli, 2015; Hannon et al., 2018). When methylation is located in a gene promoter, it results in a decreased gene transcription, silencing its expression (Yoo et al., 2016). Although the fifth untranslated promoter region (5'-UTR) of the DAT1 gene is highly susceptible to epigenetic changes, including DNA methylation (Shumay et al., 2010), the research on its possible involvement in children's psychopathological risk is scarce. Most of the studies were focused on clinical samples of children (Cimino et al., 2021; Müller-Vahl et al., 2017), especially affected by ADHD (Ding et al., 2017; Lambacher et al., 2020; Xu et al., 2015), in which a key role played by DAT1 has been evidenced (Wiers et al., 2018; Wiguna et al., 2017). Coherently, significant associations between levels of DAT1 methylation, the severity of symptomatology, and recovery after pharmacological treatment have been shown (Adriani et al., 2018; Ding et al., 2017; Lambacher et al., 2020). The few studies on the general population (Cerniglia et al., 2020; Cimino et al., 2018, 2019; Cimino, Cerniglia, et al., 2020; Lewis et al., 2019) have reported significant associations between children's DAT1 genotype and methylation, and internalizing and externalizing problems,

but focusing exclusively on the influence of parental psychopathological risk (Cerniglia et al., 2020; Cimino et al., 2018, 2019). However, DNA methylation changes are reversible (Ziegler et al., 2016), and highly responsive to both negative and positive environmental exposures (Bowes & Jaffee, 2013; Schiele & Domschke, 2018). This growing evidence lays the foundation on the importance of implementing the research on the role played by DAT1 and their interplay both with environmental risk and protective factors within the family context in shaping the (mal-)adaptive functioning of the child.

The Present Study

Based on a bio-psycho-social model (Calkins et al., 2013) we examined the role played by different variables across multiple domains (from genetic and epigenetic levels to the quality of environment provided by mothers and fathers), and which literature has shown to be commonly associated with children's psychopathological risk (Camisasca et al., 2019; Cerniglia et al., 2017; Middeldorp et al., 2016). Smeekens et al. (2007) have underlined the importance of four specific domains in studying children's psychopathological difficulties: children's variables (e.g., temperament, genetic disposition), parental factors (e.g., personality traits, psychopathological difficulties), factors related to parenting (e.g., the quality of the parent–child relationship, parenting stress), and contextual variables (e.g., socio-economic status, the quality of couple relationship). Coherently, we selected variables afferent from these domains, including: children's DAT1 genotype and methylation (children's variables), mothers' and fathers' psychopathological risk (parental factors), parenting stress perceived by parents in the relationship of their children (parenting factors), and the quality of dyadic adjustment (contextual variable). Specifically, we explored the possible relationship between children's ADHD problems and emotional-behavioral dysregulation, children's DAT1 methylation, and affective environment provided by mothers and fathers, considering the moderation role played by children's DAT1 genotype. We hypothesized that: (a) children's ADHD and DP symptoms are associated with the levels of children's DAT1 methylation at specific CpG sites, and that children's DAT1 genotype would moderate these relationships. We hypothesized that parental variables would show associations with the same CpG sites associated with children's emotional-behavioral functioning; (b) the quality of the environment provided by parents would demonstrate a relationship with children's DAT1 methylation, and that this relationship is moderated by children's DAT1 genotype. We hypothesized to find different relationships in response to the maternal and paternal environment; and (c) there would be relationships with maternal and paternal variables in predicting children's ADHD and DP symptoms, with children's DAT1 genotype again moderating the relationship.

Methods

Participants

In collaboration with both public and private primary schools of Central Italy, we recruited 161 families of the general population, with children aged from 6 to 11 years. In the case of multiple children, parents were asked to report on one child only. For the aims of this study, we excluded families in which: one and/or both parents were not biological (n = 8); parents were separated and/or not living together (n = 15); parents and/or children had psychical

and/or mental disorders (n = 12) and/or were under pharmacological or psychological treatment (n = 14); mothers and/or fathers did not complete all the questionnaires (n = 9); children's biological samples could not be collected (n = 12); mothers and/or fathers refused to participate in this study (n = 15). The final sample included 76 children (40 males and 36 females; mean age = 7.76; SD = 1.56), their mothers (mean age = 41.1; SD = 4.31), and fathers (mean age = 44.08; SD = 4.79). Almost all of the families recruited (91.3%) had a middle-high socioeconomic status, and most of them had high school or university education (87%). 85.4% of the families were Caucasian, and 86.3% of children were first-borns. Parents gave their written informed consent, which explained the aims and scope of the study and all relative procedures and measures. Children were also orally informed. None of the research participants received monetary compensation for taking part in the study. However, with the parents who requested it, expert psychologists reporting on what emerged in their family conducted clinical interviews. This study was approved before its start by the Ethical Committee of the Department of Dynamic and Clinical Psychology at Sapienza, University of Rome (protocol number 27/2016), in accordance with the Declaration of Helsinki.

Procedure

Primarily, parents were informed that their children were not allowed to eat (including sweets, chewing gum, etc.), consume any drinks other than water, or brush teeth at least 1 h before children's biological samples collection. Children's biological samples, consisting of buccal salivary swabs, were collected at children's schools. Once collected, the buccal swabs were chilled by normal ice (+4°). Then, on the same day, mothers and fathers (separately) filled out self-report and report-form questionnaires (described below), for the assessment of children's ADHD and emotional-behavioral dysregulation problems, their own psychopathological risk, parenting stress perceived in the relationship with their children, and the perceived quality of couple adjustment. All parents filled out the pen-and-paper questionnaires in the presence of expert psychologists inside a room made available by the children's schools. The order of administration of these tools was randomized.

Measures

To assess children's ADHD and emotional-behavioral dysregulation problems, mothers and fathers (separately) filled out the *Child Behavior Check-List/6–18* (CBCL/6–18; Achenbach & Rescorla, 2001; Italian validation, Frigerio et al., 2004), a 113-item report-form questionnaire through which the parent is asked to answer on a three-point Likert scale (from 0 = "not true" to 2 = "very true or often true") to rate specific emotional/behavioral problems of their child during the past 6 months. Items could be grouped in six DSM-5-oriented scales (Depressive Problems, Anxiety Problems, Somatic Problems, Attention-Deficit/Hyperactivity Problems, Oppositional Defiant Problems, and Conduct Problems) and/or in eight empirically-based syndrome scales (Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Rule-Breaking Behavior, and Aggressive Behavior). The CBCL DP scores were obtained by the sum of the items of the syndrome scales Anxious/Depressed, Attention Problems, and Aggressive Behavior (Basten et al., 2013). For the aims of this study, we used the mean scores reported by mothers and fathers of the DSM-5-oriented ADHD Problems scale and CBCL DP. In this study, the internal consistency of the two scales was, respectively,

acceptable (*ADHD Problems*, Cronbach alpha = 0.77, ICC = 0.88, 95% CI 0.8–-0.96) and good (*Dysregulation Profile*, Cronbach alpha = 0.87, ICC = 0.97, 95% CI 0.95–0.99). To evaluate parental psychopathological risk, the *Symptom Check-List-90 item-Revised* (SCL-90-R; Derogatis, 1983; Italian validation, Prunas et al., 2012) was administered. The SCL-90-R is a 90-item self-report questionnaire widely used for screening and for assessment of psychological symptoms in adults of both clinical and general populations. Items are rated on a Likert scale of 0 (not at all) to 4 (extremely), which composed the nine primary dimensions of the SCL-90-R (Somatization, Obsessive-Compulsivity, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism). However, through this instrument, it is possible to obtain an overall score—the Global Severity Index (GSI)—which allows providing the severity and degree of psychological distress. For the aim of this study, we used maternal and paternal scores of GSI. The Italian validation (Prunas et al., 2012) showed adequate to excellent reliability in terms of internal consistency (Cronbach's alpha = 0.70–0.96). In this study, the internal consistency of GSI was also acceptable (*GSI mother,* Cronbach alpha = 0.73, ICC = 0.76, 95% CI 0.53–0.88) and good (*GSI father,* Cronbach alpha = 0.84, ICC = 0.88, 95% CI 0.56–0.95). For the assessment of maternal and paternal stress experienced in the relationship with their children, mothers and fathers filled out the *Parenting Stress Index-Short Form* (PSI-SF; Abidin, 1990; Italian validation—Guarino et al., 2008). It is a self-report screening questionnaire used to assess parental stress in three specific domains of stress related to parenting system (Parental Distress, deriving from personal factors directly related to parental role; Difficult Child, relating to child's characteristics, and Parent–Child Dysfunctional Interaction, related to the stress deriving from their interactions with children). The short form of the questionnaire (used in this study) is composed of 36 items evaluated on a scale of 1 (strongly agree) to 5 (strongly disagree). For the aims of this study, we used maternal and paternal scores of Parent–Child Dysfunctional Interaction (P–CDI) scale, which is focused on the fact that the parent perceives the child as not meeting their expectations and that the interactions with the child do not strengthen them as a parent. The scale showed good internal consistency in this study for both mothers (*P-CDI mother,* Cronbach alpha = 0.81, ICC = 0.82, 95% CI 0.76–0.91) and fathers (*P-CDI father,* Cronbach alpha = 0.83, ICC = 0.88, 95% CI0.81–0.95). Finally, to evaluate marital relationship adjustment, the *Dyadic Adjustment Scale* (DAS, Spanier, 1976; Italian validation, Gentili et al., 2002) was administered to mothers and fathers (separately). The Dyadic Adjustment Scale (DAS) is a 32-item self-report measure to assess the relationship quality of intact (married or cohabiting) couples, and it is composed of varying response scales, including ordinal, Likert, and dichotomous scales. The 32 items consist of questions and statements related to activities, behaviors, attitudes, and feelings, frequent in a couple's life. The scores were summed to create a total score ranging from 0 to 151, with higher scores indicating more positive dyadic adjustment. In this study, the DAS internal coherence was adequate (*DAS mother,* Cronbach alpha = 0.75, ICC = 0.76, 95% CI 0.53–0.88) and good (*DAS father,* Cronbach alpha = 0.83, ICC = 0.85, 95% CI 0.56–0.95).

DNA Isolation and Genotyping

DNA extraction from the buccal wall cells was performed using the Buccal-Prep Plus DNA isolation (Isohelix), following the manufacturer's instructions. The DAT1 polymorphism was determined by amplifying the repeated sequence of the 3'-untranslated (3′-UTR) region, by the polymerase chain reaction (PCR) technique (Adriani et al.,

2018). Allelic distributions were calculated through chi-square analyses (Ledwina & Gnot, 1980) and were consistent with Hardy–Weinberg equilibrium ($\chi^2_1 = 0.07$, $p = .79$). Given the relative rarity of 9-repeat homozygotes (i.e., n = 11 children), 9-repeat homozygotes and 9-repeat heterozygotes were grouped as 9/x carriers and contrasted with 10-repeat homozygotes, as been done by previous studies in the field of developmental psychopathology (Adriani et al., 2018; Carpentieri et al., 2021; Cimino et al., 2019; Cimino, Marzilli, et al., 2020; Hayden et al., 2013; Li & Lee, 2012, 2013). Table 1 shows descriptive statistics of the variables under study among the two genotype groups.

Analysis of DNA Methylation

The DNA extracted from the buccal swabs was further processed to evaluate the amount of methylation in the 5′-UTR sequence of DAT. The amount of methylation was determined in six specific CpG sites (named M1, M2, M3, M5, M6, and M7). The following primers (5′–3′) were used to amplify the gene: Fwd, AGCTACCATGCCCATCCCTA TGTGGG; Rev, TCAGCACTCCAACCCAACCCAAC. The DNA was amplified with the PyroMark PCR kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol, which calculates the methylation percentage [mC/(mC + C)] for each CpG site, allowing quantitative comparisons (mC is the methylated cytosine and C is unmethylated cytosine). The PCR conditions were as follows: 95 °C for 15 min, followed by 45 cycles of 94 °C for 30 s, 56 °C for 30 s, 72 °C for 30 s and 72 °C for 10 min. PCR products were verified by agarose electrophoresis.

Table 1 Means and standard deviation of the study variables among the two genotype groups

		9/x M (SD)	10/10 M (SD)
DAT1 CpG site	M1	5.31 (1.90)	5.87 (2.22)
	M2	3.51 (2.13)	4.23 (2.90)
	M3	4.77 (3.72)	5.94 (4.83)
	M5	10.40 (5.56)	12.10 (7.52)
	M6	6.96 (3.49)	6.67 (4.43)
	M7	6.16 (2.09)	5.73 (1.92)
CBCL 6/18	ADHD	4.22 (3.19)	4.15 (4.04)
	Dysregulation profile	11.94 (8.91)	11.74 (7.58)
SCL-90/R	GSI mothers	.30 (.25)	.42 (.37)
	GSI fathers	.46 (.29)	.25 (.27)
PSI	P-CDI mothers	22.97 (8.51)	21.89 (6.40)
	P-CDI fathers	22.74 (6.40)	22.06 (7.06)
DAS	DAS total mothers	116.20 (16.82)	119.79 (15.21)
	DAS total fathers	122.45 (17.12)	116.51 (19.52)

CBCL/6–18 child behavior check-list/6–18, *SCL-90/R* symptom check-list-90 item-revised, *GSI* global severity index of SCL-90/R, *PSI* parenting stress index-short form, *P–CDI* parent–child dysfunctional interaction scale of PSI, *DAS* dyadic adjustment scale, *DAS Total* total score of DAS

Statistical Analyses

Preliminary analyses were performed using descriptive statistics (frequencies, percentages, and mean scores). To verify the presence of associations between children's DAT1 methylation, their own emotional-behavioral problems, and parental environmental variables, we carried out Pearson correlation analyses considering the levels of children's DAT1 methylation at all six-CpGs (i.e., M1, M2, M3, M5, M6, and M7), the CBCL/6–18 scores of the ADHD DSM-oriented and DP, and maternal and paternal scores of GSI/SCL-90/R, P-CDI/PSI, and the total dimension of DAS. Any CpG sites that demonstrated a significant association with ADHD and/or DP were further explored in a hierarchical regression, performed to verify whether children's DAT1 genotype moderated the relationship between children's DAT1 methylation levels and, respectively, children's ADHD problems and DP. In Step 1, children's DAT1 genotype and DAT1 methylation levels were entered as independent variables, while scores from the CBCL-6/18 ADHD problems and DP were separately entered as dependent variables in the respective regression analyses. In Step 2, we entered the interactions between DAT1 genotype and methylation status at each considered CpGs. Then, to verify whether children's DAT1 genotype moderated the association between maternal and paternal environment and children's DAT1 methylation, we carried out hierarchical regressions, separately for mothers and fathers. In Step 1, children's DAT1 genotype and parental environmental variables (i.e., maternal and paternal score of GSI/SCL-90/R, P-CDI/PSI, and total score of DAS) were entered as independent variables. The levels of children's DAT1 methylations at the same CpGs that we found in association with children's emotional-behavioral problems were entered as dependent variables. In Step 2, we entered the interaction terms between children's DAT1 genotype and all parental environmental variables inserted at Step 1. Then, Pearson correlation analyses between children's DAT1 genotype and all maternal and paternal environmental variables were carried out to verify the possible presence of gene-environment correlations which could confuse the presence of gene-environment interactions. Finally, hierarchical regression analyses were performed to verify the possible moderation role played by children's DAT1 genotype on the relationship between maternal and paternal environmental variables (considered separately) and children's emotional-behavioral functioning. Before performing hierarchical regression analyses, main and interaction terms were centered to minimize multicollinearity. Moderation analyses were conducted through the PROCESS macro for SPSS (Hayes, 2017). We standardized the score of the independent variable before performing the moderation analyses. All analyses were performed with Statistical Package for the Social Sciences, SPSS software, version 25.

Results

Associations Between Children's Methylation and Psychological and Environmental Variables

Results showed that children's ADHD problems were significantly associated with children's methylation at M1 CpG site ($r = 0.34$) and negatively associated with the levels of methylation at M2 ($r = -0.32$) and M6 ($r = -0.26$) CpGs. Children's scores of CBCL Dysregulation Profile (DP) were significantly associated only with the levels of methylation

at M3 CpG site (r = 0.56). Interestingly, the same CpGs that were found associated with children's emotional and behavioral problems, were found to significantly correlate with maternal and paternal environment. Significant associations between both maternal and paternal variables and children's emotional-behavioral functioning were also found (for more detail, see Supplementary Materials).

The Predictive Role of Children's DAT1 Methylation on Their Own ADHD and Dysregulation Problems, Moderated by Children's DAT1 Genotype

Based on previous analyses, we verified the possible moderation role played by children's DAT1 genotype on the relationship between children's ADHD problems and children's DAT1 methylation at M1, M2, and M6 CpGs, and between children's Dysregulation Profile (DP) and children's DAT1 methylation at CpG M3. As possible to see in Table 2, for ADHD problems, results of hierarchical regression analyses showed that, at Step 1, there was a significant positive association with levels of children's DAT1 methylation at M1 ($p < 0.001$), but a negative association with M2 CpG site ($p < 0.01$). The main effect of children's DAT1 genotype was not significant ($p > 0.05$). This model accounted for 24% of the variance. However, in Step 2, children's methylation at M2 ($p < 0.05$) and M6 ($p < 0.05$) CpGs was negatively associated with children's ADHD problems, and there were significant interactions between children's DAT1 genotype and methylation at M1 ($p < 0.001$) and M6 ($p < 0.01$) CpGs, accounting for an additional 32% of the variance.

Moderated effects were evaluated using the PROCESS macro (Hayes, 2017) and reported in Fig. 1.

Specifically, the results showed that DAT1 methylation at M1 CpG site were positively associated with children's ADHD problems among children with 10/10 genotype ($\beta = 3.20$, SE = 0.49, $p < 0.001$). This relation was not significant for children with a 9-repeat allele ($\beta = -0.30$, SE = 0.41, $p = 0.46$) (Fig. 1a). Moreover, high levels of DAT1 methylation at M6 CpG site were associated with low scores of ADHD problems for children with 9/x genotype ($\beta = -1.89$; SE = 0.52, $p < 0.001$), whereas for children with 10/10 genotype this relationship was not significant ($\beta = 0.10$, SE = 0.52, $p = 0.83$) (Fig. 1b). Regarding

Table 2 Results of the hierarchical regression analyses for children's DAT1 methylation predicting children's ADHD problems

	Children's ADHD problems	
	Step 1	Step 2
Predictors	B (SE)	B (SE)
DAT1[a]	.59 (.72)	.71 (.56)
M1	.70 (.16)***	.09 (.17)
M2	− .67 (23)**	− .47 (.22)*
M6	.06 (.14)	− .30 (.12)*
DAT1xM1[a]	–	1.50 (.25)***
DAT1xM2[a]	–	− .59 (.42)
DAT1xM6[a]	–	.85 (.27)**
Adjusted R^2	.24	.57
ΔR^2		.32

[a]Reference group is 9/x genotype

*$p < .05$; **$p < .01$; ***$p < .001$

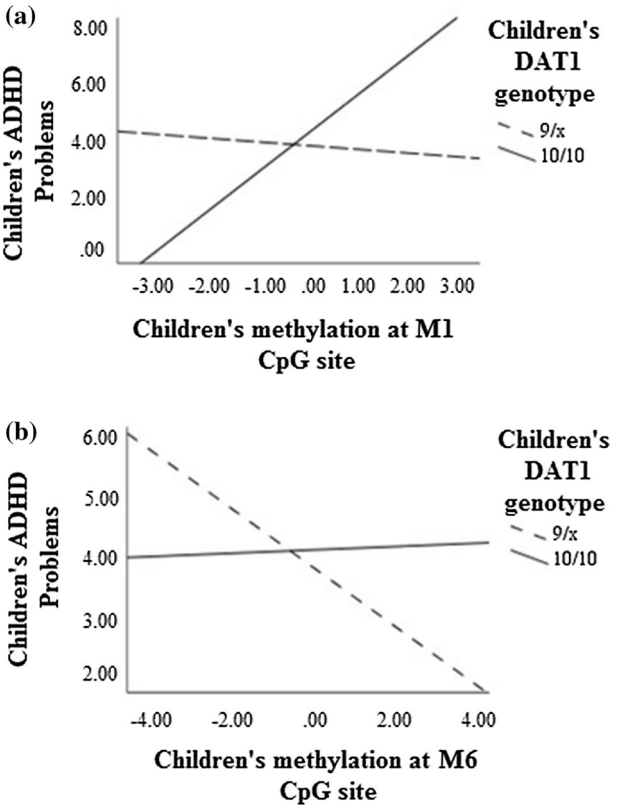

Fig. 1 Conditional line plots showing the moderation of children's DAT1 genotype on the relationship between children's ADHD problems and children's DAT1 methylation. **a** The moderation of children's DAT1 genotype on the relationship between children's ADHD Problems and children's DAT1 methylation at M1 CpG site. **b** The moderation of children's DAT1 genotype on the relationship between children's ADHD Problems and children's DAT1 methylation at M6 CpG site

children's DP, results showed that children's genotype did not have an effect, neither direct nor in interaction with children's methylation, but there was a significant positive association with children's methylation at M3 CpG site, both in Step 1 ($\beta = 1.07$, SE = 0.18, $p < 0.001$) and Step 2 ($\beta = 0.88$, SE = 0.25, $p = 0.01$), accounting for the 30% of the variance.

The Predictive Role of Maternal Affective Environment on Children's DAT1 Methylation, Moderated by Children's DAT1 Genotype

As possible to see in Table 3, children's methylation at M1 CpG site was predicted by maternal psychopathological risk (GSI) both directly ($p < 0.001$) and in interaction with children's DAT1 genotype ($p < 0.01$), explaining the 32% of the variance. The levels of children's methylation at M2 CpG site were positively associated with high levels of maternal dyadic adjustment (DAS) ($p < 0.05$) and with their interaction with children's genotype ($p < 0.01$). This model accounted for 25% of the variance. Children's methylation at M3 CpG site was predicted by maternal stress perceived in the relationship with their children (P-CDI) at Step 1 ($p < 0.05$), but at Step 2, there was a negative significant association with maternal DAS ($p < 0.05$) and a significant interaction between children's genotype and maternal P-CDI ($p < 0.05$), accounting for an additional 12% of the variance (Total variance, 28%). Finally, the levels of children's

Table 3 Results of the hierarchical regression analyses for maternal variables predicting children's DAT1 methylation

Step	Children's DAT1 CpG sites			
	M1	M2	M3	M6
	B(SE)	B(SE)	B(SE)	B(SE)
1				
DAT1[a]	− .32 (.45)	.32 (.57)	1.34 (.97)	− .88 (.91)
GSI	3.52 (.79)***	1.01 (1.1)	− 1.67 (1.70)	1.78 (1.59)
P-CDI	.03 (.04)	− .08 (.05)	.17 (.08)*	− .06 (.08)
DAS	.01 (.01)	.02 (.02)	− .03 (.03)	.06 (.03)
Adjusted R^2	.22	.08	.11	.07
2				
DAT1[a]	− .26 (.42)	.58 (.51)	1.65 (.92)	− .47 (.81)
GSI	.73 (1.17)	.72 (1.42)	− 2.50 (2.53)	− .14 (2.23)
P-CDI	.06 (.04)	− .10 (.05)	.05 (.09)	− .03 (.08)
DAS	.03 (.02)	.05 (.02)*	− .04 (.04)*	.14 (.04)***
DAT1xGSI[a]	4.22 (1.56)**	− 1.38 (1.89)	− 1.29 (3.38)	.53 (2.45)
DAT1xP-CDI[a]	− .06 (.08)	.14 (.10)	.47 (.17)*	.05 (.15)
DAT1xDAS[a]	− .05 (.03)	− .10 (.04)**	− .01 (.07)	− .22 (.06)***
Adjusted R^2	.32	.25	.28	.26
ΔR^2	.12	.19	.12	.21

GSI Global severity index, *P–CDI* parent–child dysfunctional interaction, *DAS* total score of dyadic adjustment scale

[a]Reference group is 9/x genotype

*$p < .05$; **$p < .01$; ***$p < .001$

methylation at M6 CpG site were positively associated with maternal scores of DAS ($p < 0.001$), at Step 2, and with their interaction with children's genotype ($p < 0.001$). This model explained 26% of the variance.

Results of moderation analyses showed that children's methylation at M1 CpG site were significantly positively associated with maternal psychopathological risk among children with 10/10 genotype ($\beta = 1.61$, SE = 0.25, $p < 0.001$). The same association was not significant in the presence of 9/x children's genotype ($\beta = 0.22$, SE = 0.33, $p = 0.50$). For children's methylation at M2 CpG site, there was a positive relationship with maternal perception of dyadic adjustment for children with 9/x genotype ($\beta = 1.44$, SE = 0.29, $p < 0.001$), but not for children with 10/10 genotype ($\beta = 0.82$, SE = 0.41, $p = 0.06$). High levels of methylation at M3 CpG site were positively associated with high levels of maternal stress perceived in the relationship with their children among children with 10/10 genotype ($\beta = 3.53$, SE = 0.80, $p < 0.001$). For children with 9/x genotype the same relationship was not significant ($\beta = 0.65$, SE = 0.51, $p = 0.20$). Finally, among children with 9/x genotype, high levels of methylation at M6 CpG site were associated with high scores of maternal dyadic adjustment ($\beta = 2.54$, SE = 0.45; $p < 0.001$), but among children with 10/10 genotype, with low scores of maternal dyadic adjustment ($\beta = -1.35$, SE = 0.64, $p = 0.03$).

The Predictive Role of Paternal Affective Environment on Children's DAT1 Methylation, Moderated by Children's DAT1 Genotype

Results of hierarchical regression analyses showed that, for children's methylation at M1 CpG site, there was a negative association with paternal dyadic adjustment (DAS) ($p < 0.001$), which also significantly interacted with children's DAT1 genotype ($p < 0.001$) at Step 2, accounting for the 30% of the variance. The levels of children's methylation at M2 CpG site were negatively associated with paternal psychopathological risk (GSI) ($p < 0.01$) and paternal stress perceived in the relationship with their children (P-CDI) ($p < 0.05$) and positively related with paternal DAS ($p < 0.01$), at Step 1. At Step 2, considering the role played by genotype moderation, only the direct association of DAS remained significant. However, there was an interactive effect between children's DAT1 genotype and paternal P-CDI ($p < 0.001$), accounting for the 53% of the variance. For children's methylation at M3 CpG site, there was a negative association with paternal scores of DAS ($p < 0.05$), and a positive association with paternal GSI, both directly and in interaction with children's genotype ($p < 0.001$), which explained the 40% of the variance. Finally, the levels of children's methylation at M6 CpG site were negatively associated with paternal P-CDI ($p < 0.001$) and with the interactions between children's genotype with paternal P-CDI ($p < 0.001$), accounting for 47% of the variance (Table 4).

Table 4 Results of the hierarchical regression analyses for paternal variables predicting children's DAT1 methylation

Step	Children's DAT1 CpG sites			
	M1	M2	M3	M6
	B (SE)	B (SE)	B (SE)	B (SE)
1				
DAT1[a]	− .01 (.50)	.30 (.57)	2.17 (.95)	− 1.05 (.98)
GSI	.51 (.89)	− 2..77 (1.02)**	3.25 (1.69)**	− 3.20 (1.74)
P-CDI	− .01 (.04)	− .10 (.05)*	.20 (.08)	− .04 (.08)
DAS	− .05 (.01)**	.04 (.02)**	− .03 (.03)*	− .01 (.03)
Adjusted R^2	.13	.14	.22	.02
2				
DAT1[a]	− .03 (.46)	.40 (.44)	1.51 (.86)	− .92 (.74)
GSI	.89 (1.09)	− .26 (1.03)	3.63 (2.01)***	1.32 (1.03)
P-CDI	− .03 (.05)	− .10 (.05)	− .02 (.10)	− .47 (.09)***
DAS	.01 (.02)	.08 (.02)**	− .06 (.03)	.01 (.03)
DAT1xGSI[a]	− .34 (1.23)	− 3.03 (1.52)	− 4.33 (2.16)***	− .03 (1.12)
DAT1xPCDI[a]	.06 (.08)	.40 (.07)***	.29 (.15)	.81 (.13)***
DAT1xDAS[a]	− .10 (.03)**	− 06 (.03)	− .10 (.05)	− .04 (.05)
Adjusted R^2	.30	.53	.40	.47
ΔR^2	.19	.38	.20	.44

GSI global severity index, *P–CDI* parent–child dysfunctional interaction, *DAS* total score of dyadic adjustment scale

[a]Reference group is 9/x genotype

*$p < .05$; **$p < .01$; ***$p < .001$

Results of moderation analyses showed that children's methylation at M1 CpG site were significantly negatively associated with paternal perception of dyadic adjustment, but only among children with 10/10 genotype ($\beta = -1.31$, SE = 0.31, $p < 0.001$). The same relationship was not significant for children with 9/x genotype ($\beta = 0.09$, SE = 0.31, $p = 0.77$). Moreover, high levels of paternal stress perceived in the relationship with their children (P-CDI) predicted low levels of methylation at M2 among children with 9/x genotype ($\beta = -1.40$, SE = 0.29, $p < 0.0001$), but high levels of methylation at the same CpG among children with 10/10 genotype ($\beta = 1.67$, SE = 0.33, $p < 0.0001$). Moreover, high levels of methylation at M3 CpG were predicted by high levels of paternal psychopathological risk (GSI) among children with 9/x genotype ($\beta = 3.02$; SE = 0.53, $p < 0.0001$), but not among children with 10/10 genotype ($\beta = -0.12$, SE = 0.72, $p = 0.86$). Finally, among children with 9/x genotype, high levels of methylation at M6 CpG were associated with low levels of paternal P-CDI ($\beta = -2.85$, SE = 0.44, $p < 0.0001$). Conversely, among children with 10/10 genotype, high levels of methylation at the same CpG site were associated with high levels of paternal P-CDI ($\beta = 2.22$, SE = 0.50, $p < 0.0001$).

The Predictive Role of Maternal and Paternal Affective Environment on Children's ADHD and Dysregulation Problems, Moderated by Children's DAT1 Genotype

Pearson correlation analyses showed no significant association between children's DAT1 genotype and maternal and paternal variables (all $p > 0.05$). Consequently, hierarchical regression analyses were carried out to verify the possible moderation role played by children's DAT1 genotype on the relationship between maternal and paternal environment and children's ADHD problems and dysregulation symptoms. As possible to see in Table 5, results showed that children's ADHD problems were positively associated with maternal psychopathological risk (GSI) ($p < 0.001$) and maternal stress perceived in the relationship with their children (P-CDI) ($p < 0.05$), and negatively associated with the maternal perception of dyadic adjustment (DAS) ($p < 0.001$) at Step 1. At Step 2, the direct association with maternal P-CDI ($p < 0.0001$) and maternal DAS remained significant, whereas the direct association with maternal GSI was not. However, maternal GSI significantly interacted with children's DAT1 genotype ($p < 0.001$), explaining 73% of the variance. Similarly, there was a significant positive association between children's ADHD problems with paternal psychopathological risk (GSI) ($p < 0.001$) and paternal stress perceived in the relationship with their children (P-CDI) ($p < 0.05$), and a negative association with paternal levels of dyadic adjustment (DAS) ($p < 0.001$) at Step 1. However, at Step 2, only the direct association with paternal P-CDI remained significant ($p < 0.001$), accounting for 69% of the variance. Regarding children's Dysregulation Profile (DP), children's DAT1 genotype did not moderate the relationship with maternal variables ($p > 0.05$). However, high scores of CBCL DP were associated with high levels of maternal P-CDI at Step 1 ($p < 0.001$) and Step 2 ($p < 0.01$), and with low scores of maternal DAS at Step 1 ($p < 0.001$) and Step 2 ($p < 0.01$), explaining 55% of the variance. Similarly, there were significant positive associations between children's DP problems and paternal GSI ($p < 0.001$) and P-CDI ($p < 0.05$), and a negative association with paternal scores of DAS ($p < 0.001$). At Step 2, the direct relationship with paternal GSI ($p < .001$), P-CDI ($p < 0.05$) and DAS ($p < 0.05$) remained significant, but children's DAT1 genotype also moderated the relationship between paternal GSI and children's DP ($p < 0.01$), accounting for 61% of the variance.

Significant moderated relationships emerged were reported in Fig. 2.

Table 5 Results of the hierarchical regression analyses for maternal and paternal variables predicting children's ADHD and DP problems

Step	Predictors: maternal variables		Predictors: paternal variables	
	Children's ADHD	Children's DP	Children's ADHD	Children's DP
	B (SE)	B (SE)	B (SE)	B (SE)
1				
DAT1[a]	− .18 (.50)	1.02 (1.27)	.47 (.55)	1.23 (1.34)
GSI	5.52 (.87)***	.83 (2.23)	3.47 (.99)***	3.50 (1.38)**
P-CDI	.10 (.04)*	.47 (.11)***	.10 (.04)*	.57 (.11)*
DAS	− .07 (.20)***	− .19 (.05)***	− .10 (.01)***	− .10 (.04)***
Adjusted R^2	.64	.56	.59	.56
2				
DAT1[a]	− .34 (.43)	1.06 (1.30)	.15 (.50)	.41 (1.29)
GSI	1.14 (1.18)	2.28 (1.55)	2.00 (1.17)	3.22 (1.02)***
P-CDI	.12 (.04)***	.41 (.13)**	.28 (.06)***	.39 (.16)*
DAS	− .09 (.02)***	.21 (.06)**	− .03 (.02)	− .15 (.05)*
DAT1xGSI[a]	4.22 (1.58)***	− 2.91 (2.75)	.93 (1.84)	4.58 (2.74)**
DAT1xP-CDI[a]	− .12 (.08)	.20 (.25)	− .36 (.08)	.15 (.28)
DAT1xDAS[a]	− .05 (.03)	.04 (.10)	− .15 (.03)	.02 (.08)
Adjusted R^2	.73	.55	.69	.61
ΔR^2	.10	.00	.10	.07

GSI global severity index, *P–CDI* parent–child dysfunctional interaction, *DAS* total score of dyadic adjustment scale

[a]Reference group is 9/x genotype

*$p < .05$; **$p < .01$; ***$p < .001$

In particular, maternal psychopathological risk (GSI) was significantly associated with children's' ADHD problems, both among children with 9/x ($\beta = 1.22$, SE = 0.47, $p = 0.01$) and 10/10 genotype ($\beta = 2.98$, SE = 0.36, $p < 0.0001$), but with a higher effect in the presence of 10/10 genotype (Fig. 2a). Conversely, paternal psychopathological risk (GSI) was significantly associated with children' DP problems, but only among children with 9/x genotype ($\beta = 6.10$, SE = 0.97, $p < 0.0001$). The same relationship was not significant in the presence of 10/10 genotype ($\beta = 0.74$, SE = 1.32, $p = 0.57$) (Fig. 2b).

Discussion

We explored the complex relationship between children's ADHD problems and emotional-behavioral dysregulation, children's DAT1 genotype and methylation, and the affective environment provided by mothers and fathers. We considered a sample of the general population, based on the recent evidence that sensitive periods of development (such as school-age) represent windows of risk in which children's psychopathological difficulties may manifest in sub-threshold forms (Gupta et al., 2017), but still leading to children's maladaptation in the family environment (Thurston et al., 2008). Although international research has widely shown the central role played by DA in a wide range of central functions to

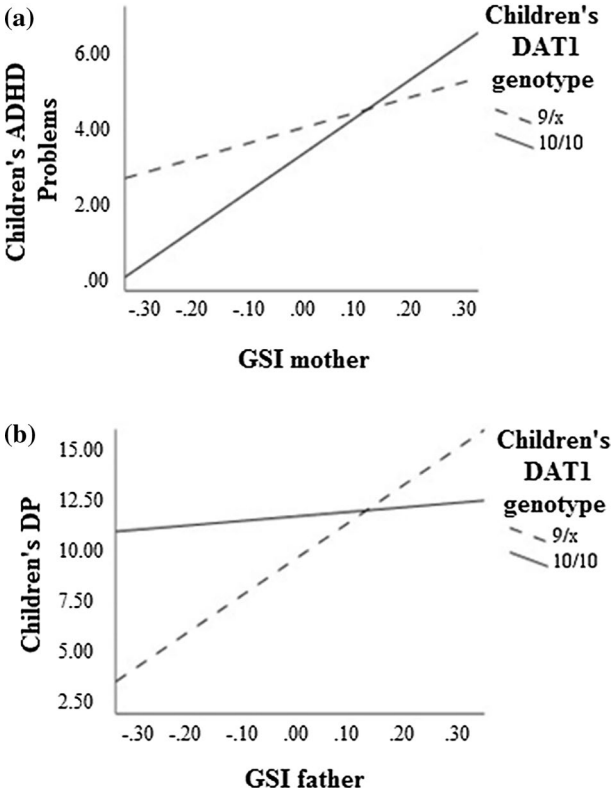

Fig. 2 Conditional line plots showing the moderation of children's DAT1 genotype on the relationship between children's ADHD and dysregulation problems and parental psychopathological risk. **a** The moderation of children's DAT1 genotype on the relationship between children's ADHD Problems and maternal Global Severity Index (GSI). **b** The moderation of children's DAT1 genotype on the relationship between children's Dysregulation Profile (DP) and paternal GSI

the regulation of children's emotional-behavioral adjustment (Bromberg-Martin et al., 2010; Deyoung, 2013; Radwan et al., 2019), the research focused on the possible interplay between DAT1 and the family environment is scarce.

Preliminary Results

Our preliminary analyses confirmed that children's psychopathological risk was associated with both children's DAT1 methylation and parental variables. Specifically, we found that high scores of children's ADHD problems were associated with high levels of DAT1 methylation at M1 CpG site and with low levels of DAT1 methylation at M2 and M6 CpG sites. These findings are in accordance with previous studies (Adriani et al., 2018; Carpentieri et al., 2021) showing that children's ADHD symptoms and externalizing problems were significantly associated with the hyper-methylation at M1 and hypo-methylation at M2 and M6 CpGs. Moreover, we found that children's scores of Dysregulation Profile (DP) were associated with high levels of DAT1 methylation at M3 CpG sites. Although the study by Cimino et al. (2021) showed a significant association between children's DAT1 total methylation and their dysregulation problems in a sample of early children with feeding disorders, this is the first study to explore this association in a community sample of school-aged children. Moreover, we aimed to verify the possible role played by levels of methylation relative to six specific CpG residues of the DAT1 (i.e., M1, M2, M3, M5, M6, and M7) in children's emotional-behavioral dysregulation symptoms, evidencing a specific

role played by the methylation level at M3 CpG site. Interestingly, results also showed significant associations between maternal and paternal environmental variables with the same CpGs that we found in association with children's ADHD and DP. Consequently, we explored whether these associations may be moderated by children's DAT1 genotype.

On the Relationship between Children's DAT1 Genotype and Methylation, and Their Own ADHD and Emotional-Behavioral Dysregulation Problems

We did not find the presence of a main effect of children's DAT1 genotype with any of the psychopathological areas investigated. However, children's DAT1 genotype moderated the relationships between ADHD problems and methylation levels at M1 and M6 CpGs. In particular, high levels of methylation at M1 were associated with high scores of ADHD problems, among children with 10/10 genotype, whereas high levels of methylation at M6 CpG were associated with low scores of ADHD problems, but only for children with 9/x genotype. Moreover, high levels of children's ADHD problems were associated with low levels of methylation at M2 CpG site among children of both DAT1 genotypes. For children's Dysregulation Profile (DP), children's DAT1 genotype did not play a moderator role, but there was a significant association with high levels of methylation at M3 CpG site. These findings are in accordance with previous studies that found significant associations between the levels of DAT1 methylation at M2 and M6 CpGs and children's internalizing and attention problems (Cimino et al., 2018, 2019). Moreover, the study by Adriani et al. (2018) found that hyper-methylation at CpG M1 was associated with the severity of ADHD among children with 10/10 genotype, whereas elevated methylation at CpG M6 (and M2) was associated with reduced symptoms severity following treatment (i.e., cognitive-behavioral therapy and/or pharmacological treatment) among children with 9/x genotype. In this context, it is important to note that a significant influence of DAT1 genotypes on gene expression and the subsequent phenotypic variation has been reported, with a greater DAT1 expression among individuals with 10/10 genotype and consequent excessive removal of DA (Heinz et al., 2000; Šerý et al., 2015), suggesting that the worst developmental outcomes associated with the 10/10 genotype (Adriani et al., 2018; Mick et al., 2008; Tonelli et al., 2020) may be also dependent on the associated DA imbalance in the brain (Dreher et al., 2009). However, the research reported conflicting results, with other studies evidencing either that gene expression was greater for the 9/x genotype (Jacobsen et al., 2000) or no genotype's effect on DAT1 expression (Martinez et al., 2001). In addition, to our knowledge, our study was the first to explore the possible association with children's DP, suggesting a specific role played by the methylation at CpG M3. In this context, it is important to note that when DNA hyper-methylation occurs at the level of the gene promoter, it is typically associated with inhibition of gene transcription (Jones, 2012), resulting in lower availability of DAT and increased levels of extracellular DA (Serra-Mestres et al., 2004). Therefore, it could be hypothesized that the high levels of methylation found at M1 and M3 CpGs may alter DA levels in the mesolimbic pathway, which in turn may predispose children to impulsive behavior (Seo et al., 2008) and emotional and behavioral dysregulation (Stahl, 2017). Conversely, the relationship between high levels of methylation at the M2 and M6 CpGs and low ADHD problems (and vice versa) may appear more difficult to interpret. In this field, some studies have underlined that methylation at specific CpGs of a genomic sequence can increase (Lopez-Serra et al., 2006) or reduce (Doerfler, 1983; Egger et al., 2004; Holliday, 1987) transcription factors's attachment to regulatory regions of DNA. Indeed, as suggested by Lopez-Serra et al. (2006), specific CpG sites, whether

methylated, may act as binding sites for other molecules that stimulate transcription instead of suppressing it. In the specific context of the 5'-UTR of DAT1, recent studies (Adriani et al., 2018; Rubino et al., 2020) have shown that M2 and M6 CpG sites represent binding sites of a molecule that promotes transcription, resulting in more mRNAs translation. Consequently, methylation at M2 and M6 could regulate DAT1 expression by affecting the ability of transcription factors to access and bind specific regions in the promoter region of DAT1 (Domcke et al., 2015). Moreover, M6 CpG represents a CGCG motif that is a putative target for members of a family of calmodulin-binding transcription activators (CAMTAs) noted as integrators of response to stress (Mollet et al., 2016; Shen et al., 2015). In addition, using cross-correlation approaches, recent studies (Carpentieri et al., 2021; De Nardi et al., 2020; Tafani et al., 2020) have shown the presence of specific patterns in the dynamics of CpG methylation of DAT1 5'-UTR, evidencing both a methylated and a demethylated loci status. In particular, in the presence of children's externalizing problems, a profile composed of hypo-methylation at M2 and M6 CpGs while M1 CpG gets methylated (and vice versa) was found (Carpentieri et al., 2021). Our study further supported the presence of this specific methylation pattern also in the presence of children's ADHD problems.

Main and Moderated Effects of Maternal and Paternal Environment on Children's DAT1 Methylation

As expected, we found significant associations between children's methylation both with maternal and paternal variables, and children's DAT1 genotype moderated many of these relationships. In particular, among children with 10/10 genotype, we found that: (a) high levels of children's methylation at CpG M1 (which were found to be associated with high ADHD symptoms) were predicted by high levels of maternal psychopathological risk, whereas paternal perception of a good dyadic adjustment significantly predicted low levels of methylation at the same CpG; (b) high levels of methylation at M3 CpG (which were found to be associated with high children's DP symptoms) were predicted by high maternal stress perceived in the relationship with their children; and (c) high levels of methylation at M6 CpG were associated with the maternal perception of low dyadic adjustment, whereas low levels of methylation at the same CpG were associated with high levels of paternal stress perceived in the relationship with their children. Conversely, among children with 9/x genotype, we found that: (a) high levels of methylation at CpG M2 (which were associated with low ADHD problems) were predicted by the maternal perception of a good dyadic adjustment; (b) high levels of methylation at M3 CpG were predicted by high levels of paternal psychopathological risk; and (c) low levels of methylation at M6 CpG site (which were found to be inversely associated with ADHD symptoms for children with 9/x genotype) were associated with high levels of paternal stress perceived in the relationship with their children, whereas high levels of methylation at the same CpG were associated with high scores of maternal dyadic adjustment. Finally, although children's genotype did not moderate these relationships, low levels of methylation at CpG M2 were predicted by high levels of paternal psychopathological risk and paternal stress perceived in the relationship with their children, and both maternal and paternal scores of dyadic adjustment were negatively associated with the methylation at CpG M3. These results are in accordance with previous studies that have shown significant associations between maternal and paternal psychopathological risk and children's DAT1 methylation (Cerniglia et al., 2020; Cimino et al., 2018), with significant interactive effects played by

children's DAT1 genotype (Cimino et al., 2019; Cimino, Cerniglia, et al., 2020). A growing body of research has evidenced that parenting stress may act as an environmental factor influencing levels of methylation (Monk et al., 2012; Naumova et al., 2016). Mulder et al. (2017), reviewing recent literature in the field, suggested that DNA methylation may mediate the relationship between parental stress and children's adjustment. However, this study was the first to evidence the role played also by children's DAT1 methylation in these processes, although it has been shown that the dopaminergic system is widely involved in stress response processes (Moriam & Sobhani, 2013), with increased DA release at the striatum and prefrontal cortex level (Vaessen et al., 2015). Moreover, we found that maternal and paternal perception of high dyadic adjustment levels had an inverse impact on CpG sites associated with risk factors. We found these associations both in interaction with a specific children's genotype and across both genotypes, supporting the importance of implementing preventive programs focused on the promotion of marital support (Lavner et al., 2020). Indeed, interventions aimed at reducing risk factors and promoting protective factors can reverse epigenetic signs (Szyf, 2013), modifying the sequence of events called "developmental cascade" (Cicchetti & Curtis, 2007), to obtain the maximum effect on the change of a negative cascade into a positive one (Lavigne et al., 2013).

It is interesting to note that we found the presence of different and inverse effects of maternal versus paternal contribution on children's methylation levels in the same CpG (i.e., M1, M2, and M6 CpGs). In particular, the influence exerted by maternal psychopathological risk on children's M1 methylation was opposite with respect to the effect of paternal perception of a high dyadic adjustment on the same site; on the other hand, the influence exerted by paternal stress perceived in the relationship with their children on children's M2 and M6 methylation was opposite with respect to the effect of maternal perception of a high dyadic adjustment, suggesting that the risk influence exerted by one parent may be counterbalanced by the protective influence exerted by the other parent. For the methylation levels at M3 CpG, maternal and paternal contributions exerted their influence in the same direction, suggesting the possibility of mutual reinforcement. Overall, our finding evidenced a complex and dynamic relationship between maternal, paternal, and children's contribution in shaping those children's epi-genetic features that are predictive of children's emotional and behavioral functioning. In the field of developmental psychopathology, many studies have shown that maternal and paternal influences may have a different effect on children's psychopathological symptoms (Field et al., 2020; Malmberg & Flouri, 2011), due to their typically different roles in children's upbringing and the resulting rearing environments provided to them (Bögels & Perotti, 2011). The quality of environment provided by a parent may moderate the effect of the other parent's characteristics, acting as a protective factor and/or an additional risk factor for children's emotional and behavioral functioning (Gaumon et al., 2016; Gere et al., 2013). In the specific context of epigenetic studies, a growing body of research is aimed at increasing knowledge on the specific contribution of both mothers and fathers on offspring's DNA methylation (Cerniglia et al., 2020; Cimino et al., 2021; Pellicano et al., 2021). In line with our findings, recent evidence has suggested the presence of differential effects of maternal versus paternal factors (i.e., psychopathological symptoms, and the quality of attachment to the child) on children's methylation (Pellicano et al., 2021; Yehuda et al., 2014). The study by Yehuda et al. (2014) demonstrated a moderation effect of maternal post-traumatic psychopathological symptoms on the relationship between paternal post-traumatic psychopathological symptoms and children's methylation. In addition, the study by Pellicano et al. (2021) evidenced an inverse effect of mothers' and fathers' psychopathological symptoms on children's methylation, with higher and lower levels of methylation predicted, respectively, by maternal

and paternal contribution. Our results go further in this direction, adding to the previous literature that a parent's characteristics (i.e., low psychopathological risk, low levels of parenting stress, and the perception of a high dyadic adjustment) may exert a protective role in relation to the adverse effect exerted by the other parent risk factors (and vice versa). Moreover, in line with a transactional perspective of development (Sameroff, 2009), our findings have evidenced a significant moderation contribution played also by children's genetic features in these complex processes. Specifically, our findings suggested that children carrying the 10/10 genotype were more susceptible to the risk influence exerted by mothers (i.e., maternal psychopathological risk and parenting stress levels) on children's methylation, and to the protective influence exerted by fathers (high dyadic adjustment perceived by fathers, lower levels of parenting stress). Conversely, we found inverse associations among children carrying the 9/x genotype. These findings are in accordance with studies rooted in the Differential Susceptibility model (Belsky & Pluess, 2009) that have underlined that DAT1 polymorphisms may contribute to children's susceptibility to environmental influences in response to both adverse and supportive environmental influences (Belsky et al., 2015; Lahey et al., 2011) and can act as moderators in the complex relationship between the affective family environment, methylation of DNA, and children's developmental outcomes (Beauchaine & Gatzke-Kopp, 2012). However, only a few studies have focused on possible GxE effects on children's DNA methylation (Barker et al., 2018; Duman & Canli, 2015), and to our best knowledge, this is the first study to show similarities and differences of maternal versus paternal affective environmental influences and their interaction with children's DAT1 genotype on children's DNA methylation changes.

DAT1 × Environment Interactions on Children's ADHD and DP Problems

We did not find a main effect of children's genotype on their ADHD and DP problems. In this context, although significant associations between DAT1 genotype and a wide range of children's psychopathological difficulties have been shown (Adriani et al., 2018; Grünblatt et al., 2019; Guo et al., 2007; Mick et al., 2008), the international literature has reported conflicting results on the specific genotype that can be considered at higher psychopathological risk (Faraone et al., 2014; Joyce et al., 2009; Li & Lee, 2013; Tonelli et al., 2020). Moreover, as evidenced above, also in vivo and in vitro studies have reported conflicting results on the possible influence exerted by DAT1 genotype on gene expression (Heinz et al., 2000; Jacobsen et al., 2000; Šerý et al., 2015), supporting the importance to considering gene-environment interactions when studying children's psychopathological risk. In this field, although GxE research has evidenced that children's DAT1 genotype can make the child more susceptible to the effects of both positive and negative environmental exposure (Cimino et al., 2019, Cimino, Cerniglia, et al., 2020a, Cimino, Marzilli, et al., 2020b; Lahey et al., 2011; Li & Lee, 2012; Sonuga-Barke et al., 2009; van den Hoofdakker et al., 2012), we found an interactive effect only on the association between maternal psychopathological risk and children's ADHD symptoms, and between paternal psychopathological risk and children's DP symptoms. Interestingly, children's with 10/10 genotype had a higher risk in response to the maternal environment, whereas children's with 9/x genotype had a higher risk in response to the paternal environment, suggesting that children's genetic disposition may influence the degree of individual influence in response to maternal and paternal environmental exposures. These findings integrate previous results of this study that have shown a higher susceptibility in response to maternal unsupportive environment (and to the paternal supportive environment) on children's methylation among children

with 10/10 genotype, whereas a higher susceptibility in response to maternal unsupportive versus paternal supportive environment for children with 9/x genotype. Overall, our study added to the previous literature that children carrying specific DAT1 polymorphisms would not only be more susceptible to both risk and supportive environmental influences (Bush & Boyce, 2016; Lahey et al., 2011) but that the parent (mother versus father) and its characteristics also play a key role in these processes. In addition, the research in the field of gene-environment interplay has also evidenced that children's genotype may, in turn, affect their own environmental experiences within a process of mutual and bidirectional influences defined as gene-environment correlation (rGe; Knafo & Jaffee, 2013), modifying, creating, and/or eliciting specific type of parental responses (Jaffee & Price, 2007; Scarr & McCartney, 1983).

Limitation and Strengths

This study has some limitations. First, the small sample size and the cross-sectional nature of the study imply to take with caution the causal conclusions provided, which may be supported by further studies with larger populations and within longitudinal designs. For the same reasons, we have could not evaluate whether children's DAT1 methylation mediated the relationship between environmental influences and children's psychopathological risk, and future studies should implement research in this direction. Moreover, for the assessment of psychological and environmental variables, we used report-form and self-report instruments. Although they are validated tools widely used by researchers in the field of children's and parental psychopathological risk (Ammaniti et al., 2004; Lucarelli et al., 2003), these variables should be evaluated by more robust methodologies (e.g., clinical interview and/or observation procedures). Finally, the (epi-)genetic characteristics of mothers and fathers have not been evaluated, although the literature has shown that DNA methylation changes are potentially heritable (McRae et al., 2014) and that parental DAT1 genotype can in turn influence the quality of the environment experienced by children (Lee et al., 2010). Notwithstanding the above limitations, the present study has several strengths. Indeed, this is one of the first studies that has shown the key role played by children's DAT1 genotype and methylation and their interplay with the family environment in shaping children's DP symptoms. The child's dysregulation profile (DP) represents a psychopathological condition of poor self-regulation in early childhood, characterized by co-occurring internalizing and externalizing problems. Longitudinal studies have evidenced that it is prospectively associated with psychopathological difficulties over time (Deutz et al., 2020; Holtmann et al., 2011). Our study further supported the relevance of this phenomenon even in children of the general population. These findings supported the recent evidence on the importance of implementing the research on community samples of children, where children's emotional and behavioral dysregulation problems may manifest in sub-threshold forms (Willner et al., 2016), but still affect the children's adaptation to the family environment. Consequently, further research in the field of GxE should focus on this empirically-based profile in studying psychopathological risk in childhood, also considering the possible role played by other genes commonly involved in the regulation of dopaminergic activity (e.g., serotonin). Moreover, to our knowledge no other study has considered the possible relationship between children's DAT1 methylation and children's ADHD and DP symptoms, considering the role played by a wide range of paternal and maternal affective environmental variables and their interaction with children's DAT1 genotype. Most studies only focused on mothers' role, but the research of children's DAT1 genotype

and methylation, and their interplay with the maternal and paternal environment is still underway. In this context, our study has added new evidence on the moderation role played by children's genotype on the relationship between DAT1 methylation and their emotional-behavioral functioning, and between maternal versus paternal environment and children's DAT1 methylation and psychopathological risk. Specifically, our results could be informative for the early identification of children that, due to their genetic influence that can significantly interact with specific maternal and paternal qualities (i.e., maternal and/or paternal psychopathological risk, parenting stress, and dyadic adjustment), may be at higher risk for psychopathology. Our findings suggested that children with 10/10 genotype are more vulnerable to the risk influence of maternal environment while benefiting more from the paternal supportive environment, compared to 9/x children (and vice versa). Consequently, intervention programs may be potentially targeted on the change of these environmental factors related to a higher susceptibility in the presence of a specific children's DAT1 genotype. Moreover, our findings have supported the importance of implementing preventive programs focused on family and marital support and parenting interventions, involving both mothers and fathers, which may reduce the risk of children's mental illness both promoting protective factors (and reducing risk factors) (England-Mason & Gonzalez, 2020; Lavner et al., 2020) and reversing the DNA methylation following adverse caregiving and early childhood adversities (Szyf, 2013). Overall, our findings have supported the recent evidence on the complex nature of children's emotional-behavioral functioning, involving contributions from multiple domains that may increase or mitigate children's vulnerability to psychopathological risk, with important implications for the planning of more targeted psychological interventions.

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Data Availability The data that support the findings of this study are available at https://doi.org/10.6084/m9.figshare.14135216.

Declarations

Conflict of interest The authors declare they have no conflict of interest.

Ethics Approval This study was approved before its start by the Ethical Committee of the Department of Dynamic and Clinical Psychology at Sapienza, University of Rome (Protocol Number 27/2016), in accordance with the Declaration of Helsinki.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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