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Dopamine transporter (*DAT1/SLC6A3*) polymorphism and the association between being born small for gestational age and symptoms of ADHD

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ABSTRACT

Being small for gestational age (SGA) has been established as a risk factor for Attention Deficit Hyperactivity Disorder (ADHD). Likewise, several molecular genetic studies have found a link between *DAT1* and ADHD. This study investigated whether SGA moderates the effect of dopamine transporter gene variants on the risk of ADHD. A total of 546 children of European descent were genotyped at age 11 for seven *DAT1* SNPs (rs6347, rs11564774, rs40184, rs1042098, rs2702, rs8179029 and rs3863145). The Strengths and Difficulties Questionnaire was used to measure symptoms of ADHD at ages 3.5, 7 and 11. We found significant gene-environment interactions between birth weight and *DAT1* SNPs (rs6347, rs40184, rs1042098, rs3863145) on ADHD symptoms at 3.5 years only. Results suggest that genotypic variation of *DAT1* may confer a relative protective effect against ADHD in SGA individuals. This study supports the idea that being born SGA moderates the effect of the *DAT1* gene on ADHD symptoms in the preschool years and may help to explain some of the heterogeneity in ADHD outcomes.

1. Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a heterogeneous disorder both in terms clinical presentation and aetiology, arising from complex interactions between genetic and environmental factors [1]. It is typically characterised by a persistent pattern of inattention, hyperactivity and impulsivity and has a prevalence of approximately 5% in the school age population [2]. ADHD is most commonly diagnosed and treated between the age of 7 and 12 [3], and is associated with poorer academic performance and fewer friends during their schooling years [4]. Later in life, ADHD is associated with antisocial behaviour [5], high rates of criminality [6], low job performance [7] and substance abuse [8].

The interaction between the prenatal environment and the foetal genome is known to influence foetal growth [9]—for example, being born with intra-uterine growth restriction (IUGR), typically defined as the lowest 10th percentile of birth weight (small for gestational age, SGA; [10] has shown a positive correlation with ADHD symptoms (sADHD; [11]. Risk factors for SGA individuals range from maternal malnutrition to low maternal pre-pregnancy weight, also including factors such as hypertension, maternal smoking during pregnancy, and placental dysfunction [12–15]. Reduction in cortical and white matter in growth-restricted children [16] aligns with similar findings in ADHD children [17]. Such brain volume atrophy has been shown to lead to poorer developmental outcomes [18].

The role of the intra-uterine environment in the prediction of birth weight is widely acknowledged in the literature. However, potential genetic factors are yet to be fully understood. As individuals born SGA are at an increased risk of developing ADHD [19], neurotransmitters associated with ADHD may also be implicated in SGA Morgan et al., 2012. Alterations in the dopamine system in particular are hypothesised to be implicated in the link between SGA (a proxy for foetal adversity) and ADHD [20]. The dopaminergic system is highly dependent on a constant supply of various nutrients and oxygen, making it particularly vulnerable during adverse foetal conditions and postnatal environments such as maternal stress [21], malnutrition [22], environmental toxins [23] and maternal separation [24]. SGA children have been reported to show increased excretion of urinary dopamine

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compared with appropriate for gestational age (AGA) children [25]. Dopamine dysfunction is supported further by mouse models of IUGR (via early protein restriction), indicating changes in dopamine distributions and behavioural abnormalities [26].

The dopamine transporter (DAT) is involved in the termination of neurotransmission via the reuptake of dopamine from the synaptic cleft [27]. Changes in the density of DAT at the synapse can directly influence the amount of dopamine actively available in neurotransmission [28]. Imbalances in DAT density in ADHD individuals indicate the possible involvement of genetic alterations in the dopamine transporter gene (SLC6A3*DAT1*; [29,82]). Sequence analysis of the 3′UTR of this gene revealed a variable number of tandem repeat (VNTR) polymorphisms with a 40-bp unit repeat length, ranging from 3 to 11 repeats [30]. In humans, the 9R and 10R are most common [31]. *DAT1,* specifically a 40-bp variable number tandem repeat (VNTR) in the untranslated region (3′UTR), was the first gene to be examined in ADHD candidate gene association studies [32], and some studies have reported a significant association between the *DAT1* VNTR and ADHD (e.g., [33,34].

The 10R has been associated with reduced verbal inhibition [35] and higher impulse errors [36]. It has also been suggested that these polymorphisms may have a developmental stage-specific effect on cognition and behaviour, with 10R associated with higher risk at childhood and 9R at adulthood [37]. The 10R allele has also been found to increase risk with specific haplotypes and environmental situations [38], suggesting potential dopamine gene-environment interactions. Other research suggests that *DAT1* variants may be associated with processes such as aversion delay rather than cognitive performance [39]. However, due to the inconsistencies between studies, much remains unknown about the complex mechanisms surrounding *DAT1* throughout development [40].

Although the analysis of *DAT1* SNPs (single nucleotide polymorphisms) has been promising over the years with ADHD, the effect sizes found remain small [41–43]. There have also been failures to replicate these findings [44]. As such, there has been a shift in focus within the literature to look at gene x environment interactions (GxE; genotypic changes dependent on specific environmental exposures; [45,46]. With regard to ADHD, a number of studies have reported GxE interactions for the *DAT1* 40-bp VNTR located in the 3′UTR. The majority of these studies found that the 10R allele conferred increased risk for ADHD when exposed to prenatal smoke [47,48], psychosocial adversity [49], low parental expressed emotion [50], institutionalised deprivation [51] and maltreatment in girls [52]. Despite this, little is known on how exposure to a suboptimal environment could influence susceptible dopamine variants.

Commonly, investigations into how environmental factors moderate the effects of genes have focussed on increased vulnerability to environmental adversity in individuals with a certain genetic make-up. Belsky and Pluess [53] proposed a theory that extends this classic diathesis-stress model [53]. Their framework of ‘differential susceptibility’ proposes that individuals may be more responsive to both aversive and enriched environments [53,54]. Here, we test the hypothesis that prenatal adversity (as namely, SGA) moderates the effects of common *DAT1* SNPs on the risk of increased symptoms of ADHD in terms of the differential susceptibility framework.

2. Methods

2.1. Participants

This study was part of the Auckland Birth weight Collaborative (ABC) study, which has been described in detail previously [15]. Participants were singleton infants born full term (37 or more completed weeks of gestation) in the Auckland and Waitamata District Health Boards, between 16 October 1995 and 30 November 1997. Approximately half of the infants (N = 844) were SGA with birth weights equal to or below the sex-specific tenth percentile for gestation, and the remainder (N = 870) were a random sample of infants born appropriate for gestational age (AGA) [10]. Infants were excluded from the study if they were not born in a designated study region, were from multiple births or had congenital abnormalities likely to affect subsequent growth or development. Gestational age was estimated using the date of the last menstrual period, where it was available and was within two weeks of the best clinical estimate of gestational age at birth; otherwise the best clinical estimate was used.

Data were collected at five phases: birth, 1 year, 3.5 years, 7 years, and 11 years. Extensive psychological, developmental, social and physical data have been collected on children and their families at all phases. Due to the differential response rates amongst ethnic groups at earlier phases, this study has been restricted to New Zealand European mothers and their infants (N = 871 at birth).

The study received ethical approval from the Northern Regional Ethics Committee. Signed consent to take part in each phase of the study was obtained. Parents gave consent for the extraction of their child’s DNA at age 11 years. Assent was provided by all children.

2.2. Symptoms of ADHD

sADHD were measured at ages 3.5, 7 and 11 years using hyperactivity – inattention subscale of the parent format of the Strengths and Difficulties Questionnaire (SDQ) [55]. Compared with other child behaviour rating scales, the SDQ is considered to be a brief measure of child behaviour which inquires about 25 positive and negative emotional and behavioural attributes. Each child is given a score on 5 subscales, each consisting of 5 items. The subscales relate to difficulties in conduct, emotion, hyperactivity-inattention, peer group relationships and pro-social behaviour. Each item is scored on a 3 point Likert scale (0 = ‘not true’, 1 = ‘somewhat true’ and 2 = ‘certainly true’). The total scores for each subscale were calculated by summing scores on their respective items. The hyperactivity-inattention subscale consisted of the following items: ‘restless, overactive, cannot stay still for long’, ‘constantly fidgeting or squirming’, ‘easily distracted, concentration wanders’, ‘can stop and think things out before acting’ and ‘sees tasks through to the end, good attention span’ (score range = 0–10). The SDQ has a test-retest stability of 0.62 after 4–6 months, and the internal consistencies of the subscales range from 0.62 to 0.75 [55].

2.3. Socio-economic status (SES) adversity

In order to control for differences in social background, we created an index of socio-economic adversity. This included the following measures: parental recent paid employment/income (based on the Elley Irving Index; [56], maternal school leaving age, and maternal age at the time of the child’s birth. These three variables were summed to create a total index of SES adversity (with a range of 0–6). The total index of SES adversity was used as a continuous covariate measure in all analyses.

2.4. Genotyping

At the 11 year assessment, a total of 546 participants consented to collection of peripheral blood (n = 397) or a buccal swab (n = 149) for DNA extraction and genotyping. Of these, 227 samples were from SGA children and 319 were from appropriate for gestational age (AGA) children. DNA was extracted from the blood/buccal samples using Qiagen’s DNA extraction kit, following the manufacturer’s instructions.

Genotyping was performed with the MassARRAY and iPlex systems of the Sequenom genotyping platform (Sequenom, San Diego, CA), which uses the MALDI-TOF primer extension assay [57,58], according to the manufacturers’ recommendations. Assays were optimised in 24 samples consisting of 20 reference Centre d’Etude du Polymorphisme Humain (CEPH) samples and 4 blanks.

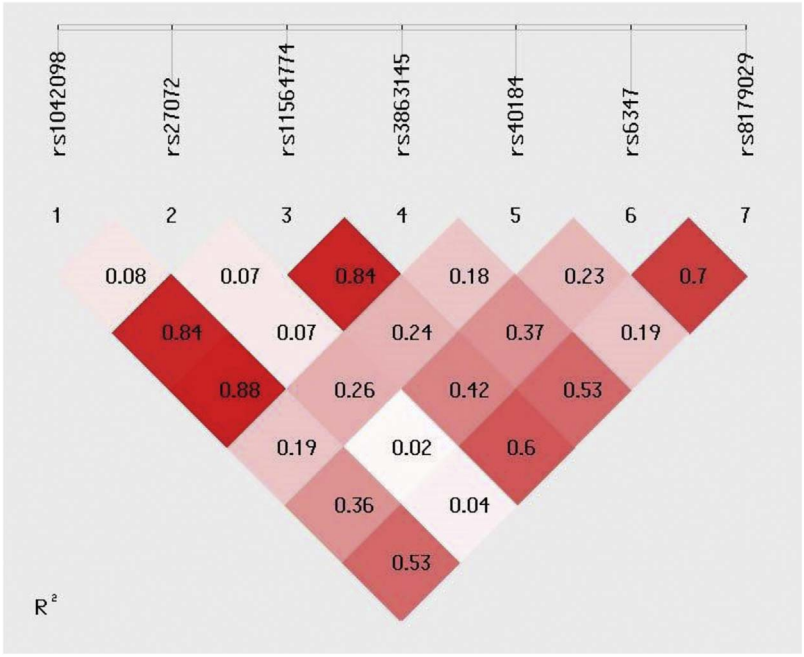

Fig. 1. LD plot for 7 SNPs of the *DAT1* gene. r^2 is used to indicate whether SNPs are in LD and is shown in the region where the SNPs diagonally intersect. High r^2 ($r^2 > 0.80$) are provided in bright red boxes and indicate SNPs that are in LD. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

All sample plates contained cases, controls, blanks, CEPH and duplicate samples. Quality control measures included independent double genotyping, blind to sample identity and blind to the other caller, and where available comparison of our CEPH genotypes to those in the HapMap (www.hapmap.org).

SNPs examined in this study were identified using the National Center for Biotechnology Information SNP database (http://www.ncbi.nlm.nih.gov/snp). Departure from Hardy Weinberg Equilibrium (HWE) was tested using a chi square goodness-of-fit test. There were no significant HWE deviations in either the SGA or AGA groups.

A linkage disequilibrium (LD) test of the SNPs on *DAT1* found that rs1042098, rs11564774 and rs3863145 to be high in LD ($r^2 > 0.80$; see Fig. 1). As such, the results of these SNPs should not be considered independent of each other. Of those children with ADHD scores, 529 had genotype data for rs1042098, 502 had data for rs3863145 and 533 had data for rs11564774.

2.5. Statistical analyses

The interaction between SNP and birth weight on sADHD at ages 3.5, 7 and 11 years was examined using Analysis of Covariance (ANCOVA) in SAS (version 9.3) and SPSS (version 22). SES adversity index and sex were covariates in all analyses. The repeated option of the proc mixed statement in SAS was used to examine all seven *DAT1* SNPs longitudinally (ages 3.5, 7 and 11). To investigate the findings further, separate ANCOVA's were conducted for each phase (age 3.5, 7 and 11) for each *DAT1* SNP in SPSS. Post hoc comparisons were examined using Bonferroni corrections to the alpha level.

An index of genotypic susceptibly was created, which combined the effects of each of the four SNPs (rs1042098, rs40184, rs6347, rs3863145) with significant interactions at age 3.5 years. Those with the dominant genotype (major homozygous genotype + heterozygous genotype) were given a score of 0 while those with the susceptibility genotype (minor homozygous genotype) were given a score of 1. The groups were collapsed into the following categories: (1) 0 susceptibility genotype; (2) 1 susceptibility genotype; and (3) 2 or more susceptibility genotypes. The majority of observations were for children with 0 susceptibility genotype (n = 292, 77%), followed by those with 1 susceptibility genotype (n = 57, 15%) and fewer children with 2 or more susceptibility genotypes (n = 30, 8%) at age 3.5 years.

3. Results

Of the 546 children who provided samples for DNA extraction at the age 11 assessment, complete SDQ scores were available for 437 (80%) children at the 3.5 year assessment, 490 (90%) at the 7 year assessment, and 540 (99%) at the 11 year follow up assessment. Overall, 414 children had complete sADHD information at all phases of the study (3.5 years, 7 years and 11 years).

The repeated option of the proc mixed statement revealed significant main effects of age for all seven *DAT1* SNPs, showing that mean ADHD scores decreased between the ages 3.5–11 years. A significant main effect was found for rs40184 only, showing higher ADHD scores for the G carriers (M = 3.21, SE = 0.01) than the minor homozygote A carriers (M = 2.69, SE = 0.022, $F_{(1,373)} = 4.55$, p = 0.034). A significant interaction between age and SGA status for rs40184 was found ($F_{(1.90,710.14)} = 5.45$, $p = 0.005$) as well as a significant age by SGA status by SNP interaction ($F_{(1.90,710.14)} = 4.11$, $p = 0.018$).

Within the group analysis (SGA individuals only) showed that ADHD scores for G allele carriers (M = 3.73, SE = 0.18) were higher in comparison to A allele carriers (M = 2.60, SE = 0.41, $F_{(1,158)} = 6.49$, $p = 0.012$). Furthermore, between group (SGA vs. AGA) comparison (simple effects tests on the significant 3-way interaction: see Fig. 2) revealed that the those carrying AA genotype in the SGA group

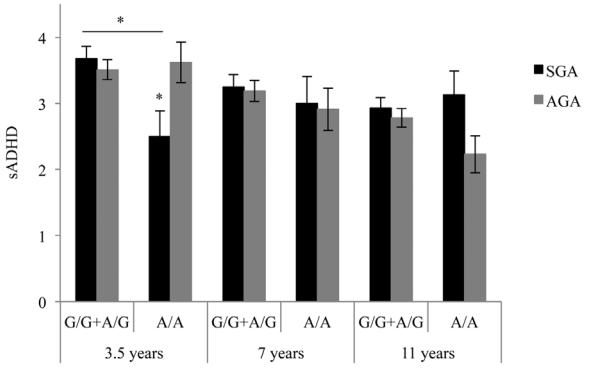

Fig. 2. Interaction between *DAT1* rs40184 and birth weight status on sADHD at ages 3.5, 7 and 11 years. SGA = small for gestational age, AGA = appropriate for gestational age, sADHD taken from hyperactivity subscale of SDQ. All analyses adjusted for gender and SES. *p < 0.05.

Table 1
Adjusted estimated marginal (EM) means and standard errors for the ANCOVA of *DAT1* SNP and birth weight status interaction on sADHD at age 3.5.

		Group 1		Group 2		Interaction
SNP		N	EM Mean (SE)	N	EM Mean (SE)	
		A/A ± A/G		G/G		
rs6347	SGA	154	3.63 (0.17)	19	2.53 (0.48)	$p = 0.024$
	AGA	215	3.51 (0.14)	16	4.10 (0.52)	
		G/G ± A/G		A/A		
rs8179029	SGA	159	3.57 (0.17)	10	2.87 (0.66)	$p = 0.197$
	AGA	215	3.56 (0.14)	9	4.13 (0.70)	
		G/G ± A/G		A/A		
rs40184	SGA	141	3.68 (0.18)	28	2.50 (0.39)	$p = 0.020$
	AGA	184	3.51 (0.15)	45	3.62 (0.31)	
		T/T ± C/T		C/C		
rs1042098	SGA	166	3.52 (0.17)	10	2.84 (0.67)	$p = 0.033$
	AGA	229	3.50 (0.14)	12	4.80 (0.61)	
		G/G ± G/C		C/C		
rs11564774	SGA	170	3.53 (0.14)	7	2.73 (0.80)	$p = 0.056$
	AGA	229	3.52 (0.14)	12	4.73 (0.64)	
		C/C ± C/T		T/T		
rs27072	SGA	167	3.49 (0.16)	6	4.30 (0.85)	$p = 0.784$
	AGA	238	3.50 (0.14)	4	4.68 (1.04)	
		C/C ± C/T		T/T		
rs3863145	SGA	160	3.56 (0.17)	10	2.83 (0.66)	$p = 0.026$
	AGA	212	3.47 (0.14)	13	4.76 (0.58)	

ANCOVA model included Age, SES adversity index, a child's sex, SGA/AGA status, SNP and the interaction SGA/AGA status*SNP*age. SGA = small for gestational age, AGA = appropriate for gestational age, EM Mean = estimated marginal mean, SE = Standard Error, N = number of participants. All values adjusted for gender and SES adversity. Group 1 (individuals with 1 or 2 susceptibility variant). Group 2 (individuals with 0 susceptibility variants).

(M = 2.50, SE = 0.35) had significantly lower ADHD scores than those in the AGA group (M = 3.50, SE = 0.28, $F_{(1,66)} = 4.89$, $p = 0.03$) at age 3.5 years.

ANCOVAs were conducted separately for each remaining *DAT1* SNP at each age. Presented in Table 1 are the descriptive statistics for the interaction between *DAT1* SNPs, SGA status and sADHD at age 3.5, adjusted for sex and SES adversity. Analyses revealed a significant main effect of SGA status for two of the SNPs at age 3.5 (rs1042098, $p = 0.033$; rs3863145, $p = 0.026$) and approaching significance for another two SNPs (rs40184, $p = 0.08$; rs6347, $p = 0.051$), with lower ADHD scores associated with SGA and higher ADHD scores associated with AGA.

There was also a significant SGA status by SNP interaction at age 3.5 years for the following SNPs: rs1042098 ($F_{(1,411)} = 4.56$, $p = 0.033$); rs40184 ($F_{(1,392)} = 5.47$, $p = 0.02$); rs6347 ($F_{(1,398)} = 5.16$, $p = 0.024$); and rs3863145 ($F_{(1,389)} = 4.979$, $p = 0.026$). In the SGA group, lower ADHD scores were observed for the following genotypes: rs1042098, C/C ($F_{(1,411)} = 4.70$, $p = 0.031$); rs40184, A/A ($F_{(1,392)} = 5.12$, p = 0.024); rs6347, G/G ($F_{(1,398)} = 4.91$, $p = 0.027$); and rs3863145, T/T ($F_{(1,389)} = 4.82$, $p = 0.029$). For the AGA group, higher ADHD scores were associated with these genotypes at age 3.5.

Simple effects tests also revealed that, within the SGA group, the minor homozygote for rs40184 (A/A) and rs6347 (G/G) had lower ADHD scores than the SGA heterozygotes ($F_{(1,392)} = 7.56$, p = 0.006 and $F_{(1,398)} = 4.66$, p = 0.031 respectively). Within the AGA group, the minor homozygote for rs1042098 (C/C) and rs3863145 (T/T) had higher ADHD scores than the AGA major heterozygotes and homozygotes ($F_{(1,411)} = 4.36$, $p = 0.037$ and $F_{(1,389)} = 4.69$, $p = 0.031$ respectively). No significant interactions were found at ages 7 or 11 years (means presented in Table 2, adjusted for sex and SES adversity).

The interaction between the genotypic susceptibility index and SGA status was examined in three ANCOVAs (one for each phase – 3.5, 7 and 11). The analyses revealed a significant effect of SGA at age 3.5 ($F_{(1,371)} = 6.78$, $p = 0.01$), showing lower ADHD scores in those born SGA (M = 2.98, SE = 0.23) compared to AGA (M = 3.82, SE = 0.22).

There was also a significant interaction between birth weight and genotypic susceptibility at age 3.5 years ($F_{(2,371)} = 5.41$, p = 0.005). The results and adjusted means for this analysis are shown in Table 3 and Fig. 3. Simple effects tests revealed that individuals who have two or more susceptibility variants have significantly higher sADHD if they

Table 2
Adjusted estimated marginal means and standard error (in parenthesis) for the ANCOVA of DAT 1 SNP and birth weight status on sADHD at ages 7 and 11.

		7 years		11 years	
		A/A + A/G	G/G	A/A + A/G	G/G
rs6347	SGA	3.32 (0.18)	2.29 (0.53)	3.01 (0.15)	2.44 (0.49)
	AGA	3.11 (0.15)	3.25 (0.53)	2.66 (0.13)	2.87 (0.45)
		G/G ± A/G	A/A	G/G ± A/G	A/A
rs8179029	SGA	3.28 (0.17)	2.81 (0.73)	3.02 (0.15)	2.99 (0.68)
	AGA	3.11 (0.15)	2.94 (0.73)	2.69 (0.13)	2.93 (0.62)
		G/G ± A/G	A/A	G/G ± A/G	A/A
rs40184	SGA	3.25 (0.19)	3.00 (0.41)	2.93 (0.16)	3.13 (0.36)
	AGA	3.19 (0.16)	2.91 (0.32)	2.78 (0.14)	2.23 (0.28)
		T/T ± C/T	C/C	T/T ± C/T	C/C
rs1042098	SGA	3.28 (0.17)	2.75 (0.70)	3.02 (0.15)	2.93 (0.63)
	AGA	3.10 (0.15)	3.94 (0.62)	2.72 (0.13)	3.17 (0.53)
		G/G ± G/C	C/C	G/G ± G/C	C/C
rs11564774	SGA	3.31 (0.17)	2.04 (0.87)	2.69 (0.13)	3.07 (0.54)
	AGA	3.10 (0.14)	3.79 (0.64)	3.04 (0.15)	2.58 (0.72)
		C/C ± C/T	T/T	C/C ± C/T	T/T
rs27072	SGA	3.20 (0.17)	4.43 (0.95)	3.00 (0.15)	3.55 (0.87)
	AGA	3.18 (0.14)	3.41 (1.16)	2.74 (0.13)	2.98 (0.89)
		C/C ± C/T	T/T	C/C ± C/T	T/T
rs3863145	SGA	3.30 (0.17)	2.50 (0.73)	3.00 (0.15)	3.03 (0.64)
	AGA	3.05 (0.15)	3.63 (0.60)	2.65 (0.13)	2.93 (0.50)

ANCOVA model included Age, SES adversity index, a child's sex, SGA/AGA status, SNP and the interaction SGA/AGA status*SNP. p values shown for SGA/AGA status and SNP interaction. SGA = small for gestational age, AGA = appropriate for gestational age, N = number of participants, sADHD measured from hyperactivity subscale of SDQ. All values adjusted for gender and SES adversity.

Table 3
Adjusted estimated marginal means and standard error (in parenthesis) for separate ANCOVA analyses at ages 3.5, 7 and 11 years for the interaction of genotypic index and birth weight status on sADHD.

		SGA		AGA		
Age	Genotypic index	N	EM Mean (SE)	N	EM Mean (SE)	Interaction
3.5 years						
	0	127	3.73 (0.18)	165	3.44 (0.16)	$p = 0.005$
	1	22	2.77 (0.44)	35	3.53 (0.35)	
	2+	16	2.45 (0.51)	14	4.51 (0.55)	
7 years						
	0	141	3.36 (0.20)	187	3.05 (0.17)	$p = 0.418$
	1	28	3.15 (0.44)	38	3.04 (0.38)	
	2+	16	2.62 (0.58)	17	3.42 (0.56)	
11 years						
	0	160	2.99 (0.17)	202	2.78 (0.15)	$p = 0.313$
	1	29	2.98 (0.40)	45	2.03 (0.32)	
	2+	16	2.85 (0.53)	19	3.05 (0.49)	

ANCOVA model included; SES adversity index, a child's sex, SGA/AGA status, genotypic index and the interaction SGA/AGA status*genotypic index. SGA = small for gestational age, AGA = appropriate for gestational age, N = number of participants, EM Mean = estimated marginal mean, SE = standard error, sADHD = symptoms of attention deficit disorder measured from the hyperactivity subscale of SDQ. All values adjusted for gender and SES adversity.

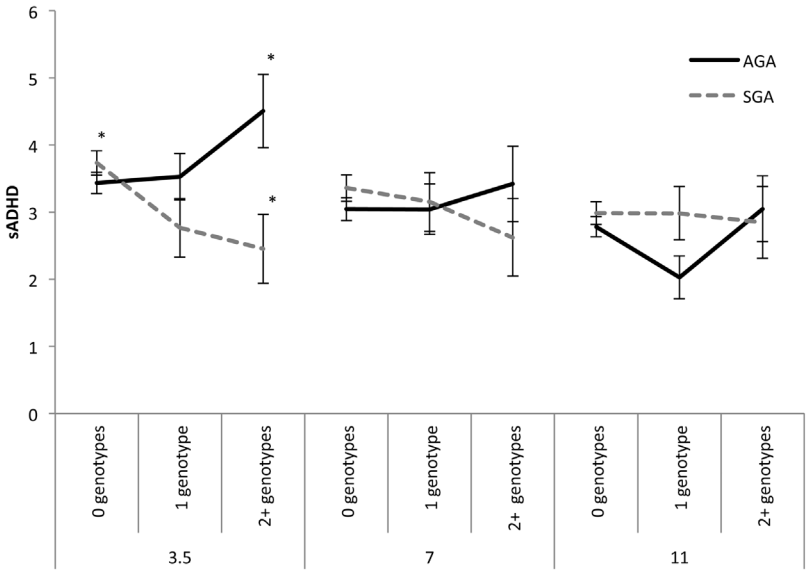

Fig. 3. The interaction between *DAT1* genotypic index and SGA/AGA status on sADHD at ages 3.5, 7 and 11 years. SGA = small for gestational age, AGA = appropriate for gestational age, genotype = number of genotypes from the genotypic index, sADHD = symptoms of attention deficit disorder measured from the hyperactivity subscale of SDQ.

are also born AGA (M = 4.51, SE = 0.55) than if they are born SGA (M = 2.45, SE = 0.51, $F_{(1,371)} = 7.53$, $p = 0.006$).

The interaction between SGA and genotypic susceptibility approached significance, whereby SGA individuals with no susceptibility alleles had higher ADHD scores (M = 3.73, SE = 0.18) compared to SGA individuals with two or more susceptibility alleles (M = 2.45, SE = 0.51, $p = 0.058$). For individuals with no susceptibility alleles, no significant difference was found between SGA and AGA groups. These findings indicate that as the number of susceptibility alleles an individual increases, sADHD decrease if they were born SGA and increase if they were born AGA.

4. Discussion

A suboptimal prenatal environment has been linked to the onset of ADHD symptoms in childhood [59]. Because previous research suggests dopamine dysfunction is implicated in several developmental disorders, including ADHD [26], we tested the idea that the association between particular SNPs in *DAT1* and ADHD might be moderated by birth weight. Specifically, the present study investigated whether being born SGA moderates the association between SNPs in *DAT1* and sADHD in early and middle childhood from a longitudinal cohort.

Nominally significant gene-environment interactions were found for four of the seven investigated SNPs at age 3.5 years: SNPs rs1042098; rs40184; rs6347; and rs3863145. The pattern of results was somewhat unexpected. There was no difference in ADHD scores between AGA and SGA groups who were heterozygotes and homozygotes for the major ADHD-risk alleles. Individuals who had the homozygote minor alleles of rs1042098 (C/C), rs40814 (A/A), rs6347 (G/G) and rs3863145 (T/T) showed lower ADHD scores within the group born SGA. Significant differences in ADHD scores within the SGA group (rs40184 and rs6347) and AGA group (rs1042098 and rs3863145) provides further support to the notion that differences in ADHD scores occur for different genotypes in light of prenatal adversity. Within the SGA group, ADHD scores were lower for the minor alleles (low-ADHD risk) compared to the heterozygotes and homozygotes for the major alleles. This contrasts with the AGA group where ADHD scores were higher for these same minor alleles. As such, the major "susceptibility" DAT1 alleles were consistent in SGA but not in AGA children.

In the current study, two SNPs were located in exons 9 and 15 (rs6347 and rs11564774), two in introns 9 and 14 (rs8179029, rs40814) and three were located in the 3′UTR (rs1042098, rs27072, rs3863145; [41,42,60]. Greenwood and Kelsoe [61] suggest that introns 9, 12 and 14 all influence *DAT1* expression, increasing genetic expression up to 2 times. This indicates that specific combinations of polymorphisms across the gene may lead to variations in *DAT1* expression [61]. Johnson et al. [62,63] have reported that the rs6347 SNP located in exon 9 may have a functional role in allelic mRNA expression imbalance [22,62,63,81]. Furthermore, Greenwood et al. [80] identified the A allele of *DAT1* SNP rs2702 to be in linkage disequilibrium with the 6R allele of the 40 bp VNTR in the 3′UTR, associated with the reduced functional activity of the DAT gene. Conversely, Pinsonneult et al. (2011) found that *DAT1* variant rs6347 influenced the DAT expression but not the 40 bp VNTR located in the 3′UTR.

Of the SNPs used in the current analysis, four have been associated with ADHD symptoms: rs40184 (G-allele); rs27072 (G-allele); rs1042098 (A-allele); and rs6347 (A-allele) [64,41,42,60,36,65,66]. However, there have also been failures to replicate these findings [67–69]. This leads to the conclusion that the overall effects of this gene are small (OR = 1.26; [41,42] and highly variable across populations [60,36].

So why was our effects observed only at the age 3.5 assessment? Wagner et al. [70] suggests that prenatal factors do not have lasting effects on behavioural outcomes later in life. Genetic overlap with other psychiatric disorders and/or age dependent epigenetic modifications could help to explain why no significant interactions were found for children aged 7 and 11 in the current study.

Overall, DNA methylation indicates one possible mechanism of how environmental influences can impact genetic expression over time. Interestingly, DNA methylation has been linked with ADHD symptoms in childhood [71,72]. Low DNA methylation levels at birth have been associated with increased ADHD scores in 6 year old children [71]. Furthermore, differences in DNA methylation in genetically identical twins and between assessments at age 5 and 10 provide evidence about how genetic expression can differ within individuals due to environmental influences over time [72]. These findings indicate that gene expression is not always fixed throughout childhood and how environmental influences may play a role in this change.

Our novel finding of a potentially protective effect of certain *DAT1* genotypes in light of a prenatal suboptimal environment does not support our original prediction that children born SGA with certain *DAT1* genotypes would show an increase in sADHD in childhood. The moderating effect of SGA on the *DAT1* genotype does, however, support the hypothesis that environmental factors affecting intrauterine growth (IGUR) also influence the central dopaminergic system. As such, certain *DAT1* polymorphisms in SGA individuals, may buffer the effects of prenatal adversity on dopaminergic signalling. That is, *DAT1* may hinder a developmental trajectory that would have otherwise manifest

as ADHD.

In contrast with our findings, birth weight has been found to moderate the association between angiogenic and neurotrophic SNPs on ADHD [73,74]. Dopaminergic SNPs, however, were not moderated by a suboptimal prenatal environment. Risk from angiogenic and neurotrophic genes were found for the minor alleles, suggesting that rare polymorphisms of these genes play an important part in ADHD development. Smith [73] suggests that the risk of later ADHD symptoms for those born with restricted foetal growth could be due to prenatal ischemia/hypoxia. Further research should be conducted to investigate the extent to which exposure to a suboptimal prenatal environment moderates the interaction between genetic factors and ADHD.

Further research into different combinations of *DAT1* polymorphisms and their impact on the expression of the DAT protein could reveal variants that are resilient and susceptible to exposure in a suboptimal prenatal environment. These different genotypic interactions may provide a link to the variations in phenotypic expressions observed in ADHD individuals [40]. However, replications with larger sample sizes are required to further understand these interactions.

As noted earlier, genetic overlap with other health disorders and ADHD (e.g., [75] could modify the influence of *DAT1* variants on later ADHD symptoms. For example, a study by Zhou et al. [66] found a significant effect of the SNPs rs40184 (A/G) and rs2652511 (A/G) in a group of ADHD children only when comorbidity with conduct disorder (CD) was not present. Further haplotype analysis of the two SNPs revealed an over transmission of the G/G haplotype, with the A/A haplotype indicative of a moderately protective effect. The finding of a protective effect of the A/A genotype aligns with findings from the present study for the SGA group.

Comorbidities with other psychiatric health disorders were not investigated in the present study (mostly due to the relatively small sample size precluding diagnosis such as bipolar or schizophrenia); therefore, differences in genotypic susceptibility cannot be ruled out. Moreover, cormorbidity with psychiatric health problems such as bipolar and depression is low at 3.5 years of age. However, the potential genetic overlap of conduct disorder, depression and bipolar with ADHD has the potential to influence *DAT1* SNPs (particularly rs40184 and rs27072) on ADHD scores for children in the present study.

In addition, differential susceptibility to prenatal glucocorticoid exposure potentially leads to variations in male and female developmental trajectories. This finding could help explain how males and females respond to later environmental adversities and provide a mechanism for the differences observed in functional impairment and comorbidity. Though sex was controlled for in the present study, sample size limitations restricted separate analyses by sex.

HPA dysregulation is thought to be associated with ADHD individuals [76] and those with low birth weights [77]. However, the link between early foetal adversity, the programming of the HPA axis and later symptoms of ADHD is still to be determined. Furthermore, mouse models of malnutrition via IUGR (a proxy for SGA) have not only identified links with behavioural abnormalities and dopamine dysfunction but a potential gene affecting both IGUR and dopamine neuron development [26]. Vucetic et al. [26] identified an imprinting gene Cdkn1c (highly susceptible to dysregulation in adverse environments) that was hypomethelated and overexpressed in the mouse model. This identifies another potential link between SGA, dopamine function and sADHD.

A further aim of the current study was to test whether the results aligned with the differential susceptibility framework [53,54]. Most studies focus on the negative “risk” genes in adverse environments (e.g. prenatal adversities, parental rearing and maltreatment). This leaves a large gap in the literature on the positive effects of this risk gene (or susceptibility gene) when in nurturing environments [78,54]. As an extension of the classic diathesis stress model, the differential susceptibility framework defines certain genotypes as more responsive to environmental influences. In the present analysis, the interaction between prenatal environmental factors and certain *DAT1* variants did not fully support the framework of differential susceptibility. In addition, our results suggested a reversed differential susceptibility. Individuals with the minor allele for two or more *DAT1* SNPs were associated with lower ADHD scores when exposed to suboptimal prenatal environmental factors, compared to an increase in ADHD scores for those with an optimal prenatal environment. It could be speculated that if there are genotypes that are more responsive to environmental exposures there could be genotypes that are resistant to their influence. Further research is required to determine if there are other potential protective factors for those exposed to prenatal adversities.

Interestingly, a recent study found results partially supporting the differential susceptibility framework with *DAT1* genotypes. Li and Lee [79] found that the 9/10 genotype of the 40pb VNTR located in the 3′UTR was associated with increased sADHD only in the presence of parental praise. Conversely parental negativity was associated with increased sADHD only for the 9/9 genotype. Though this finding is not in full support of the differential susceptibility theory, it does suggest how parental behaviour may interact with the genotype of the child in the formation of later behavioural problems.

A limitation of our study is the relatively small sample size. Due to our use of the minor SNP allele, cell frequencies for the minor SNP group were markedly reduced. For all significant associations the sample size did not drop below 10 participants for any group. Due to the resulting power limitations, the results should be interpreted with some caution.

The predominant focus of gene-environment studies has been on single time point measurements. This leaves a large gap in the literature on the impact of developmental change, whereby genetic and environmental factors may impact certain stages of development and not others. Combined with recent evidence from DNA methylation and *DAT1* studies, age dependent genetic susceptibility to ADHD symptoms is an area that needs further focus.

In conclusion, we provide initial evidence that being born SGA moderates the effect of SNPs in DAT1 (a gene previously associated with ADHD) on the risk for ADHD symptoms. A potential protective effect of individuals born SGA with minor alleles for certain DAT1 variants was found on symptoms of ADHD at 3.5 years of age. While our study did not support the differential susceptibility framework, it does provide useful information on the effects of a suboptimal environment on genetic variants. These findings help to explain some of the heterogeneity in ADHD outcomes for children born SGA, and add to current knowledge of prenatal determinants of sADHD.

Author declaration

All authors have seen and approved the final version of this manuscript. The article is our authors’ original work, it hasn't received prior publication and isn't under consideration for publication elsewhere.

Conflict of interests

All authors declare no Conflict of Interests with this manuscript. There is no financial or personal interest or belief that could affect our objectivity.

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