DAT1 and *DRD4* genes involved in key dimensions of adult ADHD

R. Hasler · A. Salzmänn · T. Bolzan ·
J. Zimmermann · P. Baud · P. Giannakopoulos ·
N. Perroud

Received: 24 September 2014 / Accepted: 23 December 2014 / Published online: 3 January 2015
© Springer-Verlag Italia 2015

Abstract Attention-deficit hyperactivity disorder (ADHD) is a highly heritable neurodevelopmental disorder often persisting in adulthood. Genetic studies of ADHD mainly focused on the *Dopamine Transporter* (*DAT1*) and the *Dopamine Receptor 4* (*DRD4*) genes. Nevertheless, polymorphisms of these genes explain only a small fraction of the assigned risk, suggesting that intermediate dimensions and environmental factors should also be considered. We investigated in 77 adult ADHD subjects compared to 474 controls, how polymorphisms within the genes coding for *DAT1* (40-bp VNTR in 3'UTR), the *Dopamine Receptor 2* (*DRD2*) (rs1799732) and *DRD4* (48-bp VNTR in exon 3), may modulate the expression of the disorder. By genotyping *DAT1*, we detected a new 9.5R allele showing a deletion of 40 bp and also an insertion of 19 bp compared to the 10R allele. This novel allele was found to be significantly protective for ADHD ($p < 0.0001$). Another significant difference was found in the distribution of *DRD4* 48-bp VNTR 6R allele when comparing patients and controls ($p = 0.0007$). In addition significant results were

also found for *DAT1* 9.5R allele, which was associated with impulsiveness ($p = 1.98 \times 10^{-4}$) and trait anger scores ($p = 7.66 \times 10^{-4}$). Moreover, impulsiveness scores were partly modulated by an interaction between the *DRD4* 48-bp VNTR 6R allele and childhood maltreatment ($p = 0.01$), however, this result did not resist correction for multiple comparisons. Altogether, our results show the putative involvement of *DAT1* and *DRD4* genes in the aetiology of ADHD with a main role in modulation of key dimensions of the disorder.

Keywords ADHD · Dopamine · *DAT1* · *DRD4* · Intermediary dimensions · Impulsivity · Anger traits

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder with prevalence between 5 and 8 % in children and teenagers [1]. The disorder often persists into adulthood with prevalence between 2.5 and 4.9 % and with variations in symptomatology and social impairment [2]. Familial and twin studies have shown a high heritability accounting for 60–90 % of the phenotypic variance [3].

Although ADHD is traditionally seen as resulting from deficits of executive functions [4, 5], many studies have also highlighted the important role played by the emotion dysregulation in the understanding of this disorder. Indeed, high reactivity of emotions in response to environmental stimuli, often manifested by poor control of anger and aggressive behaviours, are common symptoms observed in adult ADHD patients [6–9].

As described in borderline personality disorder, emotion dysregulation in adults suffering from ADHD might be the

Electronic supplementary material The online version of this article (doi:10.1007/s10072-014-2051-7) contains supplementary material, which is available to authorized users.

R. Hasler (✉) · A. Salzmänn · T. Bolzan ·
P. Giannakopoulos · N. Perroud
Department of Psychiatry, University of Geneva, Geneva,
Switzerland
e-mail: roland.hasler@hcuge.ch

R. Hasler · T. Bolzan
Neurocenter, Geneva, Switzerland

J. Zimmermann · P. Baud · P. Giannakopoulos · N. Perroud
Department of Mental Health and Psychiatry, University
Hospitals of Geneva, Geneva, Switzerland

late consequence of early environmental adversities such as childhood maltreatment [10, 11]. Moreover, prejudicious familial environment in childhood and perinatal adverse events has often been reported in adult ADHD, suggesting that childhood maltreatment is considered as a plausible etiological factor involved in the development and persistence of the disorder [12, 13].

Dopaminergic system, which is involved in movement control, reward and pleasure seeking, behavioural and emotional inhibition, is one of the main targets in genetic studies of ADHD [14, 15]. The most explored genes are *Dopamine Transporter 1 (DAT1)* and *Dopaminergic Receptor 4 (DRD4)* [14, 15]. Other dopaminergic genes have been also investigated in relation to ADHD, such as *Dopaminergic Receptor 2 (DRD2)*, *Dopaminergic Receptor 5 (DRD5)* and *Catechol O Methyl Transferase (COMT)* [16]. Two variable numbers of tandem repeats (VNTRs) polymorphisms in the 3'UTR of *DAT1* and in exon 3 of *DRD4* have been studied in ADHD: the 40-base pairs (bp) VNTR of *DAT1* and the 48-bp VNTR of *DRD4* with, respectively, the 10-repeat (10R) allele and the 7-repeat (7R) allele more frequently associated to ADHD [17]. Only a few studies have explored the link between intermediary dimensions, such as impulsiveness, anger or aggression, and dopaminergic genes, more specifically *DAT1* and *DRD4*. One study supported the influence of dopaminergic genes polymorphisms on impulsive-related measures in a sample of healthy adults [18]. The authors reported significant differences in inhibitory control in individuals with at least one 7R allele of the *DRD4* polymorphism compared to those not carrying this allele. Another investigation from Cornish and collaborators, who studied a sample recruited among the general population, found that *DAT1* gene influences ADHD symptoms and is associated with response inhibition [19]. A recent study, using genetics and electroencephalography, explored the association of both *DAT1* and *DRD4* and intermediary dimensions, such as response preparation and inhibitory response control, in an ADHD children population, using visual continuous performance tests [20]. They reported that both genes were functionally relevant risk factors for these intermediate dimensions in ADHD. Indeed, children with the *DRD4* 7R polymorphism showed reduced attentional orienting and response preparation, while the *DAT1* 10R-6R haplotype led to increased need for response preparation.

Although promising, the role of dopaminergic genes on intermediary dimensions related to emotional regulation, such as impulsiveness, anger and aggression has been poorly explored in adult ADHD. To date, only three studies in patients suffering from ADHD have investigated dopaminergic genes in relation to impulsivity-related measures [18–20].

In a sample of adult ADHD subjects, we investigated how polymorphisms within *DAT1* (40-bp VNTR in 3'UTR), *DRD2* (rs1799732) and *DRD4* (48-bp VNTR in exon 3) may modulate the expression of such intermediary dimensions. Since these intermediate dimensions may be partly determined by early life adverse events, interaction between these polymorphisms and childhood maltreatment in ADHD were also analysed.

Methods

Subjects

Seventy-seven adults suffering from ADHD were recruited in a specialised centre for the treatment of adult ADHD. Diagnosis was established prospectively according to DSM-IV-TR criteria based on the clinical assessment by trained psychiatrists (NP, BP and JZ) and using the French version of the Diagnostic Interview for Genetic Studies (DIGS), a semi-structured interview including a detailed investigation of childhood ADHD and its persistence into adulthood [21]. All diagnoses were confirmed by a best estimate procedure. All subjects also filled out the Adult Self-Report Scale (ASRS-1.1) [22], exploring current ADHD symptoms, the Wender Utah rating scale [23], establishing the childhood diagnosis of ADHD, and several self-report questionnaires investigating dimensions closely related to ADHD such as impulsiveness, anger expression and control, and aggression: Barrat Impulsiveness Scale (BIS-10) [24], state anger expression inventory (STAXI) [25], and the Life History of Aggression (LHA) [26]. The childhood trauma questionnaire (CTQ) [27] was used to assess history of child maltreatment.

Based on the DIGS, 14 ADHD subjects were not suffering from any lifetime comorbid psychiatric disorders. The remaining ones were suffering from one or several of the following lifetime psychiatric comorbidities: bipolar disorder ($N = 5$), major depressive disorder ($N = 39$), any anxiety disorder ($N = 25$), alcohol use disorder ($N = 23$), and substance use disorders ($N = 20$). ADHD subjects with psychotic-related disorders were excluded from the study.

Four hundred seventy four controls were recruited from the Blood Donor Centre of the University Hospitals of Geneva as previously described [28]. With the exception of CTQ, controls fulfilled all of the above-mentioned questionnaires.

All subjects were from European ancestry for at least two generations. The study was approved by the ethic committee of the University Hospitals of Geneva and all subjects gave their informed written consent.

Genotyping

DNA was extracted from peripheral blood leukocytes using of the Nucleon BACC 2 kit (Amersham Biosciences, GE Healthcare, Glatbrugg, Switzerland).

Genotyping methods for *DAT1* 40-bp VNTR, *DRD4* 48-bp VNTR and *DRD2* -141 ins/delC polymorphism (rs1799732) are described in details in the supplementary material.

Statistical analyses

The association between psychometric scores and clinical diagnosis was examined using linear regression on standardised values.

Allele and genotype group comparisons and their association with dimensional measures in the whole population were explored using maximum likelihood inference (LR) as implanted in UNPHASED [30]. To avoid loss of statistical power, all rare alleles with frequencies below 1 % in both controls and ADHD subjects were excluded from further analysis.

Since we compared genotypic and allelic distributions of three polymorphic markers between controls and cases as well as in association with ten-dimensional measures or subscales, a correction for multiple testing was required. One test for each gene was used for the case–control analysis. As several subscale scores were highly correlated, three tests were considered for BIS-10, four for STAXI and one for LHA. Thus, eight tests were used for each gene for the dimensional analysis. One additional test was added for the interaction term. Therefore, for a Bonferroni correction on the p values, we used $p = 0.05/(1 + 8 + 1) \times 3 = 0.002$ as a threshold for significance.

Results

Clinical characteristics

Table 1 shows the clinical and demographic characteristics of ADHD subjects and controls. ADHD subjects differed significantly from controls on all the dimensional scales and subscales. This was more pronounced for BIS-10 and within BIS-10 for motor impulsivity (Table 1).

DAT1 40-bp VNTR in 3'UTR

There was a significant group difference in the allelic distribution of *DAT1* 40-bp VNTR (LR Chi square 22.8; $df = 3$; $p = 4.44 \times 10^{-5}$) (Table 2). This was mainly explained by a lower frequency of the 9.5R, the newly discovered allele, in ADHD cases than controls [3.33 vs

12.08 %; $p = 6.67 \times 10^{-6}$; OR 0.25 (0.1; 0.64)]. This result remains significant even after correction for multiple comparisons. Subsequently, we sequenced this novel allele and compared to 10R allele sequence. In comparison to the 10R allele, 9.5R allele sequencing revealed a deletion of 40 bp combined with an insertion of 19 bp (Fig. 1). Based on the 10R allele published sequence by Mill and collaborators [31], the 9.5R allele showed a disruption in motif E (repeat 6) by the 40-bp deletion, while the 19-bp insertion induced an interruption of the motif F (repeat 7). Summing these sequence events, PCR length of the 9.5R allele became 454-bp compared to the 475-bp of the 10R allele (supplementary figure S1). Moreover, in the 9.5R allele sequence, we found 2 single nucleotide polymorphisms (SNPs) (Fig. 1), which were not described by Mill et al. [31]. SNP₁ (C > T) was found 13 bp after the deletion and SNP₂ (C > T) was uncovered at position 23 of motif D, which corresponds to motif G according to Mill et al. sequence.

In Table 2, the 11R allele was present in 25 controls but absent in our ADHD sample ($p < 0.0001$).

No significant group differences were found in genotype distribution (Table 3).

Regarding intermediary dimensions, *DAT1* 40-bp VNTR polymorphism significantly modulated STAXI Trait Anger (LR = 14.61; $df = 3$; $p = 0.002$) with the 9.5R being associated with lower Trait Anger scores [$p = 7.66 \times 10^{-4}$; $b = -0.1$ (-0.15; -0.04)]. *DAT1* 40-bp VNTR also modulated BIS-10 total score (LR = 12.83; $df = 3$; $p = 0.005$) with the 9.5R also associated with lower impulsiveness scores [$p = 1.98 \times 10^{-4}$; $b = -0.03$ (-0.05; -0.008)] (Table 4). However, these associations did not persist after correction for multiple comparisons. Finally, there was no significant interaction between childhood maltreatment and *DAT1* 40-bp VNTR when comparing 9.5R carriers to other repeat carriers.

DRD4 48-bp VNTR in exon 3

There was a significant group difference in the allelic distribution of *DRD4* 48-bp VNTR (LR Chi square: 18.4; $df = 5$; $p = 0.002$) (Table 2). This difference was mainly due to a higher frequency of the 6R allele in ADHD cases than controls [8.67 vs 1.75 %; $p = 7.31 \times 10^{-4}$; OR = 4.94 (2.28; 10.72)]. The genotype distribution was significantly different between ADHD subjects and controls (LR Chi square: 61.6; $df = 13$; $p = 2.71 \times 10^{-8}$) (Table 3). This difference was firstly accounted by several genotypes not observed in ADHD cases: 2R/2R; 3R/3R; and 5R/7R (Table 4). Importantly, the difference in genotype distribution persisted even after excluding these genotypes (LR Chi square: 46; $df = 8$; $p = 2.38 \times 10^{-7}$) and was mainly accounted by a higher frequency of the 4R/

Table 1 Clinical and demographic characteristics of ADHD subjects and controls

		ADHD (<i>N</i> = 77) <i>N</i> (%)	Controls (<i>N</i> = 474) <i>N</i> (%)	df; χ^2	<i>p</i>
Female		22 (28.6)	169 (35.6)	2; 1.46	0.226
ADHD type	Attentional	27 (35.1)	–		–
	Hyp./impul.	5 (6.1)	–		–
	Combined	45 (58.4)	–		–
		Mean (SD)	Mean (SD)	<i>b</i>	<i>p</i>
Age at onset		5.4 (2.1)	–		–
Age		38.4 (10.3)	44.8 (13.1)	–0.43	0.0004
ASRS_v1.1		47.8 (10.6)	–		–
STAXI	State anger	20.1 (7.1)	13.1 (4.1)	1.05	<0.0001
	Trait anger	25 (6.1)	19.6 (4.8)	0.81	<0.0001
	Anger in	19.2 (5.3)	16.4 (4.9)	0.57	<0.0001
	Anger out	16.1 (4.3)	12.7 (3.4)	0.64	<0.0001
	Anger cont.	20.8 (4.6)	24.5 (4.1)	–0.67	<0.0001
BIS-10	Non-planning	24.2 (7.1)	16.3 (6.4)	1.03	<0.0001
	Attentional	26.3 (6.2)	17.3 (5.8)	1.22	<0.0001
	Motor	25.4 (7.2)	12.8 (6.2)	1.37	<0.0001
	Total	75.9 (15.8)	46.5 (13.1)	1.47	<0.0001
LHA		13.1 (10.2)	3.7 (4.4)	1.09	<0.0001
CTQ	Sexual abuse	17 (22.9)	–		–
	Physical abuse	25 (33.8)	–		–
	Physical neglect	28 (37.8)	–		–
	Emotional abuse	49 (66.2)	–		–
	Emotional neglect	55 (74.3)	–		–

Table 2 Allelic distribution between ADHD subjects and controls

Allele	ADHD	Freq	Controls	Co-freq	Individual <i>p</i> value	<i>p</i> value
<i>DAT1</i> 40-bp VNTR						
9R	38	0.253	160	0.203	0.217	4.44 × 10 ^{−5}
9.5R	5	0.033	95	0.120	<0.0001	
10R	107	0.713	507	0.642	0.095	
11R	0	0	25	0.032	<0.0001	
<i>DRD4</i> 48-bp VNTR						
2R	11	0.073	81	0.102	0.228	0.002
3R	9	0.060	50	0.063	0.899	
4R	85	0.567	509	0.638	0.129	
5R	7	0.047	29	0.036	0.675	
6R	13	0.087	14	0.018	0.0007	
7R	25	0.167	113	0.142	0.532	
<i>DRD2</i> −141ins/delC (rs1799732)						
C	118	0.881	771	0.915	0.269	0.202
Del	16	0.119	71	0.084	0.269	

6R (14.67 vs 1.50 %; $p = 2.11 \times 10^{-5}$; OR = 10.94 (3.91;30.64)] and a lower frequency of the 4R/7R genotype [6.67 vs 19.55 %; $p = 2.16 \times 10^{-4}$; OR = 0.28 (0.11; 0.73)] in ADHD cases than in controls.

At the dimensional level, *DRD4* 48-bp VNTR was significantly associated with Anger In scores (LR Chi square: 18.98; df = 5; $p = 0.002$) mainly due to lower scores in carriers of the 3R allele [$p = 0.009$; $b = -0.14$ (–0.24; –

(A) 10R VNTR (475 bp) **(B) 9.5R VNTR (454 bp)**

Fig. 1 **a** 10R wild-type (wt) sequence chromatogram of *DAT1* VNTR based on Mill et al. [31]. **b** 9.5R mutant chromatogram of *DAT1* VNTR shows a 40-bp deletion at position 11 of the motif E and a 19-bp insertion at the end of motif F. This sequence chromatogram of the 9.5R allele depicts a double-peaked trace, resulting from a

deletion and an insertion of one 10R allele. This sequence contains also two genetic variations (SNP₁ and SNP₂), which are not present in 10R wt. According to Mill et al. sequence, motif D showing SNP₂ becomes motif G

0.05)]. When looking at the *DRD4* 48-bp VNTR genotype, the more significant associations were: (1) with Anger In scores (LR Chi square: 33.24; df = 13; $p = 0.002$) mainly explained by lower scores in the 3R/6R and 3R/7R carriers [$p = 1.22 \times 10^{-4}$; $b = -0.31$ (−0.68; −0.06) and $p = 2.84 \times 10^{-7}$; $b = -0.34$ (−1.09; −0.04)]; (2) with BIS-10 total score (LR Chi square: 30.65; df = 13; $p = 0.004$) mainly explained by higher scores in 4R/6R carriers [$p = 1.77 \times 10^{-4}$; $b = 0.07$ (0.003; 0.13)]; (3) with LHA scores (LR Chi square: 28.47; df = 12; $p = 0.005$) mainly explained by lower scores in 2R/7R carriers ($p = 1.12 \times 10^{-14}$; $b = -0.34$ (−2.52; −0.08)).

No interaction between this polymorphism and childhood maltreatments reached significance after correction for multiple testing. Nevertheless, there was one interaction that reached a p value < 0.05. This interaction showed that physically abused subjects, who are 6R allele carriers, had higher level of BIS-10 non-planning than physically abused subjects, who did not carry 6R allele [$p = 0.01$; $b = 12.1$ (2.98; 21.27)] (Fig. 2).

DRD2 −141ins/delC (rs1799732)

There was no significance difference in the allelic or genotypic distribution of *DRD2* −141ins/delC between ADHD cases and controls (LR Chi square: 1.62; df = 1; $p = 0.20$ and LR Chi square: 1.45; df = 2; $p = 0.48$)

(Tables 2, 3). Moreover, there was no main effect of this polymorphism on the intermediary phenotypes and also no significant interactions were found between child maltreatments and this polymorphism.

Discussion

Our data reveal that the allelic and genotype distributions of *DAT1* 40-bp VNTR in 3'UTR and *DRD4* 48-bp VNTR in exon 3 significantly differed between ADHD cases and controls. These polymorphisms also modulated the expression of intermediate dimensions such as impulsiveness and anger traits that were significantly different between adult ADHD and controls.

At the genetic level, *DAT1* 40-bp VNTR was significantly associated with ADHD and showed a lower frequency of the newly discovered 9.5R allele in patients compared to controls. Previous studies, mainly performed in ADHD children, led to discrepant results. The 9R and the 10R have been associated with ADHD, but a wide agreement on this matter is still lacking [32, 33]. Our results suggest that none of them but rather the 9.5R allele may be considered as protective against ADHD. The latter, never reported in previous studies, may have been falsely assigned to either 9R or 10R and thus contributing to the difficulty to find concordant associations between ADHD

Table 3 Genotype distribution between ADHD subjects and controls

Genotype	ADHD	ADHD-freq	Controls	Co-freq	Individual <i>p</i> value	<i>p</i> value
<i>DAT1</i> 40-bp VNTR						
9R/9R	7	0.093	25	0.063	0.40	0.021
9R/9.5R	1	0.013	10	0.025	0.43	
9R/10R	23	0.307	98	0.248	0.31	
9.5R/9.5R	0	0	20	0.051	<0.0001	
9.5R/10R	4	0.053	41	0.104	0.09	
9.5R/11R	0	0	4	0.01	<0.0001	
10R/10R	40	0.533	179	0.453	0.20	
10R/11R	0	0	8	0.02	<0.0001	
11R/11R	0	0	6	0.015	<0.0001	
<i>DRD4</i> 48-bp VNTR						
2R/2R	0	0	19	0.048	<0.0001	2.71×10^{-8}
2R/4R	8	0.107	35	0.088	0.62	
2R/6R	1	0.013	1	0.003	0.33	
2R/7R	2	0.027	5	0.013	0.45	
3R/3R	0	0	13	0.033	<0.0001	
3R/4R	7	0.093	12	0.03	0.05	
3R/5R	1	0.013	2	0.005	0.52	
3R/6R	1	0.013	5	0.013	0.96	
4R/4R	27	0.36	187	0.469	0.06	
4R/6R	11	0.147	6	0.015	<0.0001	
4R/7R	5	0.067	78	0.196	0.0002	
5R/5R	3	0.04	9	0.023	0.46	
5R/7R	0	0	6	0.015	<0.0001	
7R/7R	9	0.12	10	0.025	0.0048	
<i>DRD2</i> -141ins/delC (rs1799732)						
C/C	53	0.791	358	0.85	0.26	0.482
C/delC	12	0.179	55	0.131	0.33	
delC/delC	2	0.03	8	0.019	0.61	

Table 4 Association between dimensional measures and genotypes

	<i>DAT1</i> 40-bp VNTR main effect			<i>DRD4</i> 48-bpVNTR main effect			<i>DRD2</i> -141ins/delC main effect		
	LR test	df	<i>p</i>	LR test	df	<i>p</i>	LR test	df	<i>p</i>
STAXI									
State anger	4.71	3	0.19	11.84	5	0.037	0.25	1	0.61
Trait anger	14.61	3	0.002	4.64	5	0.46	0.03	1	0.86
Anger in	10.62	3	0.01	18.98	5	0.002	0.06	1	0.8
Anger out	8.99	3	0.03	2.32	5	0.8	1.65	1	1.19
Anger control	1.48	3	0.69	10.14	5	0.07	0.05	1	0.82
BIS_10									
Non-planning	6.34	3	0.09	14.57	5	0.01	0.76	1	0.36
Motor	7.91	3	0.048	14.7	5	0.01	0.06	1	0.8
Cognitive	13.59	3	0.004	3.65	5	0.6	0.19	1	0.66
Total	12.83	3	0.005	13.07	5	0.03	0.005	1	0.94
LHA	7.38	3	0.06	7.1	5	0.21	0.25	1	0.61

Fig. 2 Interaction between *DRD4* 48-bp VNTR (6R carriers or not) and childhood physical abuse on BIS-10 non-planning scores. PA physical abuse. Physically non-abused/6R non-carriers: $N = 41$; physically non-abused/6R carriers: $N = 7$; physically abused/6R non-carriers: $N = 19$; physically abused/6R carriers: $N = 5$

and this polymorphism. Moreover, it is not surprising to uncover a deletion plus an insertion within the 9.5R allele. As depicted by sequencing, the 9.5R allele is the result of an unequal genetic recombination caused by the misalignment of repeat units, which induce variations in sequence length [34, 35]. In the 9.5R sequence, we also detected 2 SNPs, which are likely to be found in large VNTRs as reported by Ding and collaborators [36]. As we only sequenced one homozygous patient for the 9.5R allele, we are not able to confirm if all the 9.5 alleles show the same recombination events. Further investigations are needed to validate the present sequence. The 11R frequency also differed between controls and ADHD cases. In fact, this allele was not found in ADHD patients and its frequency was very low in the current control population (3.2 %). This observation is consistent with those published by Biederman and colleagues, who reported that among 563 ADHD patients, only 11 carried the 11R allele. Consequently, the 11R allele frequency accounted for 2 % in this study [37].

Several articles reported that the 7R allele of the *DRD4* 48-bp VNTR polymorphism increases the risk of ADHD [37–39]. We were not able to corroborate this hypothesis in our adult sample. Indeed, we found that the 6R and (more specifically carriers of the 4R/6R genotype) rather than the 7R allele was associated with an increased risk of ADHD. The 7R allele may represent a vulnerability factor for the development of ADHD in childhood but not for the persistence of the disorder in adulthood. Other alleles, such as the one found in our study (6R), maybe associated with later development and/or persistence of the disorder in adulthood maybe due to interaction with environmental factors found later in the life of an individual. In this

perspective, we found that 6R allele carriers, who suffered from physical abuses in childhood, had higher level of impulsiveness (BIS-10 non-planning) than physically abused subjects, who are non-carriers of the 6R allele.

There is a wide consensus that impulsiveness, and especially of the motor type, or behavioural inhibition is one of the main characteristics that distinguish ADHD subjects from controls and other clinical populations [40, 41]. Our results are concordant with these findings showing that the dimension best discriminating adult ADHD from controls is indeed impulsiveness and within impulsiveness, motor impulsivity.

In addition, we found that the *DAT1* 40-bp VNTR 9.5R allele was associated with lower impulsiveness and anger trait scores, suggesting that the effect of this polymorphism on ADHD may be partly dependent on the modulation of these two intermediary measures [19]. Consistent with these findings, several genotypes, including the 4R/6R, significantly modulated intermediary measures, suggesting that, as for the *DAT1* 40-bp VNTR, the effect of this polymorphism on the risk for ADHD may be attributed to genetic modulation of these dimensions.

Despite the relative small size of our sample of ADHD patients that prevent for drawing definite conclusions, these results support the idea that *DAT1* 40-bp VNTR and *DRD4* 48-bp VNTR modulate impulsivity in ADHD samples [18–20]. In agreement with the notion that emotional dysregulation including the deficits in inhibiting and regulating emotions such as anger and aggression [33] is key component of ADHD, our findings indicate that both genes modulate the anger, more precisely the propensity toward anger for *DAT1*, and the tendency for anger turned inward for *DRD4*. Strengths of the present study include the presence of a pure sample of adult ADHD without other psychiatric comorbidities, careful genetic analysis of dopaminergic system-related polymorphisms and exploration of intermediary factors related to emotional dysregulation. Our study has several limitations to be considered. First, it was not designed to measure environmental factors that may play a crucial role in the persistence of the disorder in adulthood, such as marital conflicts, and/or loss of job. Those adverse life events might interact with 6R allele to favour the persistence of the disorder in adulthood. Moreover, our results are limited to the dimensions measured by the scales used in this study. In this respect, the use of self-report questionnaires to measure intermediary dimensions and childhood maltreatment may possibly differ from behavioural tests or more objectives measures [11]. Future studies in larger ADHD cohorts including characterization of life stressors and detailed behavioural analyses are needed to further explore the validity of our observations.

Conflict of interest The authors declare no conflict of interest.

References

- Bush G (2010) Attention-deficit/hyperactivity disorder and attention networks. *Neuropsychopharmacology* 35(1):278–300. doi:10.1038/npp.2009.120
- Simon V, Czobor P, Balint S, Meszaros A, Bitter I (2009) Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. *Br J Psychiatry* 194(3):204–211. doi:10.1192/bjp.bp.107.048827
- Stergiakouli E, Thapar A (2010) Fitting the pieces together: current research on the genetic basis of attention-deficit/hyperactivity disorder (ADHD). *Neuropsychiatr Dis Treat* 6:551–560. doi:10.2147/NDT.S11322
- Barkley RA (1997) Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychol Bull* 121(1):65–94
- Gau SS, Shang CY (2010) Executive functions as endophenotypes in ADHD: evidence from the Cambridge neuropsychological test battery (CANTAB). *J Child Psychol Psychiatry* 51(7):838–849. doi:10.1111/j.1469-7610.2010.02215.x
- Martel MM (2009) Research review: a new perspective on attention-deficit/hyperactivity disorder: emotion dysregulation and trait models. *J Child Psychol Psychiatry* 50(9):1042–1051. doi:10.1111/j.1469-7610.2009.02105.x
- Hofvander B, Stahlberg O, Nyden A, Wentz E, Innocenti A, Billstedt E, Forsman A, Gillberg C, Nilsson T, Rastam M, Anckarsater H (2011) Life history of aggression scores are predicted by childhood hyperactivity, conduct disorder, adult substance abuse, and low cooperativeness in adult psychiatric patients. *Psychiatry Res* 185(1–2):280–285. doi:10.1016/j.psychres.2010.05.008
- Shaw P, Stringaris A, Nigg J, Leibenluft E (2014) Emotion dysregulation in attention deficit hyperactivity disorder. *Am J Psychiatry* 171(3):276–293. doi:10.1176/appi.ajp.2013.13070966
- Villemonteix T, Purper-Ouakil D, Romo L (2014) Is emotional dysregulation a component of attention-deficit/hyperactivity disorder (ADHD)? *Encephale*. doi:10.1016/j.encep.2013.12.004
- De Sanctis VA, Nomura Y, Newcorn JH, Halperin JM (2012) Childhood maltreatment and conduct disorder: independent predictors of criminal outcomes in ADHD youth. *Child Abuse Negl* 36(11–12):782–789. doi:10.1016/j.chiabu.2012.08.003
- Prada P, Hasler R, Baud P, Bednars G, Ardu S, Krejci I, Nicastro R, Aubry JM, Perroud N (2014) Distinguishing borderline personality disorder from adult attention deficit/hyperactivity disorder: a clinical and dimensional perspective. *Psychiatry Res* 217(1–2):107–114. doi:10.1016/j.psychres.2014.03.006
- Briscoe-Smith AM, Hinshaw SP (2006) Linkages between child abuse and attention-deficit/hyperactivity disorder in girls: behavioral and social correlates. *Child Abuse Negl* 30(11):1239–1255. doi:10.1016/j.chiabu.2006.04.008
- Miller CJ, Miller SR, Newcorn JH, Halperin JM (2008) Personality characteristics associated with persistent ADHD in late adolescence. *J Abnorm Child Psychol* 36(2):165–173. doi:10.1007/s10802-007-9167-7
- Turic D, Swanson J, Sonuga-Barke E (2010) DRD4 and DAT1 in ADHD: functional neurobiology to pharmacogenetics. *Pharmacogenomics Pers Med* 3:61–78
- Prince J (2008) Catecholamine dysfunction in attention-deficit/hyperactivity disorder: an update. *J Clin Psychopharmacol* 28(3 Suppl 2):S39–S45. doi:10.1097/JCP.0b013e318174f92a
- Thapar A, Cooper M, Jefferies R, Stergiakouli E (2012) What causes attention deficit hyperactivity disorder? *Arch Dis Child* 97(3):260–265. doi:10.1136/archdischild-2011-300482
- Swanson JM, Flodman P, Kennedy J, Spence MA, Moyzis R, Schuck S, Murias M, Moriarty J, Barr C, Smith M, Posner M (2000) Dopamine genes and ADHD. *Neurosci Biobehav Rev* 24(1):21–25
- Congdon E, Lesch KP, Canli T (2008) Analysis of DRD4 and DAT polymorphisms and behavioral inhibition in healthy adults: implications for impulsivity. *Am J Med Genet B Neuropsychiatr Genet* 147B(1):27–32. doi:10.1002/ajmg.b.30557
- Cornish KM, Manly T, Savage R, Swanson J, Morisano D, Butler N, Grant C, Cross G, Bentley L, Hollis CP (2005) Association of the dopamine transporter (DAT1) 10/10-repeat genotype with ADHD symptoms and response inhibition in a general population sample. *Mol Psychiatry* 10(7):686–698. doi:10.1038/sj.mp.4001641
- Albrecht B, Brandeis D, von Sandersleben HU, Valko L, Heinrich H, Xu X, Drechsler R, Heise A, Kuntsi J, Muller UC, Asherson P, Steinhausen HC, Rothenberger A, Banaschewski T (2014) Genetics of preparation and response control in ADHD: the role of DRD4 and DAT1. *J Child Psychol Psychiatry*. doi:10.1111/jcpp.12212
- Preisig M, Fenton BT, Matthey ML, Berney A, Ferrero F (1999) Diagnostic interview for genetic studies (DIGS): inter-rater and test-retest reliability of the French version. *Eur Arch Psychiatry Clin Neurosci* 249(4):174–179
- Adler LA, Spencer T, Faraone SV, Kessler RC, Howes MJ, Biederman J, Secnik K (2006) Validity of pilot adult ADHD self-report scale (ASRS) to rate adult ADHD symptoms. *Ann Clin Psychiatry* 18(3):145–148. doi:10.1080/10401230600801077
- Bayle FJ, Krebs MO, Martin C, Bouvard MP, Wender P (2003) French version of Wender Utah rating scale (WURS). *Can J Psychiatry* 48(2):132
- Patton JH, Stanford MS, Barratt ES (1995) Factor structure of the Barratt impulsiveness scale. *J Clin Psychol* 51(6):768–774
- Spielberger CD (1988) State-trait anger expression inventory, research edn. Professional Manual Psychological Assessment Resources, Odessa
- Coccaro EF, Berman ME, Kavoussi RJ (1997) Assessment of life history of aggression: development and psychometric characteristics. *Psychiatry Res* 73(3):147–157
- Bernstein DPFL (1998) Childhood trauma questionnaire. A retrospective self-report. The Psychological Corporation, San Antonio
- Perroud N, Baud P, Mouthon D, Courtet P, Malafosse A (2011) Impulsivity, aggression and suicidal behavior in unipolar and bipolar disorders. *J Affect Disord* 134(1–3):112–118. doi:10.1016/j.jad.2011.05.048
- Qian Q, Wang Y, Zhou R, Yang L, Faraone SV (2004) Family-based and case-control association studies of DRD4 and DAT1 polymorphisms in Chinese attention deficit hyperactivity disorder patients suggest long repeats contribute to genetic risk for the disorder. *Am J Med Genet B Neuropsychiatr Genet* 128B(1):84–89. doi:10.1002/ajmg.b.30079
- Dudbridge F (2008) Likelihood-based association analysis for nuclear families and unrelated subjects with missing genotype data. *Hum Hered* 66(2):87–98. doi:10.1159/000119108
- Mill J, Asherson P, Craig I, D'Souza UM (2005) Transient expression analysis of allelic variants of a VNTR in the dopamine transporter gene (DAT1). *BMC Genet* 6:3. doi:10.1186/1471-2156-6-3
- Madras BK, Miller GM, Fischman AJ (2005) The dopamine transporter and attention-deficit/hyperactivity disorder. *Biol Psychiatry* 57(11):1397–1409. doi:10.1016/j.biopsych.2004.10.011
- Barkley RA, Smith KM, Fischer M, Navia B (2006) An examination of the behavioral and neuropsychological correlates of three ADHD candidate gene polymorphisms (DRD4 7+, DBH TaqI A2, and DAT1 40 bp VNTR) in hyperactive and normal

- children followed to adulthood. *Am J Med Genet B Neuropsychiatr Genet* 141B(5):487–498. doi:[10.1002/ajmg.b.30326](https://doi.org/10.1002/ajmg.b.30326)
34. Smith GP (1976) Evolution of repeated DNA sequences by unequal crossover. *Science* 191(4227):528–535
 35. Murray J, Buard J, Neil DL, Yeramian E, Tamaki K, Hollies C, Jeffreys AJ (1999) Comparative sequence analysis of human minisatellites showing meiotic repeat instability. *Genome Res* 9(2):130–136
 36. Ding YC, Chi HC, Grady DL, Morishima A, Kidd JR, Kidd KK, Flodman P, Spence MA, Schuck S, Swanson JM, Zhang YP, Moyzis RK (2002) Evidence of positive selection acting at the human dopamine receptor D4 gene locus. *Proc Natl Acad Sci USA* 99(1):309–314. doi:[10.1073/pnas.012464099](https://doi.org/10.1073/pnas.012464099)
 37. Biederman J, Petty CR, Ten Haagen KS, Small J, Doyle AE, Spencer T, Mick E, Monuteaux MC, Smoller JW, Faraone SV (2009) Effect of candidate gene polymorphisms on the course of attention deficit hyperactivity disorder. *Psychiatry Res* 170(2–3):199–203. doi:[10.1016/j.psychres.2008.12.016](https://doi.org/10.1016/j.psychres.2008.12.016)
 38. Muglia P, Jain U, Maciardi F, Kennedy JL (2000) Adult attention deficit hyperactivity disorder and the dopamine D4 receptor gene. *Am J Med Genet* 96(3):273–277
 39. Li D, Sham PC, Owen MJ, He L (2006) Meta-analysis shows significant association between dopamine system genes and attention deficit hyperactivity disorder (ADHD). *Hum Mol Genet* 15(14):2276–2284. doi:[10.1093/hmg/ddl152](https://doi.org/10.1093/hmg/ddl152)
 40. Malloy-Diniz L, Fuentes D, Leite WB, Correa H, Bechara A (2007) Impulsive behavior in adults with attention deficit/hyperactivity disorder: characterization of attentional, motor and cognitive impulsiveness. *J Int Neuropsychol Soc* 13(4):693–698. doi:[10.1017/S1355617707070889](https://doi.org/10.1017/S1355617707070889)
 41. Bari A, Robbins TW (2013) Inhibition and impulsivity: behavioral and neural basis of response control. *Prog Neurobiol*. doi:[10.1016/j.pneurobio.2013.06.005](https://doi.org/10.1016/j.pneurobio.2013.06.005)