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ORIGINAL ARTICLE

Influence of *DAT1* and *COMT* variants on neural activation during response inhibition in adolescents with attention-deficit/hyperactivity disorder and healthy controls

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Background. Impairment of response inhibition has been implicated in attention-deficit/hyperactivity disorder (ADHD). Dopamine neurotransmission has been linked to the behavioural and neural correlates of response inhibition. The current study aimed to investigate the relationship of polymorphisms in two dopamine-related genes, the catechol-*O*-methyltransferase gene (*COMT*) and the dopamine transporter gene (*SLC6A3* or *DAT1*), with the neural and behavioural correlates of response inhibition.

Method. Behavioural and neural measures of response inhibition were obtained in 185 adolescents with ADHD, 111 of their unaffected siblings and 124 healthy controls (mean age 16.9 years). We investigated the association of *DAT1* and *COMT* variants on task performance and whole-brain neural activation during response inhibition in a hypothesis-free manner. Additionally, we attempted to explain variance in previously found ADHD effects on neural activation during response inhibition using these *DAT1* and *COMT* polymorphisms.

Results. The whole-brain analyses demonstrated large-scale neural activation changes in the medial and lateral prefrontal, subcortical and parietal regions of the response inhibition network in relation to *DAT1* and *COMT* polymorphisms. Although these neural activation changes were associated with different task performance measures, no relationship was found between *DAT1* or *COMT* variants and ADHD, nor did variants in these genes explain variance in the effects of ADHD on neural activation.

Conclusions. These results suggest that dopamine-related genes play a role in the neurobiology of response inhibition. The limited associations between gene polymorphisms and task performance further indicate the added value of neural measures in linking genetic factors and behavioural measures.

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Introduction

Response inhibition, i.e. the suppression of actions that are no longer required or are inappropriate, is one of the key components of executive control (Ridderinkhof *et al.* 2004). Deficits in response inhibition have been reported in a range of psychiatric disorders, including attention-deficit/hyperactivity disorder (ADHD) (Slaats-Willemse *et al.* 2003). Both response inhibition and ADHD are highly heritable and share genetic loading, such that response inhibition is considered to be an endophenotype for ADHD (Faraone & Khan, 2005; Crosbie *et al.* 2013). An endophenotype is a quantitative biological trait that lies on the pathway from gene to clinical phenotype (Gottesman & Gould, 2003). However, behavioural response inhibition measures show a large overlap in performance between probands

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with ADHD and healthy controls (Lipszyc & Schachar, 2010). On the other hand, several studies (Pliszka *et al.* 2006; Cubillo *et al.* 2011; Mulligan *et al.* 2011), including one by our group (Van Rooij *et al.* 2015), have indicated that the neural activation during response inhibition shows a stronger link with ADHD than behavioural measures of response inhibition.

Response inhibition has a clear link with the neurotransmitter dopamine, as evidenced by positron emission tomography studies which have shown that response inhibition is associated with dopamine release in the striatum, mediated by dopamine D2/D3 receptor availability in the striatum (Albrecht *et al.* 2014). Additionally, the most common treatment in ADHD is prescription of methylphenidate medication, a dopamine reuptake inhibitor that interacts with the dopamine transporter in the striatum (Schwartz & Correll, 2014), has been shown to improve response inhibition performance (Costa *et al.* 2013) and to normalize neural activation during response inhibition in children with and without ADHD (Rubia *et al.* 2009).

Multiple studies have also implicated a relationship between genetic variants related to the dopamine system in response inhibition performance (Congdon *et al.* 2008). These studies have indicated that genetic variants related to less extracellular dopamine availability are associated with decreased response inhibition performance. However, to date only a handful of studies have investigated the association between genetic variants and neural activation during response inhibition. The first study demonstrated that polymorphisms in two dopaminergic genes, the catechol-*O*-methyltransferase gene (*COMT*) and the dopamine transporter gene (*SLC6A3* or *DAT1*), were related to neural activation during response inhibition (Congdon *et al.* 2009). Specifically, *COMT* gene rs4680 single nucleotide polymorphism (SNP) Met-allele carriers and 9-repeat carriers of a variable number of tandem repeats (VNTR) in the 3′-untranslated region (UTR) of the *DAT1* gene have previously shown greater activation in medial and inferior frontal brain regions during response inhibition. A more recent, larger, study has also investigated the effect of this *COMT* polymorphism, but found the opposite pattern, reporting increased activation in Val-allele carriers, and this only in males (White *et al.* 2014). Another study has further investigated the association between *DAT1* gene polymorphisms and response inhibition performance and activation (Cummins *et al.* 2012). Here, both the presence of the rs460000C allele and the rs37020T allele predicted longer stop-signal reaction time (SSRT) while rs37020T allele carriers showed decreased neural activation in medial frontal areas during response inhibition. That study did not replicate the association between the *DAT1* VNTR and neural activation (Congdon *et al.* 2009). The *DAT1* 3′-UTR 10 repeat variant (Braet *et al.* 2011) and the *COMT* rs4680 Val-allele have also been linked to increased risk for ADHD (Guan *et al.* 2009). Last, a recent large-scale imaging study has found direct evidence for a role between the monoamine oxidase A (*MAOA*) genotype and neural activation during response inhibition in ADHD (Nymberg *et al.* 2013), showing that the decreased activation in ADHD may be dependent on the *MAOA* genotype. A recent meta-analysis (Gizer *et al.* 2009) has confirmed this significant association of *MAOA* and *DAT1* variants with ADHD, but not for the *COMT* variant. Additionally, several studies have demonstrated that a haplotype of two *DAT1* VNTRs in the 3′-UTR and intron-8 region shows the strongest relationship with ADHD (Brookes *et al.* 2006*a*; Asherson *et al.* 2007).

The present study was undertaken to further investigate the association between genetic variants influencing dopamine neurotransmission and neural activation during response inhibition in individuals with and without ADHD. The influence of five variants based on the previous studies (Congdon *et al.* 2009; Cummins *et al.* 2012; White *et al.* 2014) was investigated. Both the rs37020 and rs460000 SNPs of the *DAT1* gene were included, as well as the *rs4680* SNP of the *COMT* gene and the 10–6 haplotype of the 3′-UTR and intron-8 *DAT1* VNTRs. Our study aimed to both validate previous results of whole-brain analyses of the influence of *DAT1* and *COMT* on neural measures of response inhibition (Congdon *et al.* 2009; Cummins *et al.* 2012) and to extend them to participants with ADHD. *COMT* is one of the main enzymatic regulators of dopamine availability in the prefrontal cortex (Hong *et al.* 1998), while *DAT1* is expressed mainly in striatal regions (Durston *et al.* 2005). Therefore, we expected the influence of *COMT* polymorphisms on neural activation mainly in the prefrontal regions and that of the *DAT1* polymorphisms on neural activation mainly in striatal areas. We also investigated whether *DAT1* and *COMT* variants would be associated with ADHD diagnosis, and related to the altered neural correlates of response inhibition in probands with ADHD and their unaffected siblings. The neural correlates in this latter analysis were based on data from a previous study by our group (Van Rooij *et al.* 2015), describing the altered neural activation during response inhibition in probands with ADHD as compared with controls.

Method

Participants

All participants were part of the NeuroIMAGE study, the Dutch follow-up of the International Multicenter

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ADHD Genetics (IMAGE) study into the biological nature of ADHD. Details concerning ethics improvement, recruitment, demographics, diagnostics and testing procedures can be found in the NeuroIMAGE methods publication (Von Rhein *et al.* 2015) and the online Supplementary material. The current sample included subjects with ADHD ($n = 184$), their unaffected siblings ($n = 111$) and healthy controls ($n = 124$). Participant demographics are listed in Table 1; all subjects were of European descent, and all participants were required to withhold stimulant medication use for at least 48 h before testing. The proportion of females and the average intelligence quotient (IQ) scores were significantly lower in participants with ADHD than in siblings and controls; likewise, medication use and co-morbid disorders were higher in the ADHD group. There was no difference in IQ, age or gender between the two scan sites.

Stop-signal task (SST)

Response inhibition was measured using a version of the SST adapted for functional magnetic resonance imaging (fMRI) (Van Meel *et al.* 2007). Participants were instructed to respond as quickly as possible to a go-signal, unless this was followed shortly afterwards by a stop-signal (25% of trials), in which case they were supposed to withhold their response. By varying the delay between go- and stop-signals, it was possible to derive the main outcome measure of the task, the SSRT, which reflects the time necessary for a subject to successfully inhibit their response in 50% of the stop-trials. Secondary outcome measures were the number of omission and commission errors on go-trials (errors), the intra-individual component of variation (ICV) and mean reaction time (MRT) on go-trials. The task consisted of a total of four blocks of 60 trials.

All task outcome analyses were performed in SPSS (version 19.0; USA). General estimated equations (GEE) models were used to correct for familial relationships between siblings. Separate regression models were executed for SSRT, ICV, errors and MRT, with age, gender and IQ added as covariates. A significance threshold of 0.016 (0.05/3) was entrained for all analyses.

Genotyping

An extensive description of DNA extraction and genotyping in IMAGE has been provided elsewhere (Von Rhein *et al.* 2015). Briefly, for the IMAGE sample DNA was extracted from blood samples at Rutgers University Cell and DNA Repository, NJ, USA. DNA for additional samples collected during NeuroIMAGE was isolated from saliva using Oragene® containers (DNA Genotek Inc., Canada). VNTR polymorphisms from the 3′-UTR and intron-8 of the *DAT1/SLC6A3* gene had been genotyped by the IMAGE consortium (Brookes *et al.* 2006*b*), additional samples were genotyped at the Department of Human Genetics of the Radboud University Medical Center. Standard polymerase chain reaction protocols were used, after which results were analysed with GeneMapper® Software, version 4.0 (Applied Biosystems, USA). Genotyping of the rs37020 and rs4680 SNPs was performed in Nijmegen; further details concerning genotyping can be found in the online Supplementary material.

fMRI acquisition and analysis

fMRI data were collected at two sites using similar Siemens Scanners and identical coils and protocols, and were processed using FSL FEAT (version 6.0, FMRIB's Software Library; www.fmrib.ox.ac.uk/fsl). The details regarding acquisition, preprocessing and first-level analysis can be found in the online Supplementary material.

Genetic effects on ADHD diagnosis and task performance

Direct effect of the four genetic variants (rs37020, rs460000 and rs4680 SNPs and the 10–6 VNTR haplotype) on the distribution of ADHD diagnoses or on behavioural response inhibition were investigated using χ^2 statistics and analysis of variance, respectively (see Tables 2 and 3).

Role of genetic variants in whole-brain activation in the combined ADHD–control sample

To investigate the effect of each genetic variant on brain-wide task activation, four separate analyses were conducted in FSL. ADHD diagnostic status (ADHD, unaffected sibling, control) was entered as a second factor in these models, in order to investigate any mediation or interaction between genotype, task activation and diagnosis. Age, IQ, gender and scan site were added as covariates in all group-level analyses. Correction for multiple comparisons was performed according to FSL standards, by thresholding resulting *Z*-stat clusters with a minimum *Z*-score of 2.3 and using a family-wise-corrected significance threshold of $p < 0.05$ (Woo *et al.* 2014).

Relationship between genetic variants, whole-brain fMRI activation, stop-task performance and ADHD severity

In order to further specify the size and direction of the genetic effects, inferential statistics were calculated

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Table 1. *Participant characteristics and task outcomes derived from the stop-signal task*

	Participants with ADHD	Unaffected siblings	Controls	Wald χ^2	p	Between-group effects
Males, %	69.7	56.7	55.6	28.1	<0.001	ADHD > (siblings = controls)
Stimulant medication use, %	76.7	0	0	189.54	<0.001	ADHD > (siblings = controls)
Co-morbid ODD[a], %	29.9	3.6	0	67.686	<0.001	ADHD > (siblings = controls)
Co-morbid CD[a], %	6.5	0	0	15.626	<0.001	ADHD > (siblings = controls)
ADHD[b] symptoms	12.9 (3.1)	1.3 (3.4)	0.6 (1.5)	2427	<0.001	ADHD > (siblings = controls)
Age, years	17.3 (3.2)	17.3 (4.0)	16.5 (3.3)	1.6	0.44	
Estimated IQ[c]	95.3 (16.8)	102.4 (15.9)	107.1 (14.5)	38.2	<0.001	ADHD < siblings < controls)
Education, years	12.82 (2.14)	12.82 (2.22)	13.52 (1.91)	6.387	0.041	(ADHD = siblings) < controls
SSRT, ms	268.1 (59.4)	254.1 (49.0)	258.2 (52.6)	6.421	0.04	ADHD > (siblings = controls)
ICV, ms[d]	112.0 (38.3)	93.2 (36.7)	82.2 (30.8)	37.801	<0.001	ADHD > siblings > controls
Errors, n[d]	6.3 (7.6)	4.2 (5.6)	3.1 (3.5)	16.884	<0.001	ADHD > siblings > controls
MRT, ms[d]	518.1 (93.8)	492.9 (94.6)	473.1 (82.8)	19.831	<0.001	ADHD > (siblings = controls)

Data are given as mean (standard deviation) unless otherwise indicated.

ADHD, Attention deficit/hyperactivity disorder; ODD, oppositional defiant disorder; CD, conduct disorder; IQ, intelligence quotient; SSRT, stop-signal reaction time; ICV, intra-individual coefficient of variance; Errors, number of errors on go-trials; MRT, mean reaction time; K-SADS, Kiddie Schedule for Schizophrenia and Affective Disorders; WISC, Wechsler Intelligence Scale for Children; WAIS-III, Wechsler Adult Intelligence Scale.

[a] ODD and CD diagnosis was based on K-SADS structured psychiatric interviews.

[b] ADHD diagnosis was based on K-SADS structured psychiatric interviews and Conners' questionnaires (0–18 symptoms).

[c] Estimated IQ was based on two subtests of the WISC or WAIS-III.

[d] Task effects for the stop-task derived from generalized estimating equations models, using a significance threshold of $p < 0.05$ and correcting for familiality, gender, age and IQ.

Table 2. *Distribution of genotypes per diagnostic group*

				HWE	ADHD		Siblings		Controls				
Gene	Polymorphism	Risk factor	MAF	*p*	Risk	No risk	Risk	No risk	Risk	No risk	χ^2	Odds ratio[a]	*p*
DAT1	rs37020	CC genotype	0.14	0.565	24	131	37	65	13	87	1.917	1.464	0.105
DAT1	rs460000	GG genotype	0.05	0.129	111	50	71	31	59	41	2.686	1.543	0.067
COMT	rs4680	Val-Val genotype	0.19	0.53	28	134	20	79	22	78	0.891	0.741	0.216
DAT1	3′-UTR/intron-8 VNTRs	10–6 haplotype	0.09	0.343	76	85	44	58	44	52	0.045	1.057	0.467

MAF, Minor allele frequency; HWE, Hardy–Weinberg equilibrium; ADHD, attention-deficit/hyperactivity disorder; DAT1; dopamine transporter gene; *COMT*, catechol-*O*-methyltransferase gene; UTR, untranslated region; VNTR, variable number of tandem repeats.

[a] Odds ratio illustrates the relative distribution of genotypes between participants with ADHD and healthy controls.

Table 3. *Influence of* DAT1 *and* COMT *variants on stop-task performance*

			SSRT		ICV		Errors		MRT	
Gene	Polymorphism	Risk variant	χ^2	p^a	χ^2	p^a	χ^2	p^a	χ^2	p^a
DAT1	rs37020	CC genotype	2.863	0.239	1.148	0.563	0.028	0.986	0.92	0.631
DAT1	rs460000	GG genotype	4.977	0.083	0.102	0.950	1.604	0.448	3.772	0.052
COMT	rs4680	Val-Val genotype	1.162	0.281	1.001	0.317	0.019	0.890	2.249	0.297
DAT1	VNTR haplotype	10–6 haplotype	0.440	0.803	0.584	0.747	0.111	0.946	0.814	0.666

DAT1, Dopamine transporter gene; *COMT*, catechol-*O*-methyltransferase gene; SSRT, stop-signal reaction time; ICV, intra-individual coefficient of variance; Errors, number of errors on go-trials; MRT, mean reaction time; VNTR, variable number of tandem repeats.

[a] Gene effects on the stop-task outcome measures were derived from generalized estimating equations models corrected for familiality, age, gender and intelligence quotient.

within SPSS by using exported, individual β values from those clusters that showed significant effects of genetic variants. Therefore, all inferential statistics were generated using GEE models. To demonstrate that findings did not depend on the familial structure of the data, *post-hoc* analyses using only one individual from every family were conducted. An additional set of GEE analyses was run to investigate the potential relationship of these genetic effects on neural activation with stop-task performance. The influence of age, IQ, gender, scan site, medication use and co-morbid disorders on the genetic differences was also assessed. A second set of similar analyses was run to test whether the observed genetic effects on neural activation were associated with the number of ADHD symptoms as a continuous measure of ADHD severity. Significance levels for *p* values of all models using extracted β values (both above-mentioned and subsequent) were adjusted for multiple comparisons using Bonferroni–Holm corrections (Holm, 1979).

Influence of potential confounders on whole-brain fMRI activation

Given the unbalanced distribution of our sample on several demographical and clinical factors, sensitivity analyses were performed to investigate whether whole-brain activation was influenced by the covariates age, gender, IQ, scan site, medication use, or the presence of co-morbid oppositional defiant disorder or conduct disorder. For each of the clusters from the whole-brain analyses, β values were entered as dependent variables in a GEE model, using each covariate as predictor.

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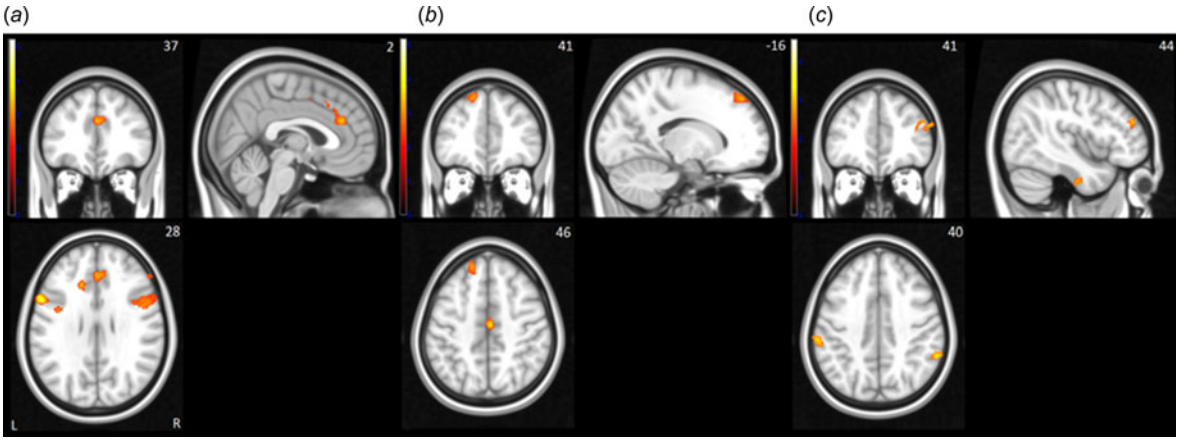

Fig. 1. Group differences of the dopamine transporter (*DAT1*) rs37020 single nucleotide polymorphism (SNP) (*a*), the *DAT1* variable number of tandem repeats (*b*) and the catechol-*O*-methyltransferase (*COMT*) rs4680 SNP (*c*) on neural activation during failed stop-trials. The right side of the image depicts the right side of the brain.

Genetic effects on between-group differences in fMRI activation

A next analysis was run to further test if the primary ADHD group effects on response inhibition activation could be explained by our genetic variants. For this analysis, we used the data describing the main effect of diagnostic status on neural activation, as described in a previous publication (Van Rooij *et al.* 2015). Here, an *F* contrast modelling the effects of diagnostic group on fMRI activation across all subjects was calculated. The activation β values from the nodes indicated in the diagnostic group contrasts of this previous study were exported and used to test the effect of the four *DAT1* and *COMT* risk variants on this activation. Specifically, a set of models was run to investigate effects of the risk genes on each node, using GEE models to correct for familial relationships, modelling the β values from each node as the dependent variable, risk genes as predictors, and gender, age, IQ and scan-site as covariates.

Results

Genetic effects on ADHD diagnosis and task performance

The distribution of the risk variants did not differ significantly between participants with ADHD, their unaffected siblings and healthy controls (see Table 2). No significant relationships between any of the risk variants and task outcome measures were observed, nor were there any main effects of (or interactions with) age, gender or IQ (see Table 3).

Role of genetic variants in whole-brain activation in the combined ADHD–control sample

The neural activation pattern during response inhibition across all groups and genotypes can be found in the online Supplementary material (see Table S1 and Fig. S1). When investigating whole-brain activation as a function of the different genetic variants, we found differences in neural activation for the *DAT1* rs37020 polymorphism and VNTR risk haplotype homozygotes and *COMT* rs4680 polymorphism. No effects were observed for the *DAT1* rs460000 polymorphism.

The effects of the *DAT1* rs37020 polymorphism were located in the right and left inferior frontal gyri, as well as the right pre-supplementary motor area and post-central qyrus (see Fig. 1, Table 4). The activation differences in the post-central gyrus were restricted to the successful stop-trials; all other differences were seen during failed stop-trials. In all instances *post-hoc* tests indicated that the carriers of the AA genotype showed lower levels of activation as compared with CC homozygotes or CA heterozygotes.

The effect of the *DAT1* 10–6 haplotype was observed during failed stop-trials in the bilateral pre-supplementary motor areas, and in the superior frontal and temporal pole areas (see Fig. 1). The former area showed higher activation in risk haplotype homozygotes; the latter two showed decreased activation in risk haplotype homozygotes.

Finally, the *COMT* Val158Met variant resulted in differential activation patterns during successful stop-trials in the thalamus, frontal pole, left supramarginal and inferior temporal gyrus; activation in hippocampus also differed between genotypes during the failed stop-trials, as did activation in the right supramarginal gyrus in both conditions (see Fig. 1). In all nodes the Val-Val genotype showed decreased activation as compared with Met alleles carriers, except in the hippocampal region, where the Met-Met homozygotes showed hypoactivation compared with both other genotypes.

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Table 4. *Risk gene effects on the response inhibition network*

Area[a]	Contrast	Side	Wald χ^2	Cramer's phi	Power[b]	p[c]	x	y	z	BA	No. voxels	Allele effect[d]
rs37020 Post-central gyrus	St suc	R	13.398	0.126	0.427	<0.001	32	12	15	2, 3, 6	590	CC = CA > AA
rs37020 Inferior frontal gyrus	St fail	L	17.463	0.144	0.63	<0.001	−58	12	28	9	642	CC = CA > AA
rs37020 Inferior frontal gyrus	St fail	R	26.115	0.176	0.902	<0.001	54	10	45	8, 9	753	CC = CA > AA
rs37020 Pre-supplementary motor area	St fail	R	14.881	0.133	0.504	<0.001	30	16	44	6	1042	CC = CA > AA
DAT1 haplotype temporal pole	St fail	R	17.939	0.146	0.655	<0.001	50	−20	−30	20	193	0 > 2 > 1
DAT1 haplotype superior frontal gyrus	St fail	L	18.069	0.147	0.655	<0.001	2	−12	42	32	182	0 > 2 > 1
DAT1 haplotype pre-supplementary motor area	St fail	L/R	30.137	0.189	0.957	<0.001	−16	44	48	8	170	2 = 1 > 0
COMT thalamus	St suc	L	9.886	0.108	0.238	0.002	−14	26	−4	N.A.	167	VM > MM > VV
COMT supramarginal gyrus	St suc	L	13.388	0.126	0.415	<0.001	−64	−28	42	40	159	MM = VM > VV
COMT frontal pole	St suc	R	18.858	0.150	0.686	<0.001	46	24	44	9	160	MM = VM > VV
COMT inferior temporal gyrus	St suc	R	14.849	0.133	0.505	<0.001	34	−16	−38	20	200	VM = MM > VV
COMT supramarginal gyrus	St suc	R	14.189	0.130	0.461	<0.001	60	−44	36	14	283	MM = VM > VV
COMT hippocampus	St fail	R	20.088	0.155	0.736	<0.001	30	−10	−22	N.A.	160	VV = VM > MM
COMT supramarginal gyrus	St fail	R	13.08	0.125	0.393	<0.001	56	−40	46	40	217	MM > VM > VV

BA, Brodmann area; St suc, successful stop-trials; R, right; St fail, failed stop-trials; L, left; *DAT1*, dopamine transporter gene; *COMT*, catechol-*O*-methyltransferase gene; N.A., not applicable.

[a] Activation clusters derived from the *F* contrasts testing differences in task activation as a function of *DAT1* and *COMT* variants over all subjects, including gender, intelligence quotient, age and scan site as covariates.

[b] Power estimates computed using Quanto software (http://biostats.usc.edu/Quanto.html).

[c] Correction for multiple comparisons was one using a cluster threshold of $Z > 2.3$ and a significance threshold of $p < 0.05$ corrected.

[d] Group effects are derived from *post-hoc* analyses, corrected for familiality.

To correct for potential effects of familial dependency in our sample, all analyses of the genetic variants on whole-brain neural activation were repeated in a reduced sample using only one child per family. These results have been added to the online Supplementary material, and show that the above-mentioned results are not influenced by the familial structure of our sample.

Relationship between genetic variants, whole-brain fMRI activation and stop-task performance

Neural activation in the right inferior frontal gyrus and pre-supplementary motor area, that were differentially activated depending on *DAT1* rs37020 genotype, showed a significant relationship with SSRT duration ($B = -0.085$, $p < 0.012$ and $B = -0.039$, $p < 0.004$, respectively). In both nodes, higher neural activation, as seen in participants without the risk genotype, was associated with shorter SSRT length (see online Supplementary Table S3).

Activation in both nodes of the right supramarginal gyrus, that were differentially active depending on the *COMT* rs4680 genotype, was significantly associated with ICV ($B = -144.12$, $p < 0.0001$ and $B = -172.09$, $p < 0.0001$, respectively). In both nodes, higher activation, seen in participants without the risk allele, was associated with lower intra-individual variation in response inhibition performance.

Relationship between genetic variants, whole-brain fMRI activation, and ADHD status or severity

No interactions between genetic effects and ADHD diagnostic status (ADHD probands *v.* unaffected siblings *v.* healthy controls) were observed in any of the whole-brain fMRI results. *Post-hoc* analysis of the β values from all differentially activated nodes indicated no main effect of ADHD status on fMRI activation, either with or without incorporation of the main gene effects. A final set of *post-hoc* models was used to associate β values with the number of ADHD symptoms, and also separately investigate the influence of these polymorphisms on the hyperactive/impulsive and inattentive subscales of the Conners' questionnaire. However, no significant effects were observed between the total symptom count, either subscale or any of the genetic variants tested.

Influence of potential confounders on whole-brain fMRI activation

No main or interaction effects of IQ, gender or scan-site were detected, indicating that these variables did not influence the reported genetic effects on fMRI activation. The activation in the superior frontal region node which showed differential effects of the *DAT1* haplotype additionally showed a main effect of age ($B = -1.031$, $p < 0.001$), indicating decreased activation with increased age. However, there was no interaction between age and the VNTR effect, indicating that the age effect was additional to the VNTR effect. No other effects of age were observed.

In previous publications, we showed there are no main effects of medication use or co-morbidity on the neural activation within this sample (Van Rooij *et al.* 2015). Also, medication or co-morbidity did not show any interaction effects with the reported genetic effects on the neural activation.

Genetic effects on between-group differences in fMRI activation

The direct diagnostic group contrast (ADHD *v.* siblings *v.* controls) of neural activation during the stop-task indicated differential activation in a number of nodes, including inferior frontal, superior frontal, supramarginal and temporal/parietal nodes in both successful and failed stop conditions. Participants with ADHD demonstrated hypoactivation in all these nodes compared with controls; the unaffected siblings displayed intermediate levels of activation. The activation maps and tables detailing the size and direction of these effects can be found in Van Rooij *et al.* (2015), and have also been described in the online Supplementary material of this paper. However, none of the genetic variants showed effects in any of these nodes, and there were no significant interactions observed of genetic variants with the ADHD effect (see online Supplementary material for details).

Discussion

The current study showed novel evidence for the role of two dopaminergic gene variants on the neural correlates of response inhibition in a large sample of adolescents with ADHD, their unaffected siblings and healthy controls. We investigated the effects of variance in the *DAT1* and *COMT* genes on whole-brain neural activation during response inhibition in the combined ADHD–control sample. These analyses indicated widespread alterations in neural activation in relation to *DAT1* rs37020 genotype and VNTR haplotype, as well as *COMT* rs4680 genotype. The genetic polymorphisms also showed associations with behavioural response inhibition outcomes but not with ADHD diagnostic status or symptom count. First, we assessed the influence of the *DAT1* and *COMT* variants on whole-brain neural activation in a hypothesis-free manner. This analysis indicated significant effects of all variants but one in *DAT1* on brain-wide neural

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activation during response inhibition. The *DAT1* rs37020 AA genotype, the *DAT1* 10–6 risk haplotype homozygotes and the *COMT* rs4680 Val-Val genotype all showed hypoactivation in superior, inferior and medial frontal nodes; the rs4680 Val-Val genotype further showed increased activation in the thalamus. These regions are key parts of the frontal–striatal network that plays a central role in the regulation, initiation and execution of the response inhibition process (Aron, 2011). We also showed that the activation in the right inferior frontal and pre-supplementary motor areas were predictive of SSRT duration, providing additional support for the role of these areas in response inhibition performance. The findings regarding the influence of the *DAT1* rs37020 variant on neural activation are largely in line with those of Cummins *et al.* (2012). Furthermore, while Cummins reported no effects of the *DAT1* VNTRs and Congdon *et al.* (2008) showed hypoactivation in the pre-supplementary motor area in carriers of the 10 repeat allele of the *DAT1* 3′-UTR VNTR, we demonstrated effects of the VNTR haplotype, including the 3′-UTR VNTR, in the same area, although we showed hyperactivation for the risk haplotype. As we additionally found hypoactivation in the superior frontal and temporal gyri for carriers of the 10–6 haplotype, our findings suggest a shift in activation from frontal to medial areas of the response inhibition network for the risk haplotype. Both the inconsistencies in the literature regarding the role of *DAT1* and the observed variation of influences between the rs37020 polymorphisms and VNTR haplotype indicate that *DAT1* has a complex role in response inhibition that deserves more intensive study.

Furthermore, the observed influence of the COMT rs4680 SNP also concurs with results reported by Congdon *et al.* (2009). We found effects of the COMT polymorphism in the supramarginal, temporal and hippocampal areas, though care should be taken when interpreting these findings, since the observed power of these effects is not sufficient to exclude the possibility of false positives. The supramarginal area is associated with the frontal–parietal network, and is thought to implement attentional direction and task-set maintenance during response inhibition (Fassbender *et al.* 2006; Chambers *et al.* 2009). We showed that activation in the supramarginal areas is associated with lower intra-individual variation in stop-task performance, supporting the role of this area in attentional processing. The presence of the Val-Val genotype was related to less activation in these areas, which may suggest that decreased attentional resources were available during cognitive performance in Val homozygotes. The results by White *et al.* (2014) showed a genotype × gender interaction for the COMT variant, indicating higher activation in the inferior frontal and supramarginal nodes of the response inhibition network in Val-Val adolescent males. Our findings diverge in both the location and direction of the genotype effect, but we found no evidence for an effect of gender in these analyses. The relationship between *COMT* and hippocampal functioning during memory tasks has been documented (Bertolino *et al.* 2006; Krach *et al.* 2010), but its relationship with response inhibition is currently unknown. Unexpectedly, individuals with the Met-Met genotype showed decreased activation in the hippocampus, as opposed to the Val-Val group, which are considered the risk group due to decreased dopamine availability (Matsumoto *et al.* 2003). Possibly, the hippocampal involvement may indicate a working memory component in stop-task performance, for example by tracking task demands of the number of trials since the last stop-signal was presented. The Val-Val genotype may rely more heavily on these cues to compensate for their decreased recruitment of the regular response inhibition nodes. However, the causal relationships between attention, memory and response inhibition processes cannot be accurately discerned from the paradigm used in the current study, indicating the need for further research into the role of *COMT* in these different neural processes.

The results in this study further showed that the effects of *DAT1* and *COMT* variants are similar in participants with ADHD, unaffected siblings and controls, a result which may be surprising given the previously found positive links between *DAT1* and *COMT* variants and ADHD (Cornish *et al.* 2005; Brookes *et al.* 2006*a*; Guan *et al.* 2009; Braet *et al.* 2011; Matthews *et al.* 2012). Alternatively, we may have had insufficient statistical power to detect small genetic effects on ADHD diagnosis or severity. Additionally, divergent findings on the influence of the *DAT1* 9–6 and 10–6 haplotypes on response inhibition in adults and children (Brookes *et al.* 2006*b*; Franke *et al.* 2010) may have obscured a direct link, or there may have been interfering effects of the long-term use of medication in our ADHD sample. The use of neural differences between participants with ADHD and controls during response inhibition as an intermediate phenotype did not prove to be more successful than the clinical phenotype in detecting significant genetic effects of our candidate genetic variants. ADHD is an aetiologically complex disorder, thought to be caused in most cases by cumulative small effects of many genetic variants as well as environmental effects. Possibly the influence of, and interaction with, other genetic variants, or interactions with the environment, may have obscured the association between our risk genes and altered neural response inhibition correlates in ADHD.

Next to ADHD, response inhibition deficits have been observed in a range of major psychiatric disorders, like

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schizophrenia (Enticott *et al.* 2008) and bipolar disorder (Passarotti *et al.* 2010). Recent evidence has shown shared genetic contributions for all these major psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013*a*), and a genome-wide effect of the *DRD2* dopamine receptor gene on schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). The results of the current study also imply a stronger link between dopaminergic genes and the neural correlate of response inhibition, as compared with the behavioural or phenotype levels, or specifically ADHD. Taken together, these findings imply that diagnostic boundaries between psychiatric disorders may not reliably represent underlying genetic mechanisms (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013*b*), and suggest that the use of neurobiological constructs may provide more valuable targets for genetic studies than single disease phenotypes.

In sum, we showed the influence of *DAT1* and *COMT* variants on the neural activation during response inhibition, indicating that variance within the catecholamine system may explain a significant part of the neural activation of response inhibition. We demonstrated widely spread genetic effects across both frontal–striatal and frontal–parietal networks during successful and failed inhibitions. These findings are consistent with the earlier studies (Congdon *et al.* 2009; Cummins *et al.* 2012) showing activation changes in medial and lateral prefrontal as well as supramarginal areas as a function of these genetic variants. Extending these findings, we also found association of variants within these dopamine genes in temporal and parietal activation. Our results further indicate that different genetic variants may influence distinct parts of the neural network underlying response inhibition. Given that the current study only investigated a limited number of genetic risk variants, a more comprehensive study of genetic variance in response inhibition may be warranted. Future implementation of polygenetic risk scores (Dudbridge, 2013) or pathway-based approaches (Bralten *et al.* 2013) may be used to further elucidate the relationship between neurotransmitter functioning and (the neural correlates of) response inhibition performance. Our power calculations show that though many of our main effects are very robust (observed power > 0.9), we cannot fully discount potential false-positive findings, specifically with regard to the activation associated with the *COMT* polymorphism. This variation in statistical power indicates that researchers should take care to not only report *p* values, but effect sizes and power calculations as well. It also emphasizes the importance of large sample sizes in genetic fMRI research. Although our results indicate a putative pathway between catecholamine gene variants and the ADHD phenotype, we have demonstrated no direct influences of these genetic effects and ADHD diagnosis. The generalizability of these genetic effects across this large age range as well as over the diagnostic groups may further indicate that these genetic effects are equally important in a wide range of adolescents with and without ADHD.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291715001130

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Declaration of Interest

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