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ORIGINAL ARTICLE

Dopamine transporter genotype predicts behavioural and neural measures of response inhibition

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The ability to inhibit unwanted actions is a heritable executive function that may confer risk to disorders such as attention deficit hyperactivity disorder (ADHD). Converging evidence from pharmacology and cognitive neuroscience suggests that response inhibition is instantiated within frontostriatal circuits of the brain with patterns of activity that are modulated by the catecholamines dopamine and noradrenaline. A total of 405 healthy adult participants performed the stop-signal task, a paradigmatic measure of response inhibition that yields an index of the latency of inhibition, termed the stop-signal reaction time (SSRT). Using this phenotype, we tested for genetic association, performing high-density single-nucleotide polymorphism mapping across the full range of autosomal catecholamine genes. Fifty participants also underwent functional magnetic resonance imaging to establish the impact of associated alleles on brain and behaviour. Allelic variation in polymorphisms of the dopamine transporter gene (*SLC6A3*: rs37020; rs460000) predicted individual differences in SSRT, after corrections for multiple comparisons. Furthermore, activity in frontal regions (anterior frontal, superior frontal and superior medial gyri) and caudate varied additively with the T-allele of rs37020. The influence of genetic variation in *SLC6A3* on the development of frontostriatal inhibition networks may represent a key risk mechanism for disorders of behavioural inhibition.
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Introduction

Problems of behavioural inhibition are central to a number of heritable psychiatric disorders, including attention deficit hyperactivity disorder (ADHD),[1] obsessive compulsive disorder,[2] drug addiction[3] and schizophrenia.[4] In the case of ADHD and obsessive compulsive disorder, an inability to cancel prepotent motor responses has been proposed as an endophenotype that is able to index the genetic vulnerability of these disorders.[2,5] Although there is now strong evidence from behaviour genetics showing that measures of behavioural inhibition are highly heritable,[6] the underlying molecular genetic architecture of this phenotype remains unknown.

Behavioural, or response inhibition, has been studied in cognitive psychology for decades, using the now classic stop-signal task. The stop-signal task requires the cancellation of a pre-potent 'go' response upon presentation of an infrequent 'stop' signal. Stop-signal inhibition can be viewed as a race between competing 'go' and 'stop' processes. By introducing a delay between the presentation of the go stimuli and any subsequent stop signal, one can bias the outcome of the race. When the theoretical assumptions underlying this race model are respected, an index of the speed of inhibition can be calculated, the stop-signal reaction time (SSRT).[7] There is now strong evidence that SSRT, as an index of inhibitory control, is related to personality constructs such as impulsivity,[7] and is elevated in clinical disorders including ADHD, obsessive compulsive disorder, addiction and schizophrenia.[2–5]

Converging evidence from lesion,[8] brain imaging[9,10] and neural disruption studies[11–13] highlight the importance of frontostriatal circuits in the control of response inhibition. These studies suggest that frontal regions act in concert with sub-cortical areas (such as the striatum and sub-thalamic nucleus) to achieve inhibitory control.[9,14]

Pharmacological evidence in rodents and humans highlights important roles for both noradrenaline and dopamine in modulating response inhibition.[15,16] Specifically, agents such as methylphenidate exert

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their beneficial effect on inhibition by targeting both prefrontal and striatal nodes of the response inhibition network.[16] Within prefrontal cortex, the effect of methylphenidate appears to be mediated by blockade of the noradrenaline transporter (SLC6A2 or NET), with subsequent receptor level effects mediated via α2-adrenoreceptors and D1 receptors.[17] Within the striatum and basal ganglia, however, the dopamine transporter (SLC6A3 or DAT1) is abundant and methylphenidate-induced increases in available dopamine may act to suppress or facilitate action via the appropriate balance of activity within the indirect or direct pathways of the basal ganglia, mediated via D2 and D1 receptors, respectively.[16] Analogous effects on noradrenaline levels within prefrontal cortex are achieved by the noradrenaline reuptake inhibitor, atomoxetine, which shortens SSRT[18] and modulates inhibitory brain activity within the inferior frontal gyrus.[19] Although some evidence suggests that serotonin may modulate some aspects of behavioural inhibition, evidence from rodents and humans suggests that serotonin is not a critical neuromodulator of stop-signal inhibition.[15,16,18]

Despite the high heritability of measures of behavioural inhibition and its relevance to psychiatry, little progress has been made in identifying the molecular genetic correlates of inhibition. Isolated associations between DNA variants of catecholamine (*DRD4*, *SLC6A3*)[20–22] and indoleamine (*TPH2*)[23,24] genes have been reported, although typically in small samples of less than 200 individuals and without consideration of other genes that could be acting within the frontostriatal circuits that mediate response inhibition.

Here we built upon the strong pharmacological evidence for catecholamine modulation of stop-signal inhibition, to predict, *a priori*, molecular targets for genetic association. We performed the first systematic genetic association study of behavioural inhibition, using an SSRT phenotype, in a sample of 405 healthy adults. High-density single-nucleotide polymorphism (SNP) mapping across all 22 autosomal catecholamine genes was performed and the additive influence of alleles at each SNP on SSRT was assessed. To establish the functional effect of associated alleles on brain function, 50 individuals from the larger cohort also underwent functional magnetic resonance imaging (MRI) while performing the stop-signal task. Functional MRI analyses were restricted to those DNA markers showing evidence of a behavioural association with SSRT that survived correction for multiple comparisons.

Materials and methods

Participants

The ethics committee of the University of Queensland approved the study. All participants gave informed consent before completing the stop-signal task[25] and prior to collection of saliva using Oragene kits (DNAgenotek, Ottowa, Canada). Right-handed Caucasian participants with normal (or corrected to normal) vision were recruited from undergraduate participant pools and via public advertisements. Full details regarding participant screening can be found in the Supplementary Information (SI). The final sample included 405 individuals (202 males and 203 females; mean age = 21.49 years, s.d. = 5.22). Fifty of these subjects (14 males, 36 females; mean age = 22.08 years, s.d. = 4.80) were then randomly selected to take part in a functional MRI (fMRI) session in which they performed the stop-signal task while in the scanner.

Stop-signal task

Briefly, the stop-signal paradigm employs a choice reaction time task in which participants are required to make rapid motor responses to either of the two 'go' stimuli. In the current study, participants responded to uppercase X and O stimuli, mapped to left and right button responses in a counterbalanced fashion. On 25% of occasions, participants were presented with a 'stop-signal', which comprised a red box surrounding the go stimulus (see Figure 1a). A critical feature of the stop-signal task is that the delay between the onsets of the go- and stop-signals, termed the stop-signal delay (SSD), is manipulated to ensure that participants inhibit their responses on approximately 50% of stop trials. SSDs are typically either varied dynamically based on the participant's success or failure at inhibition (adaptive staircase methods[7]), or chosen from a fixed set of delays that are set relative to an individual's mean response time (method of constants[13]). To allow for establishment of method invariance, participants completed one of two versions of the task that differed only in the technique used to set the SSDs. A total of 100 participants (cohort 1) performed an adaptive stop-signal task in which SSD was initially set at 250 ms and then varied in 50 ms increments/decrements, depending upon performance.[7] Thus, if a participant successfully inhibited, the SSD was shortened by 50 ms on the next stop trial to increase the difficulty of inhibition. SSRT was calculated as the difference between the mean go-signal reaction time (MRT) and the SSD at which participants could, on average, inhibit 50% of their responses. Another group of 305 participants (cohort 2) performed a method of constants version of the task in which SSDs were chosen from a set defined by MRT—150, 200 or 250 ms. SSRT was calculated as per Chambers *et al*.[13] through sigmoidal regression of the percent of correct inhibitions at SSDs of MRT—150, 200 and 250 ms (see Supplementary Information for further details). To account for the possible influence of any subtle differences in the calculation of SSRT, participant cohort was added as a covariate in all genetic analyses (see below).

Genetic variant selection

SNPs were selected from each member of the full set of autosomal catecholamine genes, namely those that

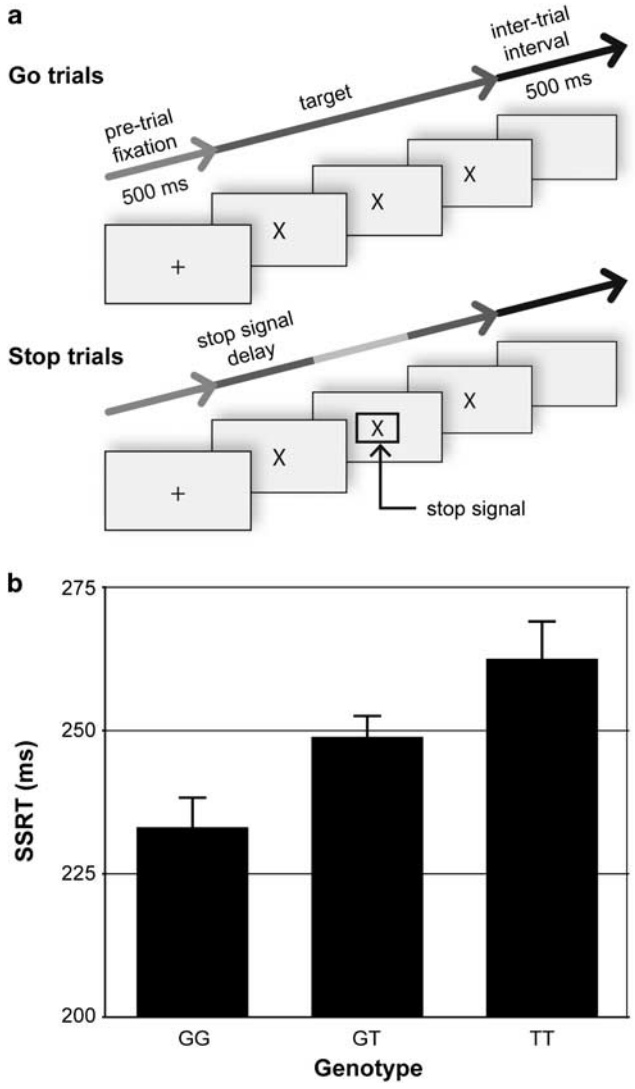

Figure 1 (**a**) Schematic illustration of the stop signal task. On 'go' trials, one of two targets is presented and participants respond with a button press ('X 'left, 'O' right), On 'stop' trials, a red square appears around the target after a given stop-signal delay (SSD), and the participant attempts to inhibit their response. (**b**) The relationship between stop-signal reaction time (SSRT) and genotype at the *SLC6A3* SNP, rs37020. SSRT (mean + s.e.) increased additively with increasing possession of the T-allele of rs37020.

are involved in synthesis, degradation, transport and receptor signalling of dopamine and/or noradrenaline. Haplotype-tagging SNPs were chosen to provide 5′—3′ coverage of each gene, using the HapMap project database (http://www.hapmap.org/) of European Caucasians.[26] Selection criteria for haplotype-tagging SNPs were a minor allele frequency (MAF) of >0.1 and a correlation to surrounding known variants of $r=0.9$ ($r^2=0.8$). We also favoured the inclusion of catecholamine SNPs that have been shown to modify the risk for ADHD, SNPs at exon–intron boundaries (300 bp) and SNPs that occur just outside of the gene (<5 kb) yet may have major regulatory roles, namely those that are mapped to the 5′-promoter region and the 5′- and 3′-untranslated regions (5′ and 3′ UTR). In total, 151 catecholamine SNPs on 22 genes were selected (see Supplementary Table 1 for included genes; SNPs for the *ADRA2C* and *PNMT* genes were sent for genotyping, but returned fails and are therefore not discussed further). In addition, two variable number tandem-repeat polymorphisms (VNTRs) in the *SLC6A3* gene (the 30-bp intron 8 VNTR and the 40-bp 3′-UTR VNTR) and one VNTR in the *DRD4* gene (the 48-bp exon 3 VNTR) were included.

Genotyping

Genotyping of all SNPs was performed by the Australian Genome Research Facility (AGRF) using iPLEX GOLD chemistry with a Sequenom MassArray on an Autoflex Spectrometer (Sequenom, San Diego, CA, USA). VNTR genotyping was performed on template DNA, amplified using established PCR protocols for the *DRD4* exon 3 VNTR,[27] the *SLC6A3* 3′-UTR VNTR[28] and the *SLC6A3* intron 8 VNTR[29] (see Supplementary Methods).

fMRI acquisition and processing

The BOLD effects of each test condition were recorded using echo planar imaging (EPI) performed in a 1.5T Siemens Sonata scanner (Siemens, Erlangen, Germany) fitted with a circular polarised headcoil (repetition time, 2000 ms; slice thickness, 3.6 mm; number of slices, 29; gap, 0.4 mm; matrix, 64×64 voxels at 3.6×3.6 mm resolution) and a high-resolution 3D T1-weighted coronal image was acquired for individual data registration (repetition time, 1930 ms; matrix, 256×256; voxel size, $0.9\times0.9\times0.9$ mm). Functional data were processed and analysed with statistical parametric mapping (SPM5, Wellcome Trust Centre for Neuroimaging, London, UK) implemented in Matlab 7.6 (Mathworks, Sherborne, MA, USA; for acquisition and pre-processing specifications see the Supplementary Information). The data were high-pass filtered, using a set of discrete cosine basis functions with a cut-off period of 128 s. First-level statistical analyses (single subject and fixed effects) modelled each trial type independently (go, successful stop, failed stop), by convolving the onset times with the haemodynamic response function[30] before successful stop–go contrasts were calculated for each subject.

At the second level, the neural correlates of response inhibition were identified by conducting a one-way analysis of variance with condition type as its factor (go, successful stop, failed stop), followed by a *t*-test that examined the difference between successful stop and go activity. This analysis used a voxel threshold of $\alpha=0.001$ and a cluster level significance of $\alpha_{FWE}=0.05$.

To assess the effect of genotype on brain activation, DNA markers that were associated with SSRT during the behavioural phase and survived correction for multiple comparisons were interrogated. Specifically, the first level successful stop–go contrasts were entered into a regression analysis, testing whether

inhibition activity varied additively with genotype. This analysis used a voxel threshold of $\alpha = 0.05$ and a cluster level significance of $\alpha_{FWE} = 0.05$.

Results

Genotyping

Seven individuals were excluded from the study as they had successful genotyping completion rates below 80%. In addition, SNPs were excluded based upon the following criteria: call rates below 90% (two SNPs); deviation from Hardy–Weinberg equilibrium (one SNP); SNPs which lacked minor allele homozygotes preventing additive genetic analyses (four SNPs); any SNP that was in perfect linkage disequilibrium (LD) with another (three SNPs). Thus, 141 SNPs with a MAF >5% remained after this quality control process (see Supplementary Table 1). Genotyping was successful for 355 of 405 samples for the *DRD4* VNTR, and for 396 and 380 samples for the *SLC6A3* 3′-UTR and intron 8 VNTR's, respectively (see Supplementary Information for VNTR allele frequencies).

Genetic association analyses

Genotype data for the VNTR's were coded with 0, 1 and 2, representing the number of copies of the repeat of interest. All association analyses were performed in SNPstats (http://bioinfo.iconcologia.net/snpstats_web), using additive regression models that controlled for age, gender and participant cohort. SNP spectral decomposition[31] was used to determine the effective number of independent loci (Meff/MeffLi)[32,33] for genes with more than one marker. This process returned a value of 99.24, giving a critical α-value of 5.04×10^{-4} (0.05/effective number of independent loci).

The association between the *SLC6A3* rs37020 SNP and SSRT was significant at the corrected level, $P = 2.33 \times 10^{-4}$ (semi-partial correlation squared (r^2_{sp}) = 2.89%), and inspection of the stop signal data revealed that SSRT increased in an additive fashion with each copy of the T allele (see Figure 1b). Likewise, the association between rs460000 and SSRT survived correction for multiple comparisons, $P = 3.57 \times 10^{-4}$ ($r^2_{sp} = 2.72\%$) (see Table 1), with SSRT increasing additively with each additional copy of the C allele. These findings were replicated at an uncorrected level when each participant cohort was examined separately, with rs37020 showing *P*-values of 6.0×10^{-4} and 7.2×10^{-3} in cohorts 1 and 2, respectively, and rs460000 showing *P*-values of 4.0×10^{-4} and 1.2×10^{-2}. Inspection of LD patterns in the *SLC6A3* gene indicated that rs37020, which lies in intron 6, and rs460000, which occurs on the intron/exon border of intron 3, are in relatively strong LD ($D' = 1$, $r^2 = 0.42$, HapMap; Figure 2). Our results could also therefore reflect the influence of a single functional variant that lies somewhere within this region or within a greater haplotype block. Full results for the SSRT analysis can be found in Supplementary Table 1.

Genetic association analyses were also performed for both Go reaction time (Go RT) and the s.d. of Go RT (s.d. Go RT). Heightened variability in reaction times is a heritable trait and is a familial marker for clinical conditions, such as ADHD.[34] Human pharmacological work with the stop-signal task suggests that catecholamines modulate response time variability independently of their effect on SSRT.[16] Crucially, neither rs37020 nor rs460000 of *SLC6A3* showed a significant association with Go RT at either a corrected or uncorrected level. There was, however, a significant association between rs460000 and s.d. Go RT at the uncorrected level, $P = 0.015$ (see Table 1). To establish that this SNP was modulating SSRT independently from any effect on response variability, genotype was regressed on SSRT, s.d. Go RT and the aforementioned covariates. This regression analysis revealed that SSRT made a significant unique contribution to rs460000 genotype, $P = 4.44 \times 10^{-4}$.

Table 1 The influence of common *SLC6A3* gene variations on SSRT, Go RT and s.d. Go RT

SNP ID	*MAF*	P-*value*		
		SSRT	*Go RT*	*s.d. Go RT*
rs40358	0.14	0.21	0.043*	0.56
rs37020	0.45	0.0002**	0.31	0.11
rs10053602	0.23	0.49	0.57	0.51
rs393795	0.22	0.0012*	0.065	0.037*
rs11737901	0.36	0.007*	0.57	0.72
rs460000	0.23	0.0004**	0.086	0.015*

Abbreviations: SSRT, stop-signal reaction time; Go RT, Go-reaction time; s.d. Go RT, Go RT variability; SNP, single-nucleotide polymorphism; MAF, minor allele frequency.
*Significant at uncorrected level, critical $\alpha = 0.05$; **significant at corrected level, critical $\alpha = 5.04 \times 10^{-4}$.

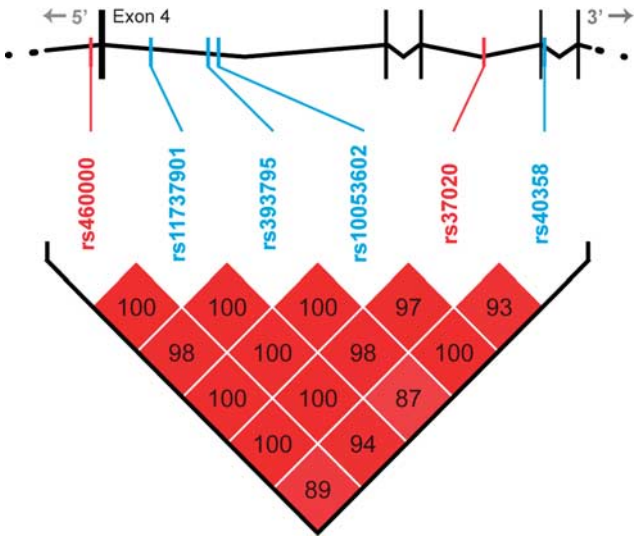

Figure 2 Linkage disequilibrium map (*D*′ values) of single-nucleotide polymorphisms (SNPs) successfully typed in the *SLC6A3* gene (SNPs that survived correction for multiple comparisons in red font).

Go RT was also found to be significantly associated with rs17605608, a SNP in the 5′-flanking region of *DRD3*, $P = 1.29 \times 10^{-4}$ ($r^2_{sp} = 2.56\%$). No other associations with Go RT or s.d. Go RT were significant at the corrected level (see Supplementary Table 1).

fMRI analyses

The whole brain analysis conducted on the 'Successful inhibition–go' contrast revealed significantly greater activation for inhibition relative to go activity in a number of clusters. These clusters included key regions of the response inhibition networks, namely bilateral interior frontal gyrus and middle frontal-gyrus, right subthalamic nucleus and left inferior parietal lobule (see Figure 3a; see also Aron and Poldrack[9] and Vaidya *et al*.[35]). To assess the effect of genotype on brain activity associated with response inhibition, an additive model was used to categorise genotype for the rs37020 marker. As the T allele was associated with longer SSRTs, genotype was coded as 0, 1 and 2 (GG, GT, TT, respectively). This regression analysis revealed a significant cluster (peak: left superior frontal cortex, (16, 54, 26), cluster size = 4848 voxels, $Z = 3.82$, $P_{obtained} = 0.001$) that included bilateral caudate, anterior frontal gyrus, superior frontal gyrus and superior medial gyrus regions (see Figure 3b). Previous fMRI studies of response inhibition have demonstrated that better response inhibition (i.e., shorter SSRTs) is associated with greater percentage signal change within activated regions.[9] In line with this expectation, activity in the caudate nucleus and frontal regions (anterior frontal, superior frontal and superior medial gyri) increased additively from the TT to the GT to the GG genotype of rs37020; this pattern was the inverse of the behavioural data shown in Figure 1b. Thus, individuals with the poorest inhibitory ability (TT genotype) showed the least activity in the response inhibition networks.

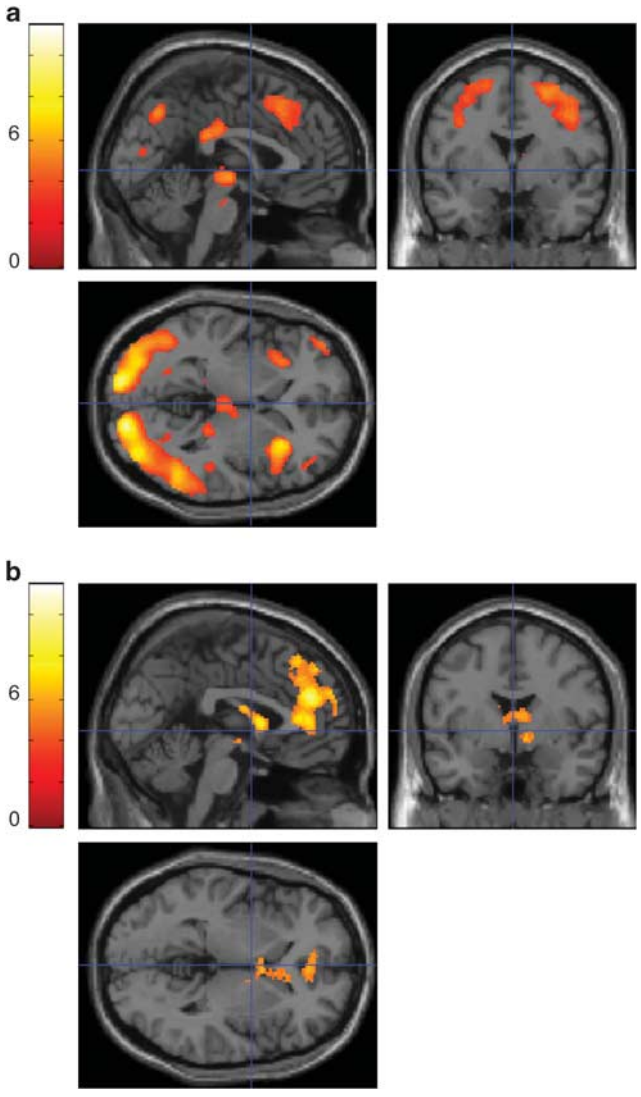

Figure 3 (**a**) Activation associated with response inhibition (successful stop–go contrast). Signal rendered on single subject T1 template ($\alpha_{FWE} = 0.05$). (**b**) Signal in the caudate nucleus and frontal regions (anterior frontal, superior frontal and superior medial gyri) increases additively from the TT to the GT to the GG genotype of *SLC6A3* rs37020. Signal rendered on single subject T1 template (extent threshold shows significant activations ($\alpha_{FWE} = 0.05$) only). Scale represents colour-coded *t*-values.

Discussion

This is the first study to perform high-density SNP mapping across the full range of autosomal catecholamine genes and test for genetic association against a response inhibition phenotype. We report novel associations between polymorphisms (rs307020; rs460000) of the *SLC6A3* gene and SSRT that survive corrections for multiple comparisons, and are independent of other associations with behavioural measures such as response speed and reaction time variability. Furthermore, allelic variation in associated *SLC6A3* variants predicted task-related brain activation within frontostriatal regions, including the caudate and superior frontal gyrus, such that genotypes that predicted poor inhibitory control were also associated with inefficient activation of response inhibition networks.

There is considerable *a priori* evidence to suspect that allelic variation in the *SLC6A3* gene might predict behavioural and neural measures of response inhibition. The dopamine transporter is the primary target of stimulant medications, such as methylphenidate, which reduce the symptoms of disorders of behavioural inhibition, such as ADHD. Furthermore, methylphenidate improves performance on the stop-signal task in both healthy[16] and clinical populations.[36] Pharmaco-imaging studies of response inhibition have shown that methylphenidate modulates task-related activation within the same frontostriatal regions, including superior frontal and caudate regions,[35] for which we here report genetic association with *SLC6A3*. Thus, the current study provides strong evidence, from an unbiased analysis of catecholamine gene variants, that allelic variation in

SLC6A3 accounts for significant variance in both behavioural and neural indices of response inhibition.

As response inhibition deficits feature prominently in a number of psychiatric disorders, are heritable[6] and may be familial in disorders such as ADHD,[1] numerous studies have attempted to identify the molecular genetic correlates of this phenotype. A number of studies have reported positive associations with common polymorphisms of both *SLC6A3* (e.g., 3′-UTR VNTR) and *DRD4* (exon 3 VNTR) and response inhibition phenotypes in both healthy and ADHD populations,[20,22] albeit in small sample sizes. Here we failed to find evidence for association with allelic variation in these polymorphisms and response inhibition. Instead, however, our comprehensive screen of all autosomal catecholamine genes revealed novel associations within *SLC6A3*. The most significantly associated polymorphisms (rs460000 and rs37020) are situated within a 14-kbp region from intron 3 (exon/intron boundary) to intron 6 of *SLC6A3*, respectively. Both markers are in relatively strong LD and neither show significant LD with either the intron 8 or 3′-UTR VNTRs. These results suggest that this 14-kbp region, or the greater haplotype block to which this region belongs, may harbour a novel quantitative trait locus for the intermediate phenotype of response inhibition. Our results may also have a number of potential implications for clinical translation. First, as response inhibition is a leading candidate endophenotype for disorders of behavioural disinhibition, such as ADHD and addiction, our results suggest that this genomic region should be interrogated further for genetic association in these disorders. Second, although speculative, it is possible that the novel *SLC6A3* variants identified herein could predict treatment response to dopaminergic agents in conditions such as ADHD and addiction. Finally, our study suggests that a response inhibition phenotype may be profitably used as a surrogate endpoint within pharmacological trials monitoring the effectiveness of dopaminergic treatments.

It is interesting to note that the SNP rs460000 maps to the branch point of intron 3. DNA variations within exon–intron boundaries have been reported to have profound effects on RNA splicing and to consequently affect protein coding and function.[37] Alternative processing has also been reported to affect protein efficacy which contributes to the development of some disease conditions.[38] Thus, in the current context, the associated *SLC6A3* SNP rs460000, which is mapped to the branch point of intron 3, may affect the expression level of the transporter, its activity, or result in a different isoform of the protein with a different function. However, further analysis is required to substantiate these speculations. An alternative explanation for the current results involves LD with one or more distant polymorphisms. A small amount of variance in rs460000 genotype ($D' = 0.65$, $r^2 = 0.19$) is explained by rs3756450, a SNP just upstream from the core promoter region, which appears to be an allele-specific binding site for transcription factors.[39] Similarly, our findings for rs37020 may reflect mild LD with SNPs such as the 3′-UTR SNP r27072 ($D' = 0.66$, $r^2 = 0.10$), which has been shown to be associated with ADHD in individual Canadian children[40] and Canadian twins.[41]

Other genes outside of the noradrenergic and dopaminergic systems may also make significant contributions to catecholamine function and/or response inhibition. For example, genes whose products are related via regulatory pathways (e.g. *STX1A*,[42] which regulates vesicle function and dopamine exocytosis) may contribute to catecholamine signalling and related behaviours. Thus, although our findings extend existing knowledge about the role of catecholamine sites and their contributions to response inhibition, it is likely that future research will include a greater breadth of genetic targets. Further, next generation sequencing approaches may uncover rare variants in catecholamine and other genes, which may also account for variation in the response inhibition phenotype.

In summary, this study has performed a comprehensive screen of all autosomal catecholamine genes and provided strong evidence that DNA variation in the *SLC6A3* gene predicts behavioural measures of response inhibition (SSRT). Furthermore, using fMRI, we have shown that the efficiency of activation within frontostriatal response inhibition circuits varies as a function of allelic variation in rs37020 of *SLC6A3*. Future studies should now examine the impact of *SLC6A3* gene variants on response inhibition across development and in the context of clinical disorders marked by behavioural disinhibition.

Conflict of interest

MAB has received reimbursement from Lilly Pharmaceuticals for conference travel expenses and for speaking at conferences. MAB has received speaker's fees from Jannsen Cilag and Lilly Pharmaceuticals. The remaining authors declare no conflicts of interest.

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)