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Short Communication

Genetic variations in dopamine and inhibitory control: Lack of influence on action restraint

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HIGHLIGHTS

- We examined genetic influences on action restraint, an aspect of inhibitory control.
- Three common and functional polymorphisms on dopaminergic genes were explored.
- 322 non-clinical individuals were genotyped and completed a Go/No-Go task.
- We did not observe genotype effects on fundamental measures of response inhibition.
- Findings reinforce a dissociation between the stop-signal and Go/No-Go tasks.

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ABSTRACT

Failures of inhibitory control can severely affect everyday life in healthy individuals and represent a common feature of many neuropsychiatric conditions, particularly disorders with dopaminergic disturbances implicated. This study's aim was to examine the interacting influences of three common and functional gene variants that influence dopaminergic pathways on an aspect of inhibitory control (action restraint). Three hundred and twenty two healthy adults were selected from an international consortium linked to Brain Research and Integrative Neuroscience (BRAINnet). DNA was extracted from cheek swab samples and participants were genotyped for the Val158Met single nucleotide polymorphism on *COMT* (rs 4680), C957T on *DRD2* (rs 6277) and the 40 bp variable number of tandem repeat on the *DAT1* (SLC6A3, 10/10 vs 9+). Response inhibition was measured using a computerised Go/No-Go task. Main effects and interactions between genotypes were explored. We did not observe a genotype effect on fundamental measures of response inhibition, i.e. reaction time (RT) and commission errors. RT variability was significantly increased in *DRD2* C957T heterozygotes. In conclusion, this large, non-clinical study reveals that the selected genetic polymorphisms regulating dopamine (*COMT*, *DRD2* and *DAT1*) do not influence one aspect of response inhibition, action restraint, as measured by the Go/No-Go task, reinforcing the neuropharmacological dissociation between stop-signal and Go/No-Go tasks. Genetic variation in striatal dopamine may, however, contribute to intraindividual RT variability.

1. Introduction

Response inhibition is a fundamental cognitive function that reflects an individual's capacity to suppress actions that are inappropriate in a given context. Response inhibition deficits can severely affect everyday life in healthy individuals and are considered a key feature of many neuropsychiatric disorders, particularly disorders with dopaminergic disturbances implicated (e.g. schizophrenia; attention deficit hyperactivity disorder; and, Parkinson's disease [1]). Several pharmacological studies suggest dopamine contributes to successful response inhibition; however, the exact role of dopamine remains equivocal and other neurotransmitter systems have also been implicated (see reviews [1,2]). Recent research has described a genetic basis for response inhibition [3]. Hence, an intermediate phenotype approach may help understand the link between dopamine system-related gene polymorphisms and response inhibition.

In relation to striatal dopamine, evidence suggests low dopamine D2-like receptor availability and/or function predicts poorer inhibitory control [4]. The dopamine D2-receptor gene

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(*DRD2*) contains a functional SNP 957C>T (rs6277) that can reduce mRNA receptor stability [5] and predict striatal D2 binding potential [6]. The T allele, associated with lower striatal *DRD2* binding, and hence lower levels of striatal DA (C/C>C/T>T/T) [6], has been associated with less efficient inhibition in healthy adults (in relation to inhibiting prepotent responses on a stop signal RT task (SSRTT) (n = 130) [7] (although see [8])). This finding is consistent with the notion that depleted levels of striatal dopamine impairs inhibitory control performance (e.g. in Parkinson's disease [9]).

The dopamine transporter gene (*DAT1*) codes for a dopamine transporter protein (SLC6A3) that is expressed abundantly in the striatum and provides the primary mechanism for regulating dopamine availability in the synapse [10]. The *DAT1* gene harbours a polymorphic 40-base pair (bp) variable number of tandem repeat (VNTR) located in the 3′ untranslated region of the gene, resulting in variants that range from 3- to 13-repeats (9 and 10 repeat alleles are the most common in humans [11]). The DAT1 VNTR polymorphism has a modulatory effect on DAT expression; however in vivo and in vitro findings are inconsistent with increased DAT protein associated with both 10-repeat [12] and 9-repeat carriers [13]. The impact of this polymorphism on response inhibition is also variable: with no association reported (n = 33 children with ADHD) [14]; a trend towards impaired response inhibition in 9-repeat healthy young adult carriers (n = 128); worse performance in children with the 10/10 genotype (n = 62) compared to children with one 10-repeat allele (n = 45) [15].

In terms of genetic regulation of prefrontal dopamine, a functional SNP on the catechol-O methyltransferase (*COMT*) gene (Val158Met, rs4680) predicts *COMT* enzyme activity and subsequent prefrontal dopamine metabolism (with the val variant associated with increased *COMT* activity and reduced prefrontal dopamine [16]). Previous studies, with relatively small sample sizes, have failed to show an effect of the *COMT* genotype on measures of behavioural inhibition (e.g. [7]; however carriers of the met allele show increased neural activation, in prefrontal and striatal brain regions, during SSRTT performance suggestive of better inhibitory control).

Hence, existing research exploring the effects of dopamine system-related gene polymorphisms and response inhibition are inconclusive, with relatively small sample sizes preventing exploration of gene–gene interactions along the dopaminergic pathway. The aim of the current study was to examine the interacting effects of three common, functional genetic variations that influence dopaminergic transmission (*COMT*, *DAT1* and *DRD2* genotypes) on response inhibition using a computerised Go/No-Go task in a large, non-clinical sample. The Go/No-Go paradigm is one of the prototypical behavioural measures of inhibitory control, specifically assessing the capacity to inhibit a pre-potent response. It was hypothesised that response inhibition performance would be impaired in individuals with presumably lower levels of striatal dopamine (i.e. expressing the T/T *DRD2* genotype; the *DAT1* 9+ genotype) and the val/val *COMT* genotype.

2. Methods and materials

2.1. Participants

The participants and data acquisition for this study involved an international consortium linked to Brain Research and Integrative Neuroscience Network (BRAINnet; www.brainnet.net). One thousand and two individuals (aged between 6 and 80) of mixed ethnicity were screened. Inclusion criteria for this study included age between 18 and 75; European ethnicity; and successful genotyping of *COMT*, *DRD2* and *DAT1*. Exclusion criteria included Axis I mental illness, neurological disorder or other serious medical condition, brain injury or loss of consciousness for 10 min or more, regular marijuana use or recreational drug use (non-prescription drugs). These criteria were assessed with a web-based questionnaire (Brain Resource WebQ™) which is a standardised battery of questionnaires. The final sample, based on inclusion and exclusion criteria, was 322 individuals (153 males) with a mean age of 41.1 years (SD = 16.74).

Informed written consent was provided in accordance with ethical requirements.

2.2. Genotyping

DNA was extracted from cheek swab samples.

COMT: rs4680 genotype was determined using polymerase chain reaction (PCR) amplification and restriction digest. PCR amplification of participant DNA was undertaken using primers 5′-TGTCACCAGGGGCGAGGCTCAT-3′ and 5′-CGGCCCTTTTTCCAGGT CTGAC-3′ and standard conditions. Genotypes were scored twice independently by two researchers, with Val/Val, Val/Met and Met/Met delineated.

DRD2: rs6277 genotype was determined using primer extension followed by mass spectrometry analysis on the Sequenom MassARRAY system (Sequenom, San Diego, CA) by the Australian Genome Research Facility (http://www.agrf.org.au/) with T/T, T/C and C/C delineated.

DAT1: *SLC6A3* VNTR genotype was determined by size separation of PCR products. PCR amplification of participant DNA was undertaken using primers 5′-TGTGGTGTAGGGAACGGCCTGAG-3′ and 5′-CTTCCTGGAGGTCACGGCTCAAGG-3′ in a reaction containing 500 mM betaine. Genotypes were scored twice independently by two researchers with 9+ (including 9/9 and 9/10) and 10/10 delineated.

2.3. Cognitive testing

The Go/No-Go task assesses the balance between automatic responding and response suppression (inhibition), specifically the capacity to inhibit a planned response before the motor response has been started ('action restraint' [17]). The word 'PRESS' was presented repeatedly on the screen (display time 500 ms, interstimulus interval (ISI) 500 ms), frequently in green font colour and infrequently in red. Participants respond to each stimulus by tapping the screen as quickly as possible to the green 'PRESS' stimuli, but not tapping the screen in response to the red 'PRESS' stimuli. There were 168 stimuli in total (126 green, 42 red). Task duration was approximately 4 min. The dependent variables were the number of *omission errors* (number of times when a button was not pressed in response to a green 'press' stimulus, reflecting inattentiveness or slow responses) and *false positives* (number of times when a button was pressed at any time in response to a red 'press' stimulus, reflecting inhibition errors), as well as *reaction time (RT)* (time in msec to button press averaged across all correctly performed green 'press' stimuli) and *RT variability* (standard deviation of the set of RTs to green 'press' stimuli in msec).

2.4. Statistical analyses

The relationship between genotyping and demographic characteristics was analysed using one-way analysis of variance (ANOVA) or chi square tests as appropriate. Cognitive data was examined for normality. The omission error data was substantially positively skewed and nonparametric analyses (Kruskal–Wallis independent samples median test) were employed. The remaining three cognitive dependent variables (RT; RT variability; and false positives) were entered into a single MANOVA with the genotypes of *COMT* (Val/Val; Val/Met; Met/Met), *DAT1* (9+ [including 9/9 and 9/10];