GENETIC MARKERS OF STRIATAL DOPAMINE PREDICT INDIVIDUAL DIFFERENCES IN DYSFUNCTIONAL, BUT NOT FUNCTIONAL IMPULSIVITY

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Abstract—Various psychiatric disorders are characterized by elevated levels of impulsivity. Although extensive evidence supports a specific role of striatal, but not frontal dopamine (DA) in human impulsivity, recent studies on genetic variability have failed to identify a functional role. Importantly, impulsivity consists of two dissociable components: functional and dysfunctional impulsivity. We compared participants with a genetic predisposition to have relatively high striatal DA levels (DAT1 9-repeat carriers, DRD2 C957T T/T homozygotes, and DRD4 7-repeat carriers) with participants with other genetic predispositions. We predicted that the first group would show high scores of dysfunctional, but not functional, self-reported impulsivity and greater difficulty in inhibiting a behavioral response to a stop-signal, a behavioral measure of impulsivity. In a sample of 130 healthy adults, we studied the relation between DAT1, DRD4, and C957T polymorphism at the DRD2 gene (polymorphisms related to striatal DA) and catechol-Omethyltransferase (COMT) Val158Met (a polymorphism related to frontal DA) on self-reported dysfunctional and functional impulsivity, assessed by the Dickman impulsivity inventory (DII), and the efficiency of inhibitory control, assessed by the stop-signal paradigm. DRD2 C957T T/T homozygotes and DRD4 7-repeat carriers indeed had significantly higher scores on self-reported dysfunctional, but not functional, impulsivity. T/T homozygotes were also less efficient in inhibiting prepotent responses. Our findings support the claim that dopaminergic variation affects dysfunctional impulsivity. This is in line with the notion that the over-supply of striatal DA might weaken inhibitory pathways, thereby enhancing the activation of, and the competition between, responses. © 2010 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: impulsivity, dopamine, striatum, stop-signal task, DII scale.

Impulsivity is a complex construct that encompasses both the failure to inhibit the expression of intrusive thoughts and the tendency to act immediately in response to stimuli in the environment (Logan and Cowan, 1984). Several psychiatric disorders are characterized by dopaminergic abnormalities and elevated impulsivity, such as substance abuse and addiction, attentional deficit hyperactivity disorder (ADHD), and impulse control disorders (American Psychiatric Association, 1994). Evidence suggesting a specific causal role of striatal dopamine (DA) in impulsivity comes from pharmacological, metabolite, lesion, and knockout studies in animals (Cardinal et al., 2001; Puumala, 1998; Winstanley et al., 2006); pharmacological studies in healthy humans (de Wit et al., 2002; Friedel, 2004), and genetic studies in human patients. The presence of the 7-repeat allele of the DA D4 receptors (DRD4) has been associated with ADHD (Langley et al., 2004) and with performance on cognitive measures of impulsivity in ADHD patients (Li et al., 2006). Alcoholism, in turn, is more often observed in 9-repeat allele carriers of the dopamine transporter (DAT1) (Kohnke et al., 2005), while cocaine addiction has been linked to the Taq A1 polymorphism related to the DA D2 receptor (DRD2) (Noble et al., 1993).

Recent studies in healthy humans have examined the association between impulsivity and genetic variability associated with striatal dopaminergic polymorphisms (Congdon et al., 2008; Forbes et al., 2007). Findings are very mixed however. Forbes and colleagues (2007) reported significantly higher self-reported impulsivity scores in 9-repeat allele carriers of the DAT1 gene, but no association with DRD2, DRD4, and catechol-Omethyltransferase (COMT) genotypes. Congdon and colleagues (2008) failed to replicate this pattern, an observation that they attributed to the possible lack of sensitivity of self-report impulsivity measures to genetic variability. Both Forbes et al. and Congdon et al. assessed impulsivity by means of the Barratt impulsiveness scale (BIS) (Patton et al., 1995), an inventory that indicates self-reported tendencies to act without thinking (motor impulsivity), to make decisions "on the spur of the moment" (cognitive impulsivity), and to fail to plan ahead (non-planning impulsiveness). There are indeed theoretical reasons to assume that the BIS scale may not be sensitive enough. Impulsivity is a complex construct that can be subdivided in more than one subtype (Claes et al., 2000; Dickman, 1990). The first subtype consists in dysfunctional impulsivity, defined as the tendency to act with less forethought than most people of equal ability when this tendency is a source of difficulty. The second subtype consists in functional impulsivity, the...
tendency to act rapidly and/or with relatively little forethought when such a style is useful. This distinction is supported by observations suggesting that impulsivity does not always impair cognitive functioning. For instance, if a task is relatively simple and well-structured, highly impulsive participants show rapid responding associated with little cost in errors (Dickman, 1985). Along similar lines, when under time pressure, high impulsives may act more accurately than low impulsives (Dickman and Meyer, 1988). Interestingly, Kumari and colleagues (2009) found that dysfunctional, but not functional, impulsivity is elevated in patients with schizophrenia with a propensity for repetitive violence.

The goal of the present study was to examine whether the association between impulsivity and genetic variability would be more straightforward when functional and dysfunctional impulsivity are assessed separately. In particular, we expected genetic variability related to the striatal dopaminergic signaling pathway to predict dysfunctional but not functional impulsivity. This implies that carriers of polymorphism that are assumed to be related to higher levels of striatal DA (DAT1 9-repeat carriers, DRD2 C957T T/T homozygotes, and DRD4 7-repeat carriers) would exhibit higher dysfunctional-impulsivity scores than individuals with other genetic predispositions. In order to address the question of specificity of this pathway, we also measured genetic variability related to the prefrontal dopaminergic pathway (COMT), which is less likely to be related to inhibitory control and impulsivity (Forbes et al., 2007). As pointed out by Honea and colleagues (2009), given prefrontal dopamine transporters are limited, COMT is assumed to play a key role in clearing dopamine in the prefrontal cortex, which has been demonstrated directly by a two-to-threefold increase in baseline frontal dopamine in male COMT knockout mice (Gogos et al., 1998). A single nucleotide polymorphism (SNP), results in the amino acid substitution of valine (Val) with methionine (Met), in the coding region of the COMT (Val158Met) gene. This substitution leads to a significant (approximately 40%) decrease in enzymatic activity in the brain and lymphocytes (Chen et al., 2004a) of the met-allele compared to the val-containing polypeptide. Consequently, met-carriers are most likely associated with a higher level of prefrontal extra-cellular dopamine (Chen et al., 2004b; Lachman et al., 1996). In contrast, the C957T polymorphism within the DRD2 gene affects D2 mRNA translation and stability (Duan et al., 2003), and postsynaptic D2 receptor density in the striatum (Hirvonen et al., 2005), without affecting presynaptic DA function (Laakso et al., 2005). Similarly, DAT gene (DAT1) is linked with reduced DAT expression and presumably greater striatal synaptic DA (Bannon et al., 2001; Van Ness et al., 2005), while the 48 bp VNTR in the third exon of the DRD4 gene leads to reduced DRD4-mediated inhibitory postsynaptic effects (Asghari et al., 1995; Wang et al., 2004).

Previous studies have shown that the C957T polymorphism of the DRD2 gene predicts the degree to which participants learn avoiding choices that had been probabilistically associated with negative outcomes, while the COMT gene predicts participants’ ability to rapidly adapt behavior on a trial-by-trial basis (Frank et al., 2007a), verbal working memory performance (Aguilera et al., 2008), and the efficiency of task switching (Colzato et al., 2010b). DAT1 and DRD4 genes seem instead to be associated with attentional processes (Colzato et al., 2010a; Bellgrove and Mattingley, 2008; Fossella et al., 2002). We assessed dysfunctional and functional self-reported impulsivity by means of the Dickman impulsivity inventory (DII; Dickman, 1990), and behavioral inhibitory efficiency by means of a stop-signal task (Logan and Cowan, 1984). In this task, participants are first presented with a stimulus (i.e. a go signal) prompting them to execute a particular manual response, and this stimulus may or may not be followed by a stop signal calling for the immediate abortion of that response. Based on the mathematical considerations formulated by Logan and Cowan (1984), the stop-signal paradigm provides a direct behavioral assessment of the individual ability to stop a planned or ongoing motor response in a voluntary fashion and a quantitative estimate of the duration of the covert response-inhibition process (i.e. stop-signal reaction time or SSRT; see Fig. 1). The employment of this measure of inhibitory control in patient studies has provided converging evidence for the involvement of DA in response inhibition and impulsive behavior. Parkinson’s patients, who suffer from loss of dopaminergic neurons in the basal ganglia, showed longer SSRTs (Gaugel et al., 2004) and impaired suppression of conflicting responses (Wylie et al., 2009, 2010) compared to matched controls. Consistent with this picture, ADHD patients show longer SSRTs (see, Alderson et al., 2007, for a recent review) and Colzato et al. (2007) observed that recreational users of cocaine, who are likely to suffer from reduced dopamine D2 receptors in the striatum (Volkow et al., 1999), need significantly more time to inhibit responses to stop-signals than non users. All these findings converge on the notion that the striatum plays a critical role in the suppression of responses that are incorrect or no longer relevant. They also fit with the assumption that dopamine, which innervates these circuits, plays a role in modulating response inhibition (see...
Mink, 1996 for a review). Considering that inhibiting prepotent responses does require cognitive control, we thus expected that participants that have relatively increased striatal DA (DAT1 9-repeat carriers, DRD2 C957T T/T homozygotes, and DRD4 7-repeat carriers) are associated with impairments in inhibitory control.

To summarize, based on the available evidence for a link between genetically driven variability in striatal DA and individual differences in impulsivity (Forbes et al., 2007), we hypothesized that the polymorphisms associated with striatal DA (C957T polymorphism at DRD2, DRD4, DAT1), but not with frontal dopaminergic functioning (COMT), predict dysfunctional, but not functional, self-reported impulsivity and the inhibition of prepotent responses.

**EXPERIMENTAL PROCEDURES**

**Participants**

One hundred and thirty young healthy Caucasian adults served as participants for partial fulfillment of course credit or a financial reward, see Table 1. The sample was drawn from adults from the Leiden and Rotterdam metropolitan area (The Netherlands), who volunteered to participate in studies of behavioral genetics. Exclusion criteria included major medical illness that could affect brain function, current medications and substance abuse, neurological conditions, history of head injury, and personal history of psychiatric medical treatment. Written informed consent was obtained from all participants after the nature of the study was explained to them. The protocol was approved by the local ethics committee of the Institute of Psychology at Leiden University.

**Apparatus and stimuli**

The experiment was controlled by an ACPI uniprocessor PC running on an Intel Celeron 2.8 gHz processor, attached to a Philips 109B6 17 inch monitor (LightFrame 3, 96 dpi with a refresh rate of 120 Hz). Responses were made by pressing the “Z” or “?” of the QWERTY computer keyboard with the left and right index finger, respectively. Participants were required to react quickly and accurately by pressing the left and right key in response to the direction of a left- or right-pointing green arrow (go trials) of about 3.5×2.0 cm² with the corresponding index finger.

**Stop-signal task**

Each experimental session consisted of a 30-min session in which participants completed a version of the stop-signal task adopted from Colzato et al. (2007, 2009). Arrows were presented pseudorandomly for maximal 1500 ms, with the constraint that they signaled left- and right-hand responses equally often. Arrow presentation was response-terminated. Intervals between subsequent go signals varied randomly but equiprobably, from 1250 to 1750 ms in steps of 125 ms. During these interstimulus intervals, a white fixation point (3 mm in diameter) was presented. The green arrow changed to red on 30% of the trials, upon which the choice response had to be aborted (stop trials). A staircase-tracking procedure dynamically adjusted the delay between the onset of the go signal and the onset of the stop signal to control inhibition probability (Levitt, 1971). After a successfully inhibited stop trial, stop-signal delay in the next stop trial increased by 50 ms, whereas the stop-signal delay decreased by 50 ms in the next stop trial when the participant was unable to stop. This algorithm ensured that motor actions were successfully inhibited in about half of the stop trials, which yielded accurate estimates of SSRT and compensates for differences in choice RT between participants (Band et al., 2003; see Fig. 1). The stop task consisted of five blocks of 104 trials each, the first of which served as a practice block to obtain stable performance.

**IQ**

Individual IQs were determined by means of a 30-min reasoning-based intelligence test (Raven Standard Progressive Matrices: SPM). The SPM assesses the individual’s ability to create perceptual relations and to reason by analogy independent of language and formal schooling; it is a standard, widely-used test to measure

<table>
<thead>
<tr>
<th>Genotype</th>
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<th>Sex</th>
<th>Age</th>
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Impulsivity scores and SSRTs with different superscript letters differ significantly at P<0.05 (lowercase) or P<0.01 (uppercase).
Spearman’s g factor as well as fluid intelligence (Raven et al., 1988). Participants completed the SPM and subsequently performed on the behavioral task measuring inhibitory control.

Impulsivity self-report inventory

Participants completed the DII (Claes et al., 2000), which comprises 23 questions. The functional impulsivity scale contains 11 items such as: “People have admired me because I can think quickly” and “Most of the time, I can put my thoughts into words very rapidly.” The dysfunctional impulsivity scale contains 12 items such as: “I often say and do things without considering the consequences” and “I often get into trouble because I don’t think before I act.” The psychometric properties of the Dutch DII are good for both subscales (Claes et al., 2000) with a Cronbach’s alpha of .77 and .80 for functional and dysfunctional impulsivity, respectively (Franken et al., 2005).

DNA laboratory analysis

Genomic DNA was extracted from saliva samples using the Oragene™ DNA self-collection kit following the manufacturer’s instructions (DNA Genotek, Inc., 2006). The COMT Val158Met; SNPs DAT1 VNTR; DRD4 third exon 48 bp VNTR, and C957T polymorphism at DRD2 gene (Frank et al., 2007a) were genotyped using Applied Biosystems (AB) TaqMan technology. Following Forbes et al. (2007), all genotypes were scored by two independent readers by comparison to sequence-verified standards. Participants were classified by genotype as follows (see Table 1). For COMT Val158Met two genotype groups were established: Met-carriers and Val/Val homozygotes. For DAT1, two genotype groups were established; 9-repeat allele carriers and 10-repeat allele homozygotes. For C957T polymorphism at DRD2, three genotype groups were established: T/T allele homozygotes, C/T allele heterozygotes and C/C allele homozygotes. All the four genotypes were available in 124 of the 130 participants. COMT, DAT1, and DRD4 genotypes were unavailable for two participants.

Procedure and design

All participants were tested individually. Participants completed the SPM (Raven et al., 1988) and the DII (Claes et al., 2000), and performed the stop-signal task for about 30-min. Participants were allowed to take a short break (maximal 5 min) between task blocks.

Statistical analysis

First, repeated-measures analysis of variances (ANOVAs) were performed for analyses of dysfunctional and functional impulsivity, age, sex, IQ differences between genotype groups. Second, to test the effect of each gene and the interactions, individual SSRTs for stop-signal trials were calculated to index response inhibition for all participants. SSRTs were analyzed separately by means of univariate ANOVAs with genotypes as between-subjects factor. For DRD1, two genotype groups were established: 7-repeat carriers and 8-repeat carriers—an attempt that however failed due to technical problems related to the TaqMan technology. For DRD4, the effect of each gene and the interactions, individual SSRTs were analyzed separately by means of univariate ANOVAs with genotypes as between-subjects factor. For DRD2, three genotype groups were established: T/T allele homozygotes, C/T allele heterozygotes and C/C allele homozygotes. For COMT, DAT1, and DRD4 genotypes were unavailable for two participants.

RESULTS

Sample information, genotype-specific demographics, and functional and dysfunctional impulsivity scores are shown in Table 1. All resulting genotype frequencies from our cohort of participants did not deviate from Hardy–Weinberg equilibrium (all P-values >0.10). No significant differences were found among genotype frequencies with respect to age, sex, estimated IQ, or functional impulsivity. As expected, dysfunctional impulsivity yielded a significant effect of genotype for C957T polymorphism at DRD2, F(2,127)=4.653, P<0.0125, MSE=7.199, σp²=0.068, for the DRD4, F(2,126)=8.772, P<0.0125, MSE=7.266, σp²=0.065. A trend was observed for DAT1, F(2,126)=2.510, P=0.116, MSE=7.591, σp²=0.020. The 7-repeat carriers (DRD4) and T/T homozygotes (C957T polymorphism at DRD2) showed significantly higher scores of dysfunctional impulsivity than other allele carriers—a pattern that fits with the numerically higher dysfunctional-impulsivity scores in 9-repeat carriers of the DAT1 gene. In contrast, COMT did not show any effect on impulsivity, F<1.

SSRTs yielded a significant effect of genotype for C957T polymorphism at DRD2, F(2,127)=3.90, P<0.0125, MSE=943.40, σp²=0.058, indicating that T/T homozygotes had significantly longer SSRTs than C/T carriers and C/C homozygotes (see Fig. 2). Despite similar result patterns (with longer SSRTs for polymorphisms associated with higher striatal DA levels), the effects of DRD4, F(2,126)=2.26, P=0.13, MSE=991.39, σp²=0.008, and DAT1, F(2,126)=1.39, P=0.23, MSE=997.95, σp²=0.011, failed to reach significance. COMT had no effect, F<1, and no significant interaction between DRD4, DAT1 and C957T polymorphism at DRD2 on SSRT was found (P>0.10).

As expected, dysfunctional impulsivity correlated with SSRT, r(130)=.265, P<.0125, while functional impulsivity did not, r(130) = -.013, P=.88.

![Fig. 2. Mean SSRT (stopping latency) as a function of C957T polymorphism at DRD2 gene (C/C homozygotes vs. C/T carriers vs. T/T homozygotes). Vertical capped lines atop bars indicate standard error of the mean.](Image 132x115 to 546x299)
CONCLUSION

We investigated the relation between DA-related genetic variability and impulsivity. In contrast to previous studies, we distinguished between functional and dysfunctional impulsivity and, indeed, observed distinct interaction patterns for these two subtypes. Whereas functional impulsivity did not interact with any other variable or genetic predisposition, dysfunctional impulsivity showed a rather systematic pattern: First, dysfunctional impulsivity correlated with stopping performance in the stop-signal task, our behavioral indicator of impulsivity. Second, impulsivity scores were also increased, or tended to be increased, in carriers of genes that drive elevated striatal DA levels. In particular, dysfunctional impulsivity was more pronounced in DRD2 C957T T/T homozygotes and DRD4 7-repeat carriers, and tended to be more pronounced in DAT1 9-repeat carriers.

The observed dissociation between functional and dysfunctional impulsivity might explain discrepancies between previous studies (Congdon et al., 2008; Forbes et al., 2007) that did not distinguish between these subtypes of impulsivity. As compared with the BIS scale, the DII inventory seems to provide a more comprehensive and differentiated picture of impulsivity patterns and is thus more sensitive in tapping into the impact of genetic predisposition. This is also suggested by our observation that dysfunctional but not functional impulsivity correlated with Parkinson’s disease and cocaine users, who have reduced dopamine function, also show longer SSRT (Gaugel et al., 2004; Colzato et al., 2007). A reasonable explanation for this apparent discrepancy might be that the relationship between response inhibition efficiency and dopamine levels is not linear but follows an inverted U-shaped function—just like other cognitive functions, such as working memory (Goldman-Rakic et al., 2000). According to this idea, it is an average dopamine level that allows for optimal cognitive performance, whereas too high or too low levels impair cognitive processes. This scenario is consistent with a recent observation of Akbari Chermahini and Hommel (2010), who studied the relationship between creativity and dopamine. Spontaneous eye-blink rates (EBRs), a clinical indicator (Shukla, 1985) considered to index dopamine production in the striatum (Blin et al., 1990; Karson, 1983; Taylor et al., 1999), predicted performance in divergent thinking, a subcomponent of creativity that has been associated with dopaminergic functioning (Ashby et al., 1999; Eysenck, 1993). Interestingly for our purposes, the relationship followed an inverted U-shaped function with average EBRs producing better performance than low or high EBRs.

Although the hypothesis of an inverted U-shaped function between SSRT and DA levels certainly requires more direct investigation using different paradigms, such as psychopharmacological studies, it in any case seems essential for DA-related manipulations that individual baseline levels of DA are taken into account. Indeed, as pointed out by Cools (2006) and Akbari Chermahini and Hommel (2010), individuals are likely to differ with respect to baseline levels of DA (be it through genetic variation, drug abuse, or other factors) and may therefore exhibit differential sensitivity to the positive and negative effects of dopaminergic drugs and manipulations. Moreover, DA levels are likely to undergo substantial intraindividual changes as well. Apart from the known decay of DA levels in older age (Li et al., 2009), DA levels also seem to fluctuate before rising to adult levels at puberty (Goldman-Rakic and Brown, 1982). Moreover, the length of axons that contain tyrosine hydroxylase (TH), an enzyme critical for the production of dopamine, continues to increase until puberty (Rosenberg and Lewis, 1995). This synchronicity has led to the speculation (cf. Lambe et al., 2000) of a causal relation between maturation of cognitive function, the attainment of maximum TH apposition density on pyramidal cells, the typical age of onset of schizophrenia (Lieberman, 1999), and the age at which certain drugs begin to trigger psychosis (Farber et al., 1999). Further variability might be due to the fact that dopaminergic genotypes may modulate phenotypes differently in healthy adults than in children and patients.

It is interesting to note that our observations are consistent with the model proposed by Frank and colleagues (2007b). According to it, the basal ganglia support adaptive decision-making by modulating the selection of frontal cortical action plans. In short, two main neuronal populations in the striatum are assumed to have opposing effects on
action via output projections through the globus pallidus, thalamus, and back to the cortex. Activity in “Go” neurons facilitates the execution of a cortical response, whereas “NoGo” activity suppresses competing responses. DA bursts and dips that occur during positive and negative outcomes drive Go learning (via D1 receptors) to seek rewarding actions, and NoGo learning (via D2 receptors) to avoid non-rewarding actions. Complementing this functionality, the subthalamic nucleus provides a self-adaptive dynamic control signal that temporarily prevents the execution of any response, depending on decision conflict. According to this model, supplying more DA than optimal (as presumably the case in DRD2 C957T T/T homozygotes associated with relatively increased striatal DA) decreases activity in the indirect pathway (NoGo), a process that would enhance the competition between responses. As a possible indicator of such enhanced competition, we found delayed SSRTs in DRD2 C957T T/T homozygotes. In agreement with the model of Frank et al. (2007b), our findings suggest that variability with respect to the DRD2 gene is the best predictor of dysfunctional impulsivity, followed by DRD4. In contrast, DAT1 was not involved in any reliable interactions, even though it numerically affected impulsivity measures in the same direction as the other genes related to striatal DA. Obviously, these genes are related but serve different purposes, identification of which would be the next empirical step.

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