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Dopamine and the Management of Attentional Resources: Genetic Markers of Striatal D2 Dopamine Predict Individual Differences in the Attentional Blink

Lorenza S. Colzato¹, Heleen A. Slagter², Mischa de Rover¹, and Bernhard Hommel¹

Abstract

The attentional blink (AB)—a deficit in reporting the second of two target stimuli presented in close succession in a rapid sequence of distracters—has been related to processing limitations in working memory. Given that dopamine (DA) plays a crucial role in working memory, the present study tested whether individual differences in the size of the AB can be predicted by differences in genetic predisposition related to the efficiency of dopaminergic pathways. Polymorphisms related to mesocortical and nigrostriatal dopaminergic pathways were considered, as well as polymorphisms related to norepinephrine (NE), a transmitter system that has also been suspected to play a role in the AB. In a sample of 157 healthy adults, we studied the dependency of the individual magnitude of the AB and the C957T polymorphism at the DRD2 gene (associated with striatal DA/D2 receptors), the DARPP32 polymorphism (associated with striatal DA/D1), the COMT Val¹⁵⁸Met polymorphism (associated with frontal DA), DBH444 g/a and DBH5⁰⁻ins/del polymorphisms (polymorphisms strongly correlated with DA beta hydroxylase, the enzyme catalyzing the DA–NE conversion) and NET T-182C (a polymorphism related to the NE transporter). DRD2 C957T T/T homozygotes showed a significantly smaller AB, whereas polymorphisms associated with frontal DA and NE were unrelated to performance. This outcome pattern suggests a crucial role of the nigrostriatal dopaminergic pathway and of nigrostriatal D2 receptors, in particular, in the management of attentional resources.

INTRODUCTION

The number of events that the human brain is able to process at one time is limited. A robust phenomenon showing the limitation of attention over time is the so-called attentional blink (AB; Raymond, Shapiro, & Arnell, 1992). The AB is observed in rapid serial visual presentation (RSVP) tasks when two masked (or otherwise difficult to identify) target stimuli appear in close temporal proximity. Although the first target (T1) is commonly easy to identify and to report, performance on the second target (T2) is dramatically impaired if it follows T1 within 100–500 msec. Consistent with this scenario, recent brain imaging studies provide evidence that the individual size of the AB is predicted by the amount of attentional resources devoted to T1 processing, as indicated by the individual amplitude of the M3, the magneto-encephalographic equivalent of the electrophysiological P3 (Shapiro, Schmitz, Martens, Hommel, & Schnitzler, 2006) or by individual differences in activity in T1 visual object-encoding areas (Slagter, Johnstone, Beets, & Davidson, 2010). This observation suggests that the AB does not reflect a structural bottleneck in information processing but the way attentional resources are managed (Hommel et al., 2006). Interestingly, creating conditions that are likely to have participants allocate more resources to T1 processing does not improve accuracy of T1 report, which suggests that people tend to overinvest attentional resources into T1 processing and thereby impair T2 performance (Taatgen, Juvina, Schipper, Borst, & Martens, 2009; Olivers & Nieuwenhuis, 2005, 2006). This possibility also fits with observations from studies that have shown that manipulations promoting a less object-focused state of attention typically reduce the size of the AB but do not affect T1 accuracy (e.g., Slagter, Lutz, Greischar, Nieuwenhuis, & Davidson, 2009; Slagter et al., 2007; Olivers & Nieuwenhuis, 2005, 2006), as well as with observations from studies on individual differences, which consistently show effects on T2 but not T1 report (e.g.,

¹Leiden University, ²University of Amsterdam

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Recent neuroimaging and patient studies have implicated a network of frontal, right parietal, and temporal brain areas involved in perceptual awareness in the AB (for a review, see Hommel et al., 2006). What remains unclear, however, is how this network communicates (for a first step, see Gross et al., 2004) and, in particular, what neurochemical mechanisms might mediate this communication. According to a recent computational theory (Nieuwenhuis, Gilzenrat, Holmes, & Cohen, 2005), norepinephrine (NE)—a neurotransmitter with a presumably important role in attentional selection (Aston-Jones & Cohen, 2005)—is the prime candidate. However, observations from two recent pharmacological studies are inconsistent with a role for the noradrenergic system in the AB: T2 report in the AB task was not affected by administration of the α2 adrenoceptor agonist clonidine (Nieuwenhuis, Van Nieuwenpoort, Veltman, & Drent, 2007) of the peripherally acting β-adrenergic antagonist nadolol or of a smaller dose (20 mg) of the centrally acting β-adrenergic antagonist propranolol (De Martino, Strange, & Dolan, 2008). De Martino et al. did report impaired T2 detection after the administration of a higher dose (40 mg) of propranolol, but this impairment was equally strong for T2s presented within and outside the time window of the AB, suggesting a nonspecific arousal effect. Thus, none of the adrenergic manipulations used in these two studies affected the size of the AB, which fails to provide evidence for a role of NE in temporal attention and the AB.

A promising alternative candidate—especially in view of its key role in WM processes (Braver & Cohen, 2000; Sawaguchi & Goldman-Rakic, 1991)—is dopamine (DA). According to Moustafa, Sherman, and Frank (2008), the nigrostriatal dopaminergic pathway serves as a gate to signal when and when not to update information in prefrontal WM. Consistent with this idea, Siessmeier et al. (2006) found that administering DA agents to healthy subjects led to a correlation between DA uptake in the striatum and BOLD activity in the dorsolateral pFC, suggesting that the striatum might drive WM activity in the pFC. Moreover, a PET study showed that individual WM capacity predicts the striatal DA synthesis capacity: Subjects with low WM capacity have a low synthesis capacity, whereas subjects with high WM capacity have a high synthesis capacity (Cools, Gibbs, Miyakawa, Jagust, & D’Esposito, 2008). Interestingly, two recent studies show that people high in WM control exhibit a smaller AB (Arnell, Stokes, MacLean, & Gigante, 2010; Colzato et al., 2007), indicating that the AB is related to WM, in general, and attributable to operational resource limitations, in particular (Hommel et al., 2006; Di Lollo et al., 2005; Gross et al., 2004; Dehaene, Sergent, & Changeux, 2003).

To summarize, these links between DA and WM on the one hand and between WM and AB on the other point to a modulatory role for DA in the AB. Consistent with this idea, Colzato, Slagter et al. (2008) found that spontaneous eyeblink rate, a functional marker of dopaminergic functioning (Karson, 1983), reliably predicts the individual size of the AB.

As noted by Cools (2006), DA receptors are divided into two major receptor families: the D1 and the D2 family receptors. These D1 and D2 receptors are differentially distributed across the pFC and the striatum and the ratio between D1 and D2 that is higher in the pFC than in the striatum (Camps, Kelly, & Palacios, 1990). This difference in distribution of dopaminergic receptors comes with functional differences: Whereas the frontal pathway is presumably involved in the maintenance of information in WM (Sawaguchi & Goldman-Rakic, 1991), the nigrostriatal pathway has been implicated in executive control WM operations (Cools et al., 2008; Moustafa et al., 2008). Given that the AB is unlikely to reflect a structural bottleneck (such as the storage capacity of WM, which is unlikely to be exhausted by one item anyway) and the evidence linking the AB to limitations in handling cognitive resources, this distribution of labor suggests that the nigrostriatal but not the frontal pathway is the most plausible candidate to mediate the AB.

**Purpose of This Study**

The present experiment aimed to test the hypothesis that the individual size of the AB is modulated by the functioning of the nigrostriatal DA/D2 subsystem, which is assumed to drive WM control and modulate attentional gating. This hypothesis was tested by predicting individual ABs from the genetic variability associated with striatal and cortical dopaminergic functioning and with the functioning of the noradrenergic system. The selection of our candidate polymorphisms was driven by available in vitro and/or in vivo assays demonstrating significant impact of these variants on aspects of biological function related to DA (see Frank, Moustafa, Haughey, Curran, & Hutchison, 2007) and NE neurotransmission (Hu, Caron, & Sieber-Blum, 2009; Yamamoto et al., 2008).

We considered six polymorphisms. Most important for testing our hypothesis were carriers of a polymorphism that is assumed to be related to lower levels of striatal DA/D2 or reduced D2 affinity (DRD2 C957T T/T homozygotes), as these individuals should exhibit a smaller blink than individuals with other genetic predispositions. Notably, a previous study has linked the C957T polymorphism of the DRD2 gene to the executive control of
WM (Jacobsen, Pugh, Menci, & Gelernter, 2006): T/T homozygotes performed significantly better on a high verbal WM load task. Moreover, the DRD2 C957T polymorphism predicts the degree to which participants are able to inhibit a behavioral response to a stop signal (Colzato, van den Wildenberg, van der Does, & Hommel, 2010) and the degree to which participants learn avoiding choices that had been probabilistically associated with negative outcomes (Frank et al., 2007).

To assess the specificity of a possible effect of the C957T polymorphism, we also considered genetic variability related to the striatal DA/D1 dopaminergic pathway (DARPP-32 polymorphism) and to the prefrontal dopaminergic pathway (COMT Val158Met polymorphism). Although there is no evidence that these two polymorphisms are related to attentional gating, they do affect cognitive processes: DARPP-32 has been shown to predict performance in probabilistic learning (Frank et al., 2007), whereas the COMT gene predicts participants’ ability to adapt behavior on a trial-by-trial basis (Frank et al., 2007), the efficiency of task switching (Colzato, Waszak, Nieuwenhuis, Posthuma, & Hommel, 2010), and general executive functioning (for a review, see Barnett, Jones, Robbins, & Müller, 2007). Three further sources of genetic variability were employed to assess the role of noradrenergic functioning in the AB, two were related to the DA beta hydroxylase (DBH), the enzyme that catalyzes the conversion of DA to NE (DBH444 g/a polymorphism and DBH5'-ins/del polymorphism), and the third was related to the NE transporter (NET T-182C polymorphism). Previous studies suggest that the DBH and NET polymorphisms may be associated with ADHD and attentional processes in general (Bellgrove & Mattingley, 2008; Kim, Waldman, Blakely, & Kim, 2008).

To summarize, the available evidence shows that (a) the DA/D2-dominated nigrostriatal pathway plays a major role in executive control WM operations (Cools et al., 2008; Moustafa et al., 2008), (b) DRD2 C957T T/T homozygotes show better performance in the control of WM operations (Jacobsen et al., 2006), and (c) individuals high in WM operation span (Colzato et al., 2007) exhibit particularly small ABs. On the basis of these observations, we hypothesized that the individual magnitude of the AB is predicted by the polymorphism associated with striatal DA/D2 (C957T polymorphism at DRD2) but not by polymorphisms related to striatal DA/D1 (DARPP-32 polymorphism), frontal dopaminergic functioning (COMT), and noradrenergic functioning (DBH and NET). Our specific prediction was that participants with presumably lower levels of striatal DA/D2 (DRD2 C957T T/T homozygotes) would exhibit a smaller blink than individuals with other genetic predispositions.

METHODS
Participants
One hundred fifty-seven young, white, healthy adults (75 men and 82 women), with a mean age of 22.2 years (SD = 2.6 years, range = 18–30 years) and an estimated IQ of 121.5 (SD = 3.1, range = 100–130), served as participants for partial fulfillment of course credit or a financial reward. The sample was drawn from adults in the Leiden and Rotterdam metropolitan area (the Netherlands), who volunteered to participate in studies of behavioral genetics. Exclusion criteria were any major medical illness that could affect brain function, current and/or past substance abuse, neurological conditions, history of head injury, and personal history of psychiatric medical treatment. Participants were selected via a phone interview using the Mini International Neuropsychiatric Interview (MINI; Lecrubier et al., 1997). The MINI is a well-established brief diagnostic tool in clinical and stress research that screens for several psychiatric disorders including schizophrenia, depression, mania, ADHD, and obsessive–compulsive disorder. Written informed consent was obtained from all participants after the nature of the study was explained to them; the protocol was approved by the ethical committee of the Department of Psychology at Leiden University.

Apparatus, Stimuli, and Task
The experiment was controlled by a Targa Pentium III computer. All stimuli were presented in a resolution of 800 × 600 pixels in 16-bit color on a 17-in. CRT refreshing at 100 Hz. Participants were seated at a viewing distance of about 50 cm. The fixation mark (“+”), as well as all RSVP items, were presented centrally in black on a gray background (RGB 128, 128, 128). Each item was set in 16-point Times New Roman font. RSVP items included letters and digits. Letters were drawn randomly without replacement from the alphabet. Digits were drawn randomly from the set 2–9.

RSVP Task
In the RSVP task adopted from Colzato et al. (2007), participants had to identify and report two digits (T1 and T2) presented in a rapid stream of letter distractors. After reading the instructions, which included a slow demonstration of the RSVP and indicating to have fully understood the task, participants were required to undergo 24 trials of training. If more than 50% of the responses were incorrect during the training, the training part was automatically repeated. A fixation “plus” sign, which was shown for 2000 msec, marked the beginning of each trial. After a blank interval of 250 msec, the RSVP commenced, consisting of 20 items with a duration of 70 msec each and an interstimulus interval of 30 msec.

The occurrence of T1 in the stimulus stream was varied randomly between positions 7, 8, and 9 to reduce the predictability of first target onset. T2 was presented directly after T1 (Lag 1) or after another two, four, or seven distractors (Lags 3, 5, and 8, respectively; see Figure 1). Both targets were to be reported (order of report was not considered).
by comparison with sequence-verified standards. All genotypes were scored by two independent readers. Following Colzato, Pratt, and Hommel (2010), 2007) were genotyped using Applied Biosystems TaqMan polymorphism and COMT Val158Met; DARP-32 polymorphism, DBH444 g/a polymorphism, NET T-182C polymorphism and COMT Val158Met. 

The DBH5’-ins/del polymorphism is a 19-bp insertion-deletion located approximately 3 kb upstream of the transcriptional start codon (Nahmias et al., 1992). The following pair of primers was used (sense: 5’-GCAAAAAGTCAGGCA-CATGGACC-3’, antisense: 5’-CAATATTGGGCCACTCA-TCTTG G-3’) to amplify a PCR product of 144 bp (DBH5’-del) or 163 bp (DBH5’-ins). PCR reactions (final volume = 10 ml) contained 10–25 ng of genomic DNA, 10 nM of each primer, 0.5 U of AmpliTaq DNA polymerase (Parkin Elmer), and 1 AmpliTaq Buffer supplied by the manufacturer. After denaturation at 94°C for 5 min, the mixture was submitted to 30 cycles each made of 30-sec denaturation (94°C), annealing (55°C), and elongation (72°C).

The DBH444 g/a polymorphism is located in the 30 end of exon 2 in the DBH gene and consists of either guanine (g) or adenine (a) at cDNA nucleotide position 444 (Nahmias et al., 1992). A 207-bp DNA fragment, containing this polymorphism, was amplified by PCR using the following primers: sense: 5’-CTTGGAGCCAGTTGCTGTC-3’, antisense: 5’-ACGCCCTCTCGGTGACTCGGC-3’.

For C957T polymorphism at DRD2 gene, the sequence-specific primers for the Taqman assays (5’-CGTGTGGGAGTGCTG-3’ and 5’-CTGTGGGAGTGCTG-3’) were used for the C and T alleles, respectively, as was the common reverse primer 5’-GCCCATCTCCTCTGGTTTGG-3’.

The Val158Met COMT polymorphism was assayed by polymerase using primers 5’-CTGTGGGACCCCTGATT-CAGG-3’ and 5’-AGGTCTGACACGGTGCA-GGC-3’. The following primers 5’-GTCTCTGAGACCTGCCTGCTCT-AGTGCTGACACGGTGCA-GGC and 5’-GAA GCC GAC TAC GGA CAG CAG to generate a 600-bp fragment.

For DBH444 g/a polymorphism, C957T polymorphism at DRD2 gene, Val158Met COMT polymorphism, NET T-182C polymorphism, and DARPP-32 polymorphism, PCR conditions were identical to those used to amplify the DBH5’ ins/del.

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 Spearman’s g factor as well as fluid intelligence (Raven, Court, & Raven, 1988).

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). DBH5’-ins/del polymorphism, DBH444 g/a polymorphism, NET T-182C polymorphism and COMT Val158Met, DARPP-32 polymorphism; C957T polymorphism at DRD2 gene (Frank et al., 2007) were genotyped using Applied Biosystems TaqMan Technology. Following Colzato, Pratt, and Hommel (2010), all genotypes were scored by two independent readers by comparison with sequence-verified standards.

IQ

Participants were classified by genotype as follows (see Table 1). For DBH5’-ins/del polymorphism three genotype groups were established: Ins/Ins allele homozygotes, Ins/Del allele heterozygotes, and Del/Del allele homozygotes. For DBH444 g/a polymorphism, three genotype groups were established: A/A allele homozygotes, G/A allele heterozygotes, and G/G allele homozygotes. For COMT Val158Met two genotype groups were established: Met carriers and Val/Val homozygotes. For DARPP-32, three genotype groups were established: A/A allele homozygotes, G/A allele heterozygotes, and G/G 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. For NET T-182C polymorphism, three genotype groups were established: T/T allele homozygotes, C/T allele heterozygotes, and C/C allele homozygotes.

The question being “which two targets did you see?”—by pressing the corresponding digit keys. A full experimental session lasted for 10 min and contained one block of 144 trials (three locations of T1 × 4 lags × 12 repetitions).

Figure 1. Example of an RSVP trial. On every trial, 20 items were presented at the center of the screen, preceded by a 2000-msec fixation cross. Most of the items were letters, presented for 40 msec each and followed by a 40-msec blank. Participants had to detect two target numbers (T1 and T2) among the items. T1 and T2 were separated by one, three, five, or eight nontarget items, defining the lag. T1 was presented at positions 7, 8, and 9 of the stimulus stream.

The Val158Met COMT polymorphism was assayed by polymerase using primers 5’-CTGTGGGACCCCTGATT-CAGG-3’ and 5’-AGGTCTGACACGGTGCA-GGC-3’. The following primers 5’-GTCTCTGAGACCTGCCTGCTCT-GTTACCTCGGC-3’ have been used to assay the DARPP-32 polymorphism.

For the NET T-182C polymorphism, we used primers T182C-R: 5’-GAG GCC GAC TAC GGA CAG CAG to generate a 600-bp fragment.

For DBH444 g/a polymorphism, C957T polymorphism at DRD2 gene, Val158Met COMT polymorphism, NET T-182C polymorphism, and DARPP-32 polymorphism, PCR conditions were identical to those used to amplify the DBH5’ ins/del.

Participants were classified by genotype as follows (see Table 1). For DBH5’-ins/del polymorphism three genotype groups were established: Ins/Ins allele homozygotes, Ins/Del allele heterozygotes, and Del/Del allele homozygotes. For DBH444 g/a polymorphism, three genotype groups were established: A/A allele homozygotes, G/A allele heterozygotes, and G/G allele homozygotes. For COMT Val158Met two genotype groups were established: Met carriers and Val/Val homozygotes. For DARPP-32, three genotype groups were established: A/A allele homozygotes, G/A allele heterozygotes, and G/G 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. For NET T-182C polymorphism, three genotype groups were established: T/T allele homozygotes, C/T allele heterozygotes, and C/C allele homozygotes.
All six genotypes were available in 150 of the 157 participants. DBH5' ins/del, DBH444 g/a, DRD1, NET T-182C, COMT, and DRD2 genotypes were unavailable for four, six, three, six, seven, and three participants, respectively.

Procedure and Design

All participants were tested individually. Participants completed the SPM and subsequently performed on the RSVP behavioral task.

Statistical Analysis

First, repeated measures ANOVAs were performed for analyses of age, sex, IQ differences between genotype groups. Second, to test the effect of each gene on AB task performance, T1 and T2 accuracy data were submitted to separate ANOVAs with lag (1, 3, 5, and 8) as a within-participants variable and genotype as a between-subjects factor. T2 accuracy was based only on those trials in which T1 was correctly reported (T2|T1). Lag-1 sparing (measured as T2|T1-Lag 1 minus minimum of T2|T1-Lag 3 and Lag 5) was analyzed separately by means of univariate ANOVAs with genotype as a between-subjects factor. Finally, we conducted a regression analysis, in which we used genotypes to predict the maximal AB (measured as T2|T1-Lag 1 minus minimum of T2|T1-Lag 3 and Lag 5), so we could directly compare the relative contributions from these six predictors.

A significance level of \( p < .0083 \) (significant group difference) was adopted for all statistical tests, correcting \( p \) values for multiple comparisons (Bonferroni correction).

### Table 1. Sample and Genotype-specific Demographics; Maximal AB Size (Measured as T2|T1 at Lag 8 Minus the Minimum of T2|T1 at Lag 3 and Lag 5) and Lag-1 Sparing (Measured as T2|T1-Lag 1 Minus Minimum of T2|T1-Lag 3 and Lag 5)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>N</th>
<th>Male</th>
<th>Female</th>
<th>Age</th>
<th>IQ</th>
<th>Max. AB Size</th>
<th>Lag-1 Sparing</th>
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<tr>
<td>DBH-G444A</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>A/A</td>
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<td>16</td>
<td>22.3</td>
<td>121.2</td>
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<tr>
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<td>0.18</td>
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<tr>
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<td>18</td>
<td>22.3</td>
<td>121.7</td>
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<td>0.18</td>
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<tr>
<td>ins/ins</td>
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<td>23</td>
<td>18</td>
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<tr>
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<td>0.19</td>
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<tr>
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<tr>
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<tr>
<td>C/C</td>
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<td>17</td>
<td>19</td>
<td>22.7</td>
<td>121.1</td>
<td>0.18*</td>
<td>0.23</td>
</tr>
<tr>
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<td>40</td>
<td>21.7</td>
<td>121.4</td>
<td>0.13*</td>
<td>0.18</td>
</tr>
<tr>
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<td>20</td>
<td>22.6</td>
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<tr>
<td>ALL</td>
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<td>75</td>
<td>82</td>
<td>22.2</td>
<td>121.5</td>
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</table>

*p < .0083 (significant group difference).
RESULTS

Participants
Sample information and genotype-specific demographics are shown in Table 1. All resulting genotype frequencies from our cohort of participants did not deviate from Hardy–Weinberg equilibrium (all p values > .10). No significant differences were found among genotype frequencies with respect to age, sex, or estimated IQ.

RSVP Task
T1 accuracy is shown in Figure 2. The ANOVA with lag as within-participant factor showed a significant lag effect, $F(3, 468) = 86.14, p < .0001, \eta^2_p = .36$. As Figure 2 shows, this effect was because of a dip in performance at Lag 1, that is, when T2 immediately followed T1. This pattern is often observed if T1 and T2 belong to the same category (e.g., digits) and satisfy the same selection criteria and when the presentation rate is fast. These conditions are thought to increase the competition between T1 and T2 representations if they occur close in time, with T2 outperforming T1 more often than at longer lags (Colzato et al., 2007; Hommel & Akyürek, 2005; Potter, Staub, & O’Connor, 2002).

The ANOVA of conditional T2 accuracy (T2|T1) revealed a significant lag effect, $F(3, 468) = 114.94, p < .0001, \eta^2_p = .42$, indicating a marked AB with good performance at Lag 1 (Lag 1 sparing; Visser et al., 1999), a considerable dip at Lags 3 and 5, and recovered performance at Lag 8 (see Figure 2).

Genetic Effects
T1 accuracy did not yield any significant effect for any of the genotypes involved: C957T polymorphism at DRD2, DARPP32 polymorphism, DBH444 g/a polymorphism, NET T-182C polymorphism, Val158Met COMT polymorphism, and DBH5-ins/del polymorphism, $Fs < 1$.

As predicted, C957T polymorphism at DRD2 affected the magnitude of the AB, as indicated by a two-way interaction between group and lag, $F(6, 447) = 2.92, p < .0083, \eta^2_p = .04$. Post hoc multiple comparison tests revealed that C/C homozygotes showed a greater AB magnitude than T/T homozygotes ($p = .03$), whereas no difference in AB size was observed between C/T carriers and T/T homozygotes ($p = .27$) and between C/C homozygotes and C/T carriers ($p = .16$; see Figure 3). At Lag 3, this effect was particularly evident in a gene–dose analysis, in which increasing numbers of T alleles (0, 1, or 2) were associated with increasing magnitudes of the AB, $r(152) = 0.23, p = .004$.

The effect of DARPP32 polymorphism, DBH444 g/a polymorphism, NET T-182C polymorphism, Val158Met COMT polymorphism, $Fs < 1$, and DBH5-ins/del polymorphism, $Fs < 1$ failed to reach significance. No significant interactions (between genotypes) were found between C957T polymorphism at DRD2, DARPP32 polymorphism, NET T-182C polymorphism, Val158Met COMT polymorphism, DBH444 g/a polymorphism, and DBH5-ins/del polymorphism. ($ps > .10$).

Lag 1 sparing did not yield any significant effect for all the genotypes involved: C957T polymorphism at DRD2, $F(2, 149) = 2.63, p = .075, \eta^2_p = .03$, DARPP32 polymorphism, $F(2, 151) = 0.67, p = .51, \eta^2_p = .009$, DBH444 g/a polymorphism, $F(2, 149) = 0.21, p = .81, \eta^2_p = .003$, NET T-182C polymorphism, $F(2, 148) = 0.65, p = .52, \eta^2_p = .009$, Val158Met COMT polymorphism, $F(2, 149) = 0.23, p = .63, \eta^2_p = .002$, and DBH5-ins/del polymorphism, $F(2, 150) = 2.23, p = .111, \eta^2_p = .03$.

Regression
The linear regression analysis with individual AB magnitude as the dependent variable and genotypes as predictor
showed that only the C957T polymorphism at DRD2 allowed for a reliable prediction of AB magnitude, $\beta = -0.22, t = -2.78, p = .006$, whereas the other genotypes did not: DARPP32 polymorphism, $\beta = -0.09, t = -1.09, p = .28$, NET T-182C polymorphism, $\beta = 0.02, t = 0.29, p = .77$, Val158Met COMT polymorphism, $\beta = 0.01, t = 0.13, p = .89$, DBH444 g/a polymorphism, $\beta = 0.07, t = 0.82, p = .41$, and DBH5-ins/del polymorphism, $\beta = 0.12, t = 1.42, p = .16$. These observations reinforce the assumption that the AB deficit is modulated by striatal DA/D2 but not by striatal DA/D1, cortical DA, or NE activity.

Conclusions

Our findings show that the C957T polymorphism at DRD2, a gene related to striatal DA/D2, reliably predicts the individual size of the AB, indicating a modulatory role for striatal DA/D2 in the AB. DRD2 C957T T/T homozygotes (associated with lower levels of striatal DA/D2) showed a significantly smaller AB than C/T heterozygotes and C/C homozygotes. Polymorphisms related to noradrenergic activity did not affect AB magnitude, which does not support the theory that NE is the principle neuromodulator involved in the AB phenomenon (Nieuwenhuis et al., 2005). Future studies should replicate our findings and examine the relationship between other polymorphisms associated with NE function and other neurotransmitters (e.g., serotonin) to further determine the specificity of striatal DA function in AB task performance.

Given that no significant differences were found among genotype frequencies by age, sex, or IQ, we can rule out an account of our results in these terms. Moreover, as participants were screened for several psychiatric disorders in the current study, we can also rule out an account in terms of preexisting psychiatric disorders (such as schizophrenia, ADHD, and obsessive compulsive disorder) that have been associated with dopaminergic abnormalities (Tripp & Wickens, 2008; Pooley, Fineberg, & Harrison, 2007; Davis, Kahn, Ko, & Davidson, 1991).

Our results are consistent with the pattern of results from previous behavioral studies. First, Olivers and Nieuwenhuis (2006) found a reduced AB when participants viewed pictures of positive affective content, which are thought to stimulate the dopaminergic system (Ashby, Valentin, & Turken, 2002; Ashby, Isen, & Turken, 1999). Second, Colzato, Slagter et al. (2008) found that spontaneous eyeblink rate, a functional marker of dopaminergic function (Karson, 1983), reliably predicts the size of AB. Third, we reported that people high in WM operation span, which is associated with striatal dopaminergic activity (Cools et al., 2008), showed a smaller AB (Colzato et al., 2007). Finally, DRD2 C957T T/T homozygotes showed better performance in WM control (Jacobsen et al., 2006) than individuals with other genetic predispositions.

Previous studies have shown also that DRD2 C957T T/T homozygotes are better at learning from negative than from positive reward prediction errors (Frank & Hutchinson, 2009; Frank et al., 2007), the latter of which would be associated with phasic DA peaks. Moreover, a recent PET study indicates that C957T genotype-dependent changes in DRD2 availability are driven by alterations in receptor affinity and, if anything, lower tonic DA levels (Hirvonen et al., 2009). An explanation of our findings, in line with these observations, is that DRD2 C957T T/T homozygotes may be more efficient in suppressing irrelevant information, such as the non-targets in an AB task. In comparison with T/T homozygotes, C/C homozygotes would be less efficient and have a less reliable temporal dynamics of distractor inhibition. The resulting delays in suppressing post-T1 distractors may lead to stronger competition between distractor(s) and T2 and/or, somewhat paradoxically, be responsible for the suppression of T2 if it appears soon after T1 (i.e., at shorter lags).

As pointed out already, D2 receptors are abundant in the nigrostriatal pathway, which is supposed to prevent gating of frontal representations (including motor actions and

![Figure 3. T1 (unconditional) performance (left) and T2 performance given T1 correct (T2|T1; right), shown separately for each lag and for T2|T1 as a function of C957T polymorphism at DRD2 gene (C/C homozygotes vs. C/T carriers vs. T/T homozygotes).](image-url)
WM) when they are irrelevant for the task at hand. Consistent with this idea, recent studies have shown that the DA/D2-dominated nigrostriatal pathway has been implicated in executive control WM operations (Cools et al., 2008; Moustafa et al., 2008), in learning to suppress negative actions (Frank & Hutchinson, 2009; Frank et al., 2007), and actions that are no longer appropriate (Colzato, van den Wildenberg, et al., 2010). In particular, the nigrostriatal pathway plays a central role in preventing the updating of WM in the face of distractors, a function that is disrupted by the administration of l-DOPA in Parkinson’s patients and of D2-receptor agonists in healthy participants (for a review, see Cools, 2006). Preventing the update of WM in the presence of distracting stimuli is crucial in the AB task, where the representations of the targets need to be prevented from being overwritten by distractors. It seems plausible to assume that T/T homozygotes would be more efficient at suppressing (ignoring) the distractors that follow T1, preventing them from interfering with T1 memory consolidation and subsequent T2 processing. That is, in T/T homozygotes the distractors would be fast in triggering the nigrostriatal pathway to suppress their own gating. In contrast, in C/C homozygotes, the triggering and/or the emission of the update-suppressing signal would be more sluggish, which opens the possibility that in some cases the signal would come too late to exclude the triggering distractor. As a consequence, the distractor would compete with T2, the more the sooner T2 appears, and the delayed inhibition might even hit T2 directly and effectively exclude it from entering WM. Obviously, both possibilities would be particularly prevalent with short rather than longer lags, that is, the closer in time the uninhibited distractor and T2 are presented and/or T1 and T2 appear. This scenario seems consistent with our pattern of results in that, first, the Lag 1 sparing effect was not affected by DRD2 polymorphism, suggesting that gating in T1 was unimpaired. Second, the C957T polymorphism at DRD2 impacted the AB at Lag 3 only—the only lag in which our participants would have recently engaged the nigrostriatal pathway to prevent distractors from interfering with T1 consolidation.

What do our findings imply for existing models of the AB? For one, they support the general claim of Nieuwenhuis et al. (2005) that neurotransmitter dynamics are crucial for the AB, although our data suggest that DA, rather than NE, is the major player. Moreover, the scenario we suggest (that the sluggishness of the distractor–inhibition mechanism leads to the failure to effectively inhibit post-T1 distractors and/or the suppression of T2) is consistent with models attributing the AB to either distractor-T2 competition (Shapiro, Raymond, & Arnell, 1994) or accidental T2 suppression (Olivers & Meeter, 2008). However, we do not consider this scenario inconsistent with models that attribute the AB to the shielding of T1 processing either. For instance, it is possible that post-T1 distractor inhibition serves to guarantee the undisturbed consolidation of T1, as assumed by various models (e.g., Taatgen et al., 2009; Bowman & Wyble, 2007; Hommel et al., 2006; Jolicoeur & Dell’Acqua, 1998; Raymond et al., 1992). The failure to inhibit interfering distractors would then prolong T1 consolidation, which again might interfere with T2 processing and, thus, increase the size of the AB.

Taken together, given the known modulatory role of striatal dopaminergic activity, in particular DA/D2, in executive control processes of WM (Cools et al., 2008; Moustafa et al., 2008), the here observed relationship between AB size and C957T polymorphism at DRD2 supports the idea that the AB phenomenon is related to activity of the striatal dopaminergic system, particularly that of the DA/D2 subsystem. Genetic variability that affects this subsystem seems to modulate the efficiency of inhibiting distractor information and, thus, the degree to which this information competes and interferes with relevant information.

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Reprint requests should be sent to Lorenza S. Colzato, Cognitive Psychology Unit, Department of Psychology, Leiden University, Postbus 9555, 2300 RB Leiden, the Netherlands, or via e-mail: colzato@fsw.leidenuniv.nl.

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