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The genetic impact (C957T-DRD2) on inhibitory control is magnified by aging

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ABSTRACT

Healthy aging beyond the age of 65 is characterized by a general decrease in cognitive control over actions: old adults have more difficulty than young adults in stopping overt responses. Responsible for this cognitive decrement is the continuous decline of striatal and extrastriatal dopamine (DA). The resource-modulation hypothesis assumes that genetic variability is more likely to result in performance differences when brain resources move away from close-to-optimal levels, as in aging. To test this hypothesis we investigated, first, whether individual differences in the C957T polymorphism at DRD2 gene (rs6277) contribute to individual differences in the proficiency to inhibit behavioral responses in a stop-signal task. Second, we assessed whether this genetic effect is magnified in older adults, due to the considerable decline in dopamine function. Our findings show that individuals carrying genotype associated with higher density of extrastriatal D2 receptors (C957T CC) were more efficient in inhibiting unwanted action tendencies, but not in term of response execution. This effect was stronger in older than in younger adults. Our findings support the idea that aging-related decline in dopamine availability alters the balance between genotypes and cognitive functions.

1. Introduction

Healthy aging beyond the age of 65 is characterized by a general decrease in cognitive control: older adults find it increasingly difficult to apply new or coordinate multiple rules, and to discriminate relevant from irrelevant information. Working memory, reasoning (Ball, Vance, Edwards, & Wadley, 2004 (chap. 36); Brehmer, Li, Müller, von Oertzen, & Lindenberger, 2007; Li, Schmiedek, Huxhold, Röcke, Smith, & Lindenberger, 2008; Shing, Werkle-Bergner, Brehmer, Muller, Li, & Lindenberger, 2010), attention abilities and speed of processing (Faust & Balota, 1997; Ball, Beard, Roenker, Miller, & Griggs, 1998; Colzato, van Muijden, Band, & Hommel, 2011) show large decrements with increasing age. Cognitive inhibition also declines throughout the life span (Williams, Ponesse, Schachar, Logan, & Tannock, 1999): old adults have more difficulty than young adults in stopping an overt response and changing to new rules in a categorization task (Kramer, Humphrey, Larish, Logan, & Strayer, 1994). Responsible for this cognitive decline is the general loss of neurochemicals, such as the continuous decline of striatal and extrastriatal dopamine (DA) systems from early to late adulthood and old age (Bäckman et al., 2000; Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006; Erixon-Lindroth et al., 2005; Volkow et al., 1998).

Interestingly, individual differences in cognitive performance increase from early to late adulthood reflecting genetic differences (Li et al., 2004; Li et al., 2010; Störmer, Passow, Biesenack, & Li, 2012). The resource-modulation hypothesis (Lindenberger et al., 2008) assumes that aging-related losses in neurochemical and structural brain resources modulate the extent to which common genetic variations affect cognitive functioning. In particular, the function relating brain resources to cognitive performance is assumed to be nonlinear, so that genetic variability is more likely to result in performance differences when resources move away from close-to-optimal levels, as in aging. In other words, the genetic setup of an individual matters more the older he or she gets.

The resource-modulation hypothesis has been supported by a number of studies. First, spatial working memory and executive functions in elderly were associated with individual differences in genetic predispositions of the gene that codes for the catechol-O-methyltransferase (COMT), an enzyme that degrades DA in prefrontal cortex, while no such relation was observed in younger adults (Nagel et al., 2008; Störmer et al., 2012). Second, a similar age magnification effect was observed between brain-derived

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neurotropic factor (BDNF) genotype and episodic memory performance under high associative demands (Li et al., 2010). The third evidence comes from the genetic modulation of training and transfer in older adults. Colzato, Slagter, de Rover, and Hommel (2011) trained participants genotyped for the brain-derived-neurotrophic factor (BDNF) Val^{66}Met polymorphism on cognitive tasks developed to improve dynamic attention. Pre-training (baseline) and post-training measures of attentional processes (divided and selective attention) were acquired. As expected, Val/Val homozygous individuals, associated with increased activity-dependent secretion of BDNF (Egan et al., 2003), showed larger beneficial transfer effects than Met/−carriers.

The current study focused, for the first time, on the inhibition of behavioral responses—another key cognitive control function (Logan & Cowan, 1984; Logan, 1994) that is known to decrease with old age (Kramer et al., 1994, Williams et al., 1999). Recently, Colzato, Waszak, Nieuwenhuis, Posthuma, and Hommel (2010) reported response inhibition (assessed in by means of a stop-signal task) to be predicted by the C957T polymorphism at the DRD2 gene, but not by COMT Val^{158}Met (a polymorphism related to frontal DA). Healthy young adults pressed a left or right button as soon as a green left- or right-pointing arrow appeared (go trials). However, if the color of the arrow suddenly changed to red, the participants were supposed to refrain from responding (stop trials). This stop-signal task measures both the efficiency of response execution (by means of reaction times to go-signals) and the efficiency in inhibitory control (by means of the stop-signal reaction time or SSRT, where longer SSRT reflect general slowing of inhibitory processes and indicate a lower level of inhibitory efficiency). C/C homozygotes, associated with increased extra-striatal D2 receptor availability (Hirvonen et al., 2009a) and higher striatal DA levels (Hirvonen et al., 2009b), stopped faster on stop trials than T/−carriers. No association between COMT Val^{158}Met polymorphism and stopping latency was found. This pattern of results was in line with a previous study by Forbes, Brown, Kimak, Ferrell, Manuck, and Hariri (2007), who reported no association between self-reported impulsivity scores (index highly correlated with the inhibitory control) with the COMT gene (Val^{158}Met polymorphism).

A number of patient studies have provided converging evidence for the involvement of striatal DA in response inhibition. Parkinson's patients, who suffer from loss of dopaminergic neurons in the basal ganglia, showed difficulties in stopping (Gauggel, Rieger, & Feghoff, 2004) and impaired suppression of conflicting responses (Wylie et al., 2009) compared to matched healthy controls. Consistent with this picture, ADHD patients (see, Alderson, Rapport, & Kofler, 2007, for a recent review) and recreational users of cocaine (Colzato, van den Wildenberg, & Hommel, 2007), who are likely to suffer from reduced dopamine D2 receptors in the striatum (Volkow, Fowler, & Wang, 1999), need significantly more time to inhibit responses to stop-signals than non-users. Moreover, spontaneous eyeblink rate, a marker of striatal dopaminergic functioning, reliably predicts the efficiency in inhibiting unwanted action tendencies in a stop-signal task (Colzato, van den Wildenberg, van Wouwe, Pannebakker, & Hommel, 2009).

Given the role of striatal DA in modulating response inhibition, we expected DRD2 C957T C/C homozygotes to be better than T/−carriers in stopping control, replicating Colzato, Waszak, et al. (2010). Moreover, based on the resource-modulation hypothesis (Lindenberger et al., 2008), we expected this effect to be magnified in old age.

2. Experimental procedures

2.1. Participants

170 healthy Caucasian adults from two age groups (younger [mean age of 21.5 years] and older adults [mean age of 69.15 years]) served as participants, 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. The advertisement was posted on the internet. To take part in the study, potential participants had to subscribe per e-mail. Given that this subscription criterion required a solid electronic knowledge, we were confident that our older participants were experienced with computers. Exclusion criteria were any major medical illness that could affect brain function, current medications and substance abuse, neurological conditions, history of head injury, personal history of psychiatric medical treatment, and a score below 28 in the mini mental state examination (MMSE; Folstein, Folstein, & McHugh, 1975) for the older adults.

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.

Table 1
Sample and genotype-specific demographics for age group (younger adults vs. older adults) and mean SSRT (stopping latency) and mean RT to go-signals (GO RT) [efficiency of response execution].

Group		N	Sex		Age	IQ	SSRT	GO RT
			Male	Female				
Younger adults	Total	118						
	C/C homozygotes	31	10	21	21.3	114.8	210*	387
	T/−carriers	87	27	60	21.7	114.2	223*	386
Older adults	Total	52						
	C/C homozygotes	32	18	14	69.1	113.9	244**	595
	T/−carriers	20	7	13	69.2	113.5	286**	627
ALL	–	170	62	108	45.3	114.1	241	499

Significant group difference.
* $p < 0.05$.
** $p < 0.01$.

2.2. Apparatus and stimuli

The experiment was controlled by a ACPI uniprocessor PC running on an Intel Celeron 2.8 gHz processor, attached to a Philips 109B6 17 in. 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 cm with the corresponding index finger.

2.3. 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 pseudo-randomly 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 yields accurate estimates of SSRT and compensates for differences in choice RT between participants (Band, van der Molen, & Logan, 2003) Individual SSRTs were calculated according to the *integration method* (see Logan & Cowan (1984), 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.

2.4. 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 Spearman's g factor as well as fluid intelligence (Raven, Court, & Raven,

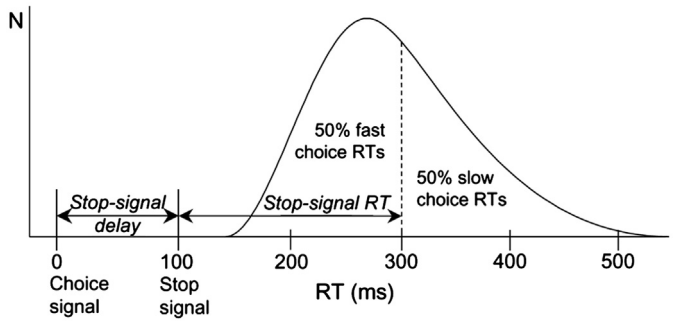

Fig. 1. Calculation of stop-signal RT (SSRT) according to a race model. Following the race model assumption of independence (Logan & Cowan, 1984), the RT distribution of the go process is the same whether or not a stop-signal is presented. The left side of the go RT distribution represents fast responses that escape inhibition. The right side represents slow responses that will be inhibited. If participants failed to stop on *n*% of the stop trials (here 50%), the finishing time of the stop process was on average equal to the *n*th percentile of the go RT distribution (here 300 ms). The mean stop-signal delay (SSD, 100 ms) was then subtracted from the *n*th percentile of the go RT distribution, resulting in the estimate of the mean SSRT (200 ms).

1988). Participants completed the SPM and subsequently performed on the behavioral task measuring inhibitory control.

2.5. 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). C957T polymorphism at DRD2 gene [rs6277] (Frank, Moustafa, Haughey, Curran, & Hutchison, 2007) was genotyped using Applied Biosystems (AB) TaqMan technology. The sequence-specific primers for the Taqman assays (5′-CTGTCGGGAGTGCTG-3′ and 5′-CTGTCAGGAGTGCTG-3′) were used for the C and T alleles, respectively, as was the common reverse primer 5′-GCCCATT-CTTCTCTGGTTTGG-3′. Following Colzato, van Muijden, et al. (2011), the genotype was scored by two independent readers by comparison to sequence-verified standards. In order to obtain two equally sized subsamples to investigate the effect of C957T polymorphism at DRD2 gene on response inhibition we collapsed C/T heterozygotes and T/T homozygotes in the subsample T/−carriers, see Table 1.

2.6. Procedure and design

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

2.7. Statistical analysis

First, repeated-measures ANOVAs were performed for analyses of age, IQ and sex differences between genotype groups. Second, in order to test whether age magnifies the genetic effect, individual SSRTs for stop-signal trials and mean RT to go-signals were calculated to index response inhibition for all participants. SSRTs and mean RT to go-signals were analyzed separately by means of univariate ANOVAs with C957T polymorphism at DRD2 (C/C homopzygotes vs. T/−carriers) and age (younger vs. older) as between-subjects factor. A significance level of $p < 0.05$ was adopted for all statistical tests.

3. Results

3.1. 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 ($p > 0.1$). No significant differences were found among genotype frequencies with respect to age, IQ or sex.

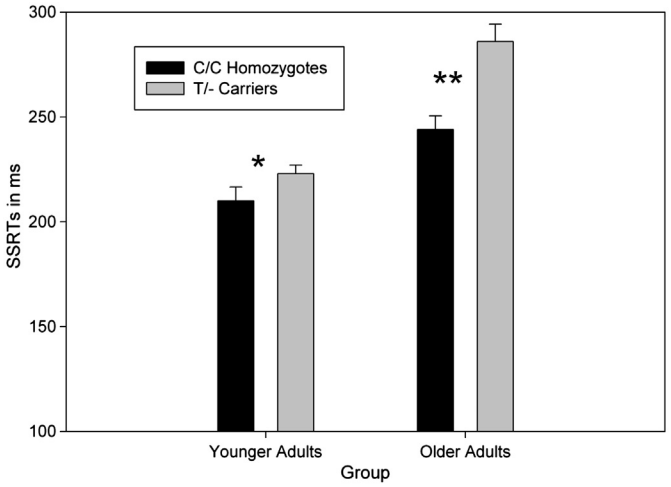

Fig. 2. Mean SSRT (stopping latency) as a function of C957T polymorphism at DRD2 gene (C/C homozygotes vs. T/−carriers) and age group (younger adults [mean age of 21.5 years] vs. older adults [mean age of 69.15 years]). Asterisks indicate significant ($^{*}p < 0.05$; $^{**}p < 0.01$) effects of the gene on mean SSRT. Vertical capped lines atop bars indicate standard error of the mean.

3.2. SSRTs for stop-signal trials

First, replicating previous work (Colzato, van den Wildenberg, van der Does, & Hommel, 2010), SSRTs yielded a significant effect of genotype for C957T polymorphism at DRD2, $F(3,166) = 17.08$, $p < 0.0001$, MSE = 1372.31, $\eta^2p = 0.093$, indicating that T/−carriers (254 ms) had significantly longer SSRTs than C/C homozygotes (227 ms). Second, we found the expected main effect of age (Kramer et al., 1994; Williams et al., 1999), $F(3,166) = 55.19$, $p < 0.0001$, MSE = 1372.31, $\eta^2p = 0.250$, showing increased SSRTs in the older (265 ms) compared to the younger group (216 ms).

Third, and most importantly, age interacted significantly with the C957T polymorphism at DRD2, $F(3,166) = 4.67$, $p < 0.05$, MSE = 1372.31, $\eta^2p = 0.027$. As suggested by Fig. 2, the genotype difference in SSRTs was reliable for both younger and older adults, $F(1,116) = 4.25$, $p < 0.05$, MSE = 896.95, $\eta^2p = 0.035$ and $F(1,50) = 8.45$, $p < 0.01$, MSE = 2475.15, $\eta^2p = 0.14$, respectively (see Table 1). However, as predicted by the resource-modulation hypothesis, the difference in SSRTs between C/C homozygotes and T/−carriers was larger in the older group than the younger group, suggesting that age magnifies the genetic effect on SSRTs.

3.3. Mean RT to go-signals

First, analyses of mean RT to go-signals did not yield a significant effect of genotype for C957T polymorphism at DRD2, $F(3,166) = 1.53$, $p = 0.218$, MSE = 5289.94, $\eta^2p = 0.009$, indicating that T/−carriers (507 ms) did not show significantly longer mean RT to go-signals than C/C homozygotes (491 ms). Second, just as in the case of SSRTs, we found an expected main effect of age (Kramer et al., 1994; Williams et al., 1999), $F(3,166) = 303.35$, $p < 0.0001$, MSE = 5289.94, $\eta^2p = 0.646$, showing increased RT to go-signals in the older (611 ms) compared to the younger group (387 ms). Last, age did not interact with the C957T polymorphism at DRD2, $F(3,166) = 1.69$, $p = 0.19$, MSE = 5289.94, $\eta^2p = 0.010$; as indication that, in contrast to SSRTs, the difference in mean RT to go-signals between C/C homozygotes and T/−carriers was not significantly larger in the older group than the younger group, see Table 1.

This suggests that age magnifies the genetic effect of C957T polymorphism at DRD2 selectively in SSRTs, but not in RT to go-signals.

4. Conclusions

We investigated the relationship between DRD2 genetic variability and response inhibition. Replicating an earlier study (Colzato, van den Widenberg, et al., 2010), DRD2 C957T C/C homozygotes, associated with higher density of extrastriatal D2 receptors, were more efficient in inhibiting unwanted action tendencies than T/−carriers were. In line with the resource-modulation hypothesis (Lindenberger et al., 2008), the observed genetic effect was larger in older adults, who are likely to suffer from compromised pre- and post-synaptic DA functions. Interestingly, this genetic effect was selective for SSRTs (an index of response inhibition) but not for RTs to go-signals (an index of response execution speed).

As suggested by Li, Papenberg, Nagel, Preuschhof, Biesenack, and Bertram (2013), given that cognitive processes, such as response inhibition, underlie various neurobiological substrates and, hence, are affected by multiple genes, it is essential for future research to further investigate the resource-modulation hypothesis in relation to gene–gene interactions. Indeed, keeping in mind that the relation between DA signaling and cognitive performance follows an inverted-U function (see Cools and D'Esposito (2011), for a review), Li speculated that such a function may account for the effects of multiple genes. The effect of single genes on cognition are expected to be larger when DA function abates from the apex of the curve, so that the additive effects of these genes should also be magnified in parts of the function that lessens from the apex.

Moreover, it should be noted that our results are in line also with recent studies showing that not only the effects of a genotype may change with increasing age, but also that the direction of genotype effects is modulated by age. First, Gajewski, Hengstler, Golka, Falkenstein, and Beste (2011) found that, mimicking findings in young subjects, Met-allele carriers of the BDNF Val^{66}Met polymorphism showed superior memory-based, but not cue-based, task switching performance in elderly because of a more efficient response selection processes. Second, the same research group observed that BDNF Met-allele carriers showed better performance in interference trials when participants had to indicate the name or the color of color-words while color was either compatible or incompatible with the name (Gajewski, Hengstler, Golka, Falkenstein, & Beste, 2012). Third, Getzmann, Gajewski, Hengstler, Falkenstein, and Beste (2013) noticed that, in an auditory distraction paradigm, BDNF Val/Val allele carriers showed evidence of less efficient response selection processes (greater susceptibility against interference from distractors) than Met-allele carriers.

Future research, with a greater sample size, is needed also to extend these preliminary findings to another major control function: the "shifting" between tasks and mental sets (also called "flexibility") (Miyake et al., 2000). Recently, genetic variability related to the COMT gene (Val^{158}Met polymorphism) has received increasing attention as a possible modulator of cognitive flexibility, but not of interference control, indexed by a task switching paradigm (Colzato, van den Wildenberg, et al., 2010). Evidence suggests that the Val^{158}Met genotype may differentially affect cognitive stability and flexibility, in such a way that Val/Val homozygous individuals (who possess low prefrontal dopamine levels) may show more pronounced cognitive flexibility than Met/−carriers (who possess high prefrontal dopamine levels) (see Cools (2006), for a review). Indeed, Met/−carriers showed larger switching costs (i.e., less cognitive flexibility) than Val/Val homozygous individuals. If the resource-modulation hypothesis (Lindenberger et al., 2008) applies also in this case, we would expect this genetic effect to be magnified in old age because of the continuous decline of DA functions from early to late adulthood and old age (Bäckman et al., 2000, 2006; Erixon-Lindroth et al., 2005; Volkow et al., 1998).

In sum, individual differences in genes that regulate the availability of D2 receptors contribute to variations in efficiency in inhibiting unwanted action tendencies in a stop-signal task, an index of inhibitory control. In accordance with the resource-modulation hypothesis (Lindenberger et al., 2008), this genetic effect was magnified in aging, which suggests that aging-related decline in dopamine availability alters the balance between genotypes and cognitive functions.

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