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Genetic factors of reaction time performance: DRD4 7-repeat allele associated with slower responses

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Twin studies indicate substantial inherited components in cognitive abilities. One of the most extensively studied candidate genes of cognitive functioning is the dopamine D4 receptor gene (*DRD4*), which has been suggested to be related to attentional disorders. Based on reaction time data of 245 Caucasians participating in different cognitive tasks, slower responses characterized the group with the 7-repeat allele. This effect was present in both sexes and was not because of fatigue. To our knowledge, this is the first report on significant association ($P = 0.0001$) between the DRD4 variable number of tandem repeat (VNTR) polymorphism and response latencies in a non-clinical adult sample. Other studied dopaminergic polymorphisms did not show an association with reaction time. These results illustrate that speed-of-performance measures derived from multiple reaction time tasks using standardization procedures could be promising tools to detect unique genetic effects in the background of cognitive abilities.

Keywords: Attention, behavior genetics, cognitive ability, individual differences, reaction time

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Burgeoning results from twin studies and modern genome-wide association studies indicate that inherited factors have a considerable impact on cognitive performance (Butcher *et al*. 2008; Plomin 2001). Candidate gene studies to date investigated specific cognitive processes or impairments of these processes, especially with relation to attention. Among different inherited components of neurotransmission, genes of the *dopaminergic system* are well-justified candidates influencing individual variation in attentional functioning.

The 7-repeat allele of the variable number of tandem repeat polymorphism in the dopamine receptor 4 gene (*DRD4 VNTR*) was first associated to novelty seeking (Ebstein *et al*. 1996). The *DRD4* gene variants are closely related to attention problems, the 7-repeat allele is the most replicated genetic risk factor for attention deficit hyperactivity disorder (ADHD) (Li *et al*. 2006). The *DRD4 -521 CT*, a single nucleotide polymorphism (SNP) in the promoter region of the DRD4 has also been related to novelty seeking in both Japanese (Okuyama *et al*. 2000) and Caucasian (Ronai *et al*. 2001) samples, confirmed by meta-analysis (Munafo *et al*. 2008). Bellgrove *et al*. (2005) showed an association between the -521 CT SNP and reaction time variability among ADHD children. A tandem duplication of 120 base pairs (*DRD4 120 bp dup*) of the *DRD4* gene was also associated to ADHD (McCracken *et al*. 2000).

Polymorphisms of the D2 dopamine receptor (*DRD2*) gene have received broad attention in relation to alcoholism (Le Foll *et al*. 2009), as well as sustained attention and inhibitory control among alcoholics (Rodriguez-Jimenez *et al*. 2006). A recent functional magnetic resonance imaging (fMRI) study showed association with the *DRD2/ANKK1 TaqIA* polymorphism: A1 allele carriers showed different functional activation of the anterior cingulate gyrus while performing the attention network test (Fossella *et al*. 2006).

Another important factor in dopamine neurotransmission is the catabolizing enzyme catecol-*O*-methyltransferase (COMT). The *COMT Val158Met* polymorphism coding a high activity (Val) or a low activity (Met) variant (Mannisto & Kaakkola 1999) has been related to attentional control (Blasi *et al*. 2005), schizophrenia, executive functions, working memory (Tunbridge *et al*. 2006) and hypnotizability (Lichtenberg *et al*. 2000; Szekely *et al*. 2010).

The dopamine transporter is also essential in dopamine neurotransmission, as it is the primary target of methylphenidate, the most widely used drug in ADHD treatment. A 40-bp VNTR in the dopamine transporter gene (*DAT1/SLC6A3 VNTR*) has been shown to associate with ADHD (Faraone & Khan 2006). The 10/10 genotype was also associated to reaction time variability among ADHD children (Bellgrove *et al*. 2005).

Information processing, a vital component of cognitive abilities, is often quantified by reaction time measures (Salthouse 2000). To date, only a few studies explored the genetic components of non-clinical adult reaction time performance, using data typically from a single task grasping a particular cognitive process (Fossella *et al*. 2002). The aim of the present study was to search for possible information processing endophenotypes detectible in various cognitive tasks. We explored the association of the above dopaminergic polymorphisms with an overall standardized response

latency measure derived from reaction time performance of Caucasian adults participating in one of six different tasks.

Subjects and methods

Participants of the study were adult volunteers of Caucasian (Hungarian) origin without past or present psychiatric history (based on self-report), recruited at the Institute of Psychology, Eötvös Loránd University. All participants provided written informed consent, the study was carried out with respect to guidelines of the Declaration of Helsinki and the study protocol was approved by the Local Ethical Committee (TUKEB). Subjects were asked to provide buccal samples and participate in a reaction time task. Two hundred and forty-five participants with valid DNA and reaction time data included 26% males and 74% females, age ranging from 18 to 33, with a mean of 22.9 (±4.1).

Genotyping

Genotyping was made with standard protocols described earlier (Grandy *et al*. 1993; Ronai *et al*. 2000; Tarnok *et al*. 2007; Vandenbergh *et al*. 1992) Two independent DNA samples per person were genotyped in separate genotyping assays. The measured genotype frequencies corresponded to the Hardy–Weinberg equilibrium (Hardy 1908). [Distribution of observed genotype frequencies and statistical values: DRD4-VNTR based on the most frequent three alleles (4/4 = 114, 4/7 = 63, 7/7 = 5, $\chi^2 = 1.150$, $df = 2$, $P = 0.563$), based on genotypes with frequencies above 1% (2/4 = 31, 2/7 = 7, 3/4 = 7, 3/7 = 8, 4/4 = 114, 4/7 = 63, 7/7 = 5, $\chi^2 = 12.598$, $df = 6$, $P = 0.050$); DRD4 120-bp DUP (1/1 = 3, 1/2 = 60, 2/2 = 171, $\chi^2 = 0.794$, $df = 2$, $P = 0.672$). For the following genotypes, see frequency values in Table 1: DRD4 -521CT SNP ($\chi^2 = 0.537$, $df = 2$, $P = 0.765$); DRD2/ANKK1 TaqIA SNP ($\chi^2 = 5.831$, $df = 2$, $P = 0.054$); COMT Val158Met SNP ($\chi^2 = 0.143$, $df = 2$, $P = 0.931$) and DAT1 (SLC6A3) 40-bp VNTR ($\chi^2 = 0.608$, $df = 2$, $P = 0.738$).]

Phenotyping

Data from six reaction time (RT) tasks were assembled for purposes of this study; each subject participated in only one of the six experiments. A total of 123 subjects took part in the *attentional selection task* (*ATT*), a 15-minute choice reaction time task adapted to Hungarian language from a modified version of the Simon task (Castel *et al*. 2007). Participants were asked to press the left or right button corresponding to the direction of an arrow stimulus, regardless of its position. The task consisted of 120 congruent, incongruent and neutral stimuli.

A total of 122 subjects participated in different language production tasks requiring voice key responses, collected as part of an international study of language production (Bates *et al*. 2003; Szekely *et al*. 2005). Stimuli items were 275 black-and-white drawings of common transitive and intransitive actions and 520 common objects, or their dominant names written or pronounced in Hungarian. Participants were asked to respond as quickly as they could, and either read the words presented on the computer screen: *Word Reading task* for Actions (*WRA*) or for Objects (*WRO*); listen and repeat these names *Word Listening task* for Actions (*WLA*) or for Objects (*WLO*); or name action pictures that appear on the screen with a short and simple name *Picture Naming task* for Actions (*PNA*). The number of participants in each task were WRA: 15, WRO: 14, WLA: 30, WLO: 29, PNA: 34. The tasks lasted about 45 min on average with short rest periods after about 100 trials. The order of stimuli presentation was varied in all six tasks.

RT data reduction and standardization

Individual *performance speed* was calculated by averaging correct response latencies of the subject for the task he/she took part in (e.g. mean of the 120 button-press responses in the ATT task or mean of the 520 verbal responses in the WRO task). Standard deviation of reaction time was used to measure individual *performance variability*. These performance measures were standardized within each task in order to make individual performance comparable across the different tasks: *Z*-scores of mean RT values as task-independent performance speed and the coefficient of variation (SD divided by the mean performance), as task-independent performance variability.

Statistical analysis

Chi-square analysis was carried out for assessment of allele and genotype frequencies. Independent samples *t*-test was used to assess sex differences; relationship with age has been tested by Spearman correlation analysis. Association analyses were carried out by one- or two-way analyses of variance.

Results

Cognitive performance of participants in the present study was tested by one of six reaction time tasks. Stimulus items and responses varied across the tasks (arrows, words or pictures were used to elicit button press or verbal responses, see *Subjects and methods*). As the tasks were characteristically different in difficulty, mean RT of responses ranged from 501 to 1387 milliseconds (Fig. 1). However, all of these cognitive tasks required participants to sustain their attention and produce prompt and accurate responses on each trial. Individual differences in performance speed and variability were substantial. Our primary goal was to link these individual differences to candidate gene polymorphisms of the dopaminergic system.

Age and sex as possible confounds of performance

Performance speed or variability measures did not correlate with age in any of the tasks. This might be because of the

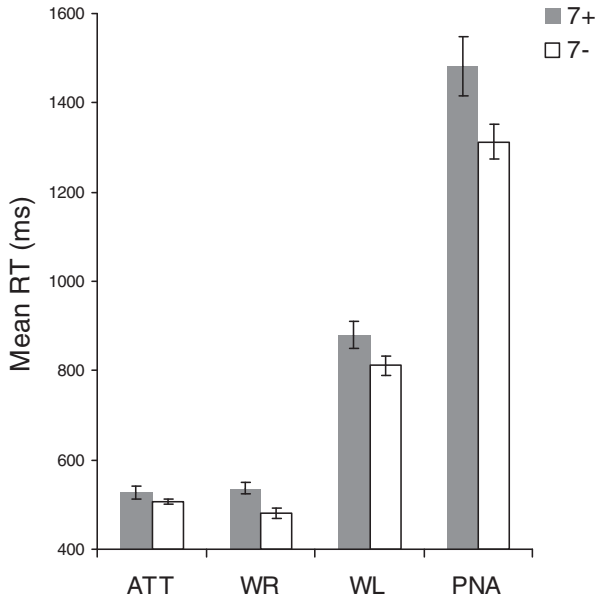

Figure 1: DRD4 effect on response latency. Mean reaction time performance in milliseconds for each task as a function of the presence (7+) or absence (7−) of the DRD4 7-repeat allele. Error bars represent standard errors of the mean.

relatively narrow age range in our sample, as 80% of participants were 18–25 years old. On the other hand, sex of participants influenced performance measures significantly in two of the six tasks: In the button-press focused attention task (ATT), male responses were significantly faster and less variable (mean difference in speed was −42 milliseconds, $t(122) = -2.966$, $P = 0.004$; mean difference in variability was −31 milliseconds, $t(122) = -3.423$, $P = 0.001$). In the word reading task (WRO), male responses were significantly slower and more variable (mean difference in speed was 84 milliseconds, $t(12) = 4.291$, $P = 0.001$; mean difference in variability was 31 milliseconds, $t(12) = 2.715$, $P = 0.02$). Owing to the observed differences, sex has been used as a covariate when testing genetic effects.

Association analysis between dopaminergic gene polymorphisms and RT performance

Slower RT performance in the presence of the 7-repeat allele in the verbal tasks

Our first question was whether the most extensively studied dopaminergic gene polymorphism, the DRD4 VNTR, would show association with RT performance in the different cognitive tasks. As this polymorphic region has many alleles, a widely used grouping principle was applied based on the presence (7+) or the absence (7−) of the 7-repeat allele (Ebstein *et al*. 1996).

Individual performance speed of the two DRD4 genotype groups was first compared by one-way analysis of covariance (ANCOVA) within each task type using raw RT mean values as the dependent variable, the genotypes as the grouping factor and sex as covariate (Fig. 1). Data from action and object word reading tasks were used as a single task type (WR), as raw RT mean of the two tasks did not differ significantly. Similarly, action and object word repetition tasks were merged into a single task type (WL).

In the presence of the 7-repeat allele (dark columns), responses were slower in all four task types compared to the raw RT means in the absence of this allele (open columns). However, the effect of the DRD4 7-repeat allele reached the level of significance only in the tasks which required verbal responses: WR ($F_{1,26} = 8.081$, $P = 0.009$, $\eta^2 = 0.237$, power = 0.781), WL ($F_{1,56} = 4.086$, $P = 0.048$, $\eta^2 = 0.068$, power = 0.511) and PNA ($F_{1,31} = 4.645$, $P = 0.039$, $\eta^2 = 0.130$, power = 0.551). [When performing multiple comparisons, the accepted level of significance should be more stringent to rule out false-positive results. In the present analyses, the corrected level of significance was $P < 0.0125$ based on the Bonferroni correction for multiple testing (the $P = 0.05$ value was divided by the number of analyses: four task types). After the stringent Bonferroni correction, main effect of the 7-repeat allele for speed of responses was significant in only one of the verbal tasks (WR).]

To explore the possible interaction effect of task type and the DRD4 7-repeat allele on reaction time performance, a two-way ANOCOVA was carried out using raw RT data from all tasks as the dependent variable, task type (1, 2, 3 or 4) and genotypes (0 or 1 based on the presence of the 7-repeat allele) as grouping factors and sex as covariate. The main effect of the DRD4 7-repeat allele was significant ($F_{1,236} = 18.945$, $P = 0.00002$, $\eta^2 = 0.074$, power = 0.991). Obviously, the main effect of task type on RT was also significant, as the tasks differed in their levels of difficulty ($F_{3,236} = 539$, $P < 0.00001$, $\eta^2 = 0.873$, power = 1.0). Moreover, a significant interaction between task type and alleles was also observed ($F_{3,236} = 3.539$, $P < 0.015$, $\eta^2 = 0.043$, power = 0.781), suggesting that task characteristics may influence the magnitude of the genetic effect. The sex covariate had no significant effect in any of the above analyses.

Testing effect of candidate polymorphisms on standardized RT measures from all tasks: a significant DRD4 effect

To assemble data from all of the subjects participating in various tasks, individual performance speed and variability measures were standardized, as described under *Subjects and methods*. As a result, genetic effects of various dopaminergic polymorphisms could be tested using performance records from 247 individuals.

Results presented in Table 1 show a significant main effect of the 7-repeat allele for speed of responses. Standardized RT performance of those carrying the 7-repeat allele was significantly slower as compared with the 7-repeat absent group ($F_{1,242} = 15.046$, $P = 0.0001$, $\eta^2 = 0.059$, power = 0.972). On the other hand, the coefficient of RT variation did not show a significant difference between the two genotype groups.

Observing a significant effect of the DRD4 VNTR on general performance measures suggested a question of considerable theoretical importance: Do other dopaminergic polymorphisms have an impact on RT performance as well, or this genetic effect is specifically that of the DRD4 7-repeat allele? Dopaminergic candidate genes investigated in the present study involve several polymorphisms in D2 and D4 receptors and two polymorphisms related to dopamine signal termination (see Table 1, the studied SNPs are also specified by their rs number). The TaqIA polymorphism is labeled as the DRD2/ANKK1 TaqIA, as this polymorphism is recently shown to be located not in the *DRD2* gene, but in a neighboring gene (ankyrin repeat and kinase domain containing 1, ANKK1), a protein involved in the signal transduction processes (Neville *et al*. 2004).

Association analyses between the standardized task-independent performance measures (standardized mean RT values and the coefficient of RT variation) and each of the six dopaminergic polymorphisms have been performed using one-way ANCOVAs with sex as covariate. No effect of the studied dopaminergic polymorphisms was observed, except the effect of the DRD4 VNTR on performance speed. The main effect of the 7-repeat allele for speed of responses in the combined data set with all tasks included was significant even after the stringent Bonferroni correction. [The corrected level of significance was $P < 0.004$ based on the Bonferroni correction for multiple testing (the $P = 0.05$ was divided by 12, the number of analyses performed: association of six polymorphisms with both performance speed and variability measures).]

Table 1: Effect of dopaminergic polymorphisms on task-independent performance measures

Candidate gene	Polymorphism		*N*	Performance speed	Significance	Performance variability	Significance
DRD4	**48-bp VNTR**	**7+**	84	**0.30 (±1.05)**	***P* = 0.0001**	0.22 (±0.09)	$P = 0.345$
		7−	161	**−0.19 (±0.87)**		0.21 (±0.08)	
	120-bp duplication	1+	63	−0.12 (±0.73)	$P = 0.307$	0.22 (±0.09)	$P = 0.346$
		1−	171	0.02 (±1.03)		0.21 (±0.09)	
	-521 CT SNP (rs1800955)	CC	43	−0.03 (±0.99)	$P = 0.953$	0.20 (±0.08)	$P = 0.525$
		CT	115	−0.01 (±0.95)		0.21 (±0.09)	
		TT	63	0.02 (±.95)		0.22 (±0.09)	
DRD2/ANKK1	TaqIA SNP (rs1800497)	CC	160	−0.09 (±0.92)	$P = 0.195$	0.21 (±0.08)	$P = 0.443$
		CT+TT*	81 + 2*	0.09 (±1.03)		0.22 (±0.09)	
COMT	Val158Met SNP (rs4680)	AA	73	−0.04 (±1.03)	$P = 0.913$	0.21 (±0.09)	$P = 0.409$
		AG	115	−0.04 (±0.94)		0.21 (±0.09)	
		GG	50	0.03 (±0.98)		0.20 (±0.08)	
DAT1 (SLC6A3)	40-bp VNTR	9 9	28	0.03 (±1.00)	$P = 0.712$	0.22 (±0.08)	$P = 0.925$
		9 10	100	−0.10 (±0.92)		0.21 (±0.09)	
		10 10	112	−0.00 (±1.00)		0.21 (±0.09)	

*Rare genotype of TaqIA is grouped as labeled. Mean values (±SD) are presented for standardized measures of performance speed and variability of the subjects with different genotypes. Statistical values in bold represent significant results at $P < 0.004$ level of significance based on the Bonferroni correction for multiple testing.

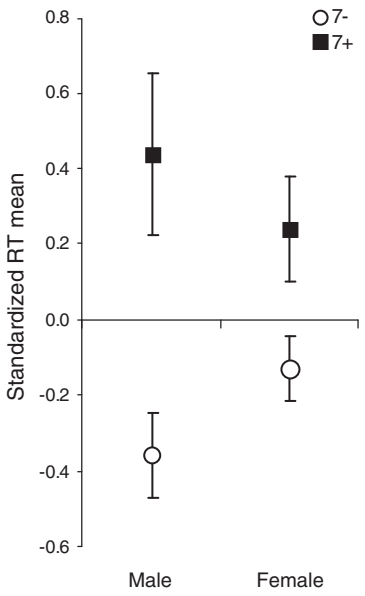

Figure 2: Sex differences in the DRD4 effect. Standardized reaction time performance in males and females as a function of the presence (7+) or absence (7−) of the DRD4 7-repeat allele.

The DRD4 effect in males and females

The presence of the DRD4 effect for both males and females was supported by *t*-tests performed separately in the subgroups (Fig. 2). Males carrying the 7-repeat allele were slower than the average, whereas males without this allele performed considerably better than average. The difference is significant: $t\ (66) = -3.613$ ($P = 0.001$). Females showed a similar pattern with smaller but significant genotype group differences of $t\ (175) = -2.404$ ($P = 0.02$).

Possible modulators of the DRD4 effect: fatigue, session length and difficulty

To explore the role of fatigue and task characteristics, standardized reaction time performance of the 7+ and 7− groups was plotted throughout the course of each task by averaging RT data for a certain amount of time-points, as described in Szekely *et al*. (2003). The six plots in Fig. 3 represent the six tasks in order of difficulty. The 7-repeat allele carriers show performance deficits in all six tasks as compared to those who do not carry this allele, and this difference is present throughout the full length of each task. The DRD4 effect does not seem to increase toward the end of the tasks, thus the DRD4 effect is not because of fatigue, and session length does not influence performance differences in the two genotype groups.

On the other hand, there is a substantial difference between the tasks: the DRD4 effect is more pronounced in the cognitively more demanding tasks, where RTs are longer, especially in WLO and PNA. To investigate the role of item difficulty in eliciting the DRD4 effect, raw reaction time data for each item from the six tasks were utilized for correlation analyses. First, a new variable was calculated to measure the magnitude of the DRD4 effect for each item within each task. Using raw response latencies, e.g. the picture 'dive' in the picture naming task, we calculated the mean RT value for the 7-repeat absent group and subtracted this value from the mean RT of the 7-repeat present group. Item difficulty for each item was measured by the mean response latency of all subjects. Correlation between the 'magnitude of the DRD4 effect' variable and item difficulty was positive and significant $r = +0.46$ ($P < 0.001$), indicating that the more difficult items elicit a more pronounced DRD4 effect. These results indicate that the performance deficit of the 7-repeat allele carriers might be moderated by task characteristics, e.g. difficulty of the item.

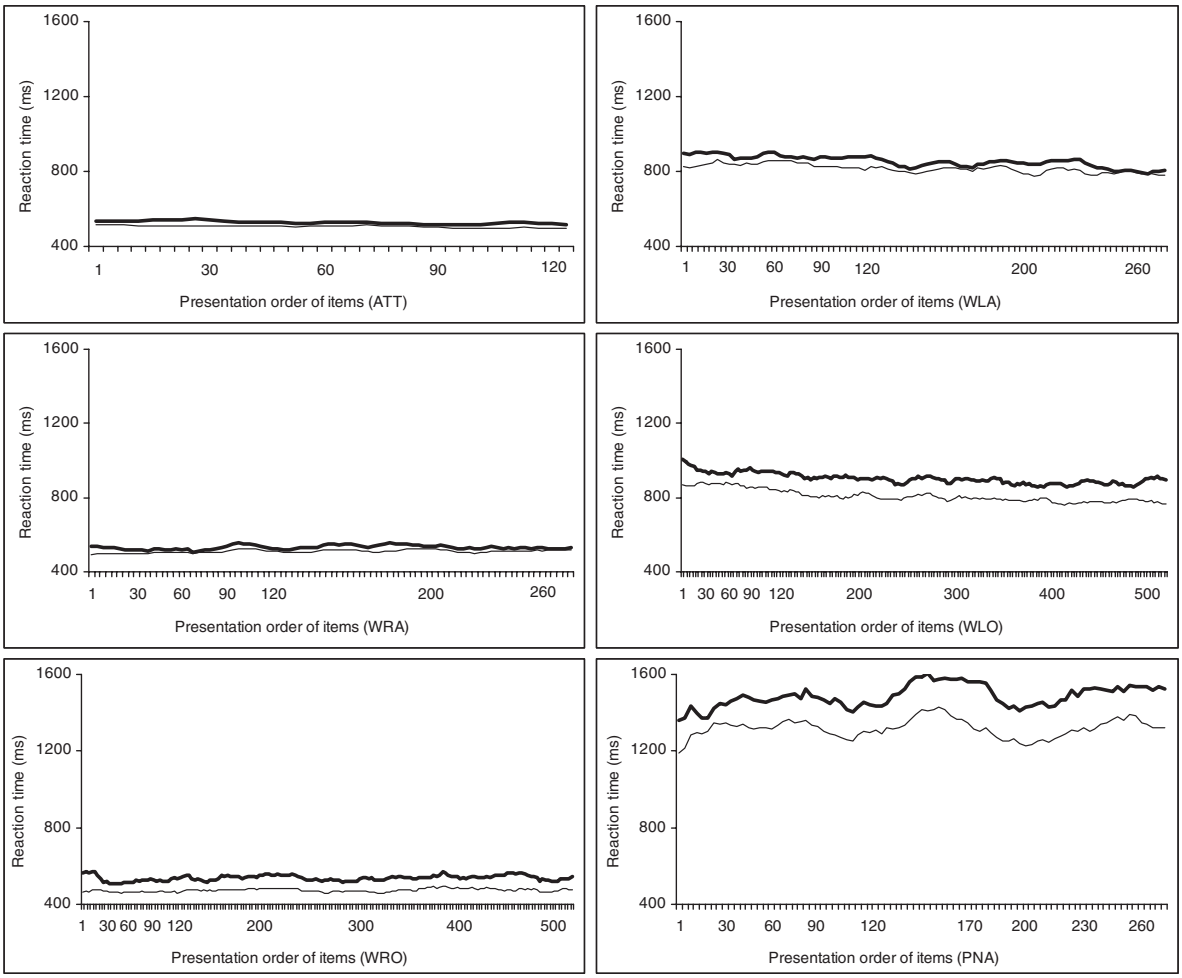

Figure 3: Influence of fatigue, session length and difficulty on the DRD4 effect. Each plot represents a task. The *x*-axis represents the timeline of the tasks, where the first point represents the mean RT for the first 20 responses; the second point represents the mean RT for responses from the 4th item to the 23rd item, etc. The *y*-axis of each plot shows mean reaction time data in the presence (thick black line) or absence (thin black line) of the DRD4 7-repeat allele.

Discussion

Cognitive resources for mental processes are limited, and ongoing activities compete for these resources (Kahneman 1973). Some activities require more attentional capacity and processing time than others depending on the type and difficulty of the tasks. Evidence from twin studies confirms the heritability of the general speed factor common to information processing tasks (Luciano *et al*. 2004; McGue *et al*. 1984). However, single gene effects on overall processing speed have not been explored in detail, existing studies typically report findings based on a single task measuring a distinct cognitive process, e.g. focused attention.

The aim of the present study was to search for possible information processing endophenotypes detectible in different cognitive tasks. Several methods have been proposed to date for eliciting estimates of performance speed from various reaction time tasks, suitable for identification of group differences, e.g. general slowing with age (Brinley 1965). Linear regression and *Z*-score transformations have been used, for example, to supplement traditional analyses of raw response latencies (Faust *et al*. 1999) to better isolate effects above and beyond general slowing.

In the present study, an overall standardized response latency measure has been derived from reaction time performance of non-clinical Caucasian adults participating in different tasks. We explored the association of several candidate dopaminergic polymorphisms with task-independent performance speed and performance variability. No significant results were found for measured polymorphisms of the *COMT*, *DRD2/ANKK1* and *DAT1* genes; however, robust and significant ($P = 0.0001$) DRD4 VNTR effect was reported for the speed-of-performance measure. Individuals carrying one or two 7-repeat alleles showed slower reaction time performance than those who did not carry the 'long' DRD4 VNTR variant. These findings characterized both males and

females, although the performance deficit was more pronounced in males.

The role of dopamine receptors in attentional processes

The model of attention suggested by Posner (Posner & Boies 1971) is built from a set of distinct components: alertness, selectivity and processing capacity. Based on converging neurobiological evidence, these networks can be linked to specific neuromodulators, with complex interactions between them. The executive control network, responsible for processing capacity, is mediated by the mesocortical dopamine system (Raz & Buhle 2006). Cognitive functioning relies strongly on an optimal dopamine level in the prefrontal cortex, and individual differences in dopaminergic gene variants may have a large impact on the dopamine level outcome in a given task within certain environmental circumstances (Tunbridge *et al*. 2006). Among the dopamine receptors, the *DRD4* gene variants are closely related to attention problems for two reasons: (1) for their predominant expression in the prefrontal cortex and (2) the polymorphic variants of this gene are widespread in the human population. The 48-bp VNTR in the third exon, expressed as 16-amino-acid repeats in the third cytoplasmic loop of the protein, was shown to influence the forskolin-activated cyclic adenosine monophosphate (cAMP) stimulation (Asghari *et al*. 1995), although differences in G-protein coupling were not proportionally related to the number of repeats (reviewed by Oak *et al*. 2000). Further studies on the functional effect of DRD4 suggest a possible role of the DRD4 VNTR in gene expression showing that the 7-repeat allele resulted in reduced RNA stability *in vitro* (Schoots & Van Tol 2003). Our results underlie a possible disadvantage of those carrying the 7-repeat allele in attentional processes in general. The DRD4 effect was not task specific according to our findings, thus it might result from an overall attentional processing deficit.

Historically, the most widely studied DRD2 polymorphism is the Taq1A SNP (rs1800498) recently localized in the neighboring *ANKK1* gene, while the Taq1B and Taq1D variants are located in introns 1 and 2 of DRD2, respectively. One of the limitations of our study is that we assessed only the Taq1A variant and did not include the DRD2 intron 6 polymorphism (rs1076560), shown to influence alternative splicing (Zhang *et al*. 2007). These SNPs are, however, in strong linkage disequilibrium (Luo *et al*. 2005).

DRD4 7-repeat deficit detectible only in difficult tasks

Candidate gene studies related to cognitive abilities in non-clinical samples to date mainly focused on distinct networks of the information processing system. The most extensively studied cognitive domains represent distinct areas of the attentional network, such as sustained and spatial attention (for a review, see Bellgrove & Mattingley 2008) or orientating, alerting and executive functions (Fossella *et al*. 2002). Fossella and colleagues investigated the effect of four candidate genes on attentional performance measured by choice reaction time data from the attention network task (ANT). One of the major questions put forward in their investigation was whether candidate genes show association with overall attentional performance and reaction time or with specific neural networks. Their results indicated no associations with overall reaction time performance measures, only a modest association of the DRD4 VNTR was reported with the efficiency of executive attention.

One of the tasks in the present study (ATT) is a simple choice reaction time task requiring button-press responses, very similar to the ANT task used by Fossella and colleagues. In accordance with their findings, the DRD4 effect on speed of responses in the ATT task was not significant (Fig. 1). Thus, it seems that the overall processing speed measures from simple choice RT tasks, such as the ANT or ATT, do not elicit well-defined genotype effects. On the other hand, verbal tasks, such as word reading, repetition or picture naming, seem to show a significant DRD4 effect. As presented in Fig. 3, picture naming, a task where more demand is placed on the information processing system (including retrieval from semantic memory), shows a more pronounced DRD4 effect. Correlation analyses confirmed that performance deficit of the 7-repeat allele carriers was moderated by item difficulty; magnitude of the DRD4 effect was larger for more difficult items. This finding is consistent with the worst performance rule: the slowest trials are the best predictors of intelligence and working memory performance (Larson & Alderton 1990). Based on the above, it seems that RT measures from tasks that demand substantial cognitive effort seem to be more efficient for detecting the DRD4 effect on performance speed than simple choice RT tasks; however, it is still a question, whether the DRD4 effect is present in more difficult, but non-verbal tasks.

It should also be noted that sufficient sample size is a key element in detecting small effects of individual genetic variants on a complex behavior, such as speed of responses. Limitations of the present study include the relatively small sample size within the individual tasks. On the other hand, the overall sample size was large enough to permit powerful analyses on the standardized RT measures; effect of the 7-repeat allele on performance speed was still significant after the stringent Bonferroni correction for multiple testing. As this is the first report of the DRD4 VNTR effect on reaction time performance using a non-clinical young adult sample, replication of these findings is essential in an independent population.

It would also be important to investigate if such association is detectible across the life span – aging studies implicate that processing speed plays an important role in cognitive decline (Salthouse 2000). A more detailed analysis assessing the role of task type and difficulty would be also interesting.

Implications for ADHD

The 7-repeat DRD4 allele is a widely replicated genetic risk factor for ADHD (Li *et al*. 2006). Attentional problems in cognitive development of non-ADHD children are also linked to the long allele of the DRD4 VNTR (Schmidt *et al*. 2001). Our present findings indicate the association of the DRD4 VNTR and speed of performance in young adults, providing further support for the notion that this polymorphism affects the full spectrum of attentional abilities, not only those that qualify as disorder.

Reaction time performance of children with ADHD is characteristically slower and more variable, with a substantial heritable component (Wood *et al*. 2010). Several candidate gene studies used the computerized continuous performance test (CPT) or other attentional tasks to investigate cognitive performance in ADHD; however, findings related to DRD4 are rather controversial. In the early study of Swanson *et al*. (2000), CPT reaction time performance of ADHD children with the DRD4 VNTR 7-repeat allele ($N = 13$) was surprisingly better (faster and less variable) as compared with the 7-repeat absent group ($N = 19$). Latter studies with larger sample size could replicate the variability but not speed of performance aspects of these findings (Bellgrove *et al*. 2005; Manor *et al*. 2002), or reported faster responses of the 7-present subgroup in one task, and slower responses in another task (Langley *et al*. 2004). Others found no association with any performance-related characteristics (Barkley *et al*. 2006). According to a recent study using time-series analysis of speed of performance, ADHD children without the 7-repeat allele can be characterized with variable and inconsistent performance because of their neurocognitive profile of drifting sustained attention and arousal (Johnson *et al*. 2008). However, this study reported no significant differences in mean RT of the DRD4 subgroups. Based on the above, among many performance characteristics of cognitive functioning, response latency does not clearly associate with DRD4 VNTR in ADHD. This might be because of the fact that mostly fast-phased, tiresome, uninteresting choice reaction time tasks have been applied in these studies. It would be interesting to utilize cognitively more demanding tasks in candidate gene studies of ADHD.

Based on the results presented here, endophenotypes measuring the speed of information processing could be promising tools to detect unique genetic effects on performance in speeded tasks. As unique genotype effects are not very strong, it seems reasonable to use large sample sizes with homogeneous ethnic background and age range, as well as standardized reaction time measures from multiple, cognitively demanding reaction time tasks.

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