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Biological Psychology/Pharmacopsychology

Neuropsychobiology

Original Paper

Neuropsychobiology 2003;47:52–56
DOI: 10.1159/000068876

Lack of Association between Polymorphisms of the Dopamine D_4 Receptor Gene and Personality

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Key Words
Dopamine · Polymorphism · DRD4 exon III · –521C/T · Association · Personality · Novelty seeking · Extraversion

Abstract
Recent studies have suggested a role of two polymorphisms of the dopamine D_4 receptor gene (DRD4 exon III and –521C/T) in the modulation of personality traits such as 'novelty seeking' or 'extraversion', which are supposed to be modulated by individual differences in dopaminergic function. However, several replication studies have not provided positive findings. The present study was performed to further investigate whether DRD4 exon III and –521C/T are associated with individual differences in personality. One hundred and fifteen healthy German volunteers completed the NEO-Five-Factor Inventory (NEO-FFI) and were genotyped for the two DRD4 polymorphisms. We found no association between DRD4 exon III and –521C/T, respectively, and estimated novelty seeking, NEO-FFI extraversion or other personality factors. Our findings are in line with several earlier studies which have failed to replicate the initial association results. Hence, our data do not provide evidence for a role of DRD4 exon III and the –521C/T polymorphism in the modulation of novelty seeking and extraversion.

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Introduction

Dopamine has long been discussed as a major neuromodulator of individual differences in personality traits comprising novelty-related behavioral tendencies and the sensitivity to signals of potential reward [1–3]. Individual differences in dopaminergic function, and correspondingly in personality traits which are supposed to be dopaminergically modulated, are likely to be attributable at least in part to variation in dopamine-relevant genes.

A variable number of tandem repeat polymorphism in exon III of the dopamine D_4 receptor (DRD4) gene [4, 5] has been reported to be associated with the personality trait 'novelty seeking' [6, 7], which is conceptualized by Cloninger [2] as a dopaminergically modulated and heritable tendency to exploration and approach in response to novelty and to cues for potential reward. The variable number of tandem repeat consists of a segment of 48 bp,

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0302–282X/03/0471–0052$19.50/0

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which is repeated 2–10 times, the most frequent alleles being the 4-repeat and the 7-repeat [4, 5]. Despite relatively small functional differences between DRD4 exon III variants [8, 9], the finding of higher novelty seeking scores assessed with the Tridimensional Personality Questionnaire (TPQ [10]) in carriers of the 7-repeat allele [6, 7] has been replicated several times [11, 12]. Furthermore, higher scores in the personality trait 'extraversion', which is also supposed to be dopaminergically modulated [3] and which can be measured by several personality questionnaires including the NEO Personality Inventory (NEO-PI-R) or its short form, the NEO-Five-Factor Inventory (NEO-FFI) [13], have been associated with the presence of the 7-repeat allele [7, 12]. Finally, in 1 study, the presence of the 7-repeat allele was associated with lower NEO 'conscientiousness' scores [7]. However, a number of studies have not found any evidence for an association between DRD4 exon III and novelty seeking [14, 15], extraversion [16], and conscientiousness [12, 16], which raises the question whether the positive findings have to be regarded as false-positive results [8].

Nevertheless, the DRD4 gene seems to be of importance in the modulation of novelty-related behavior. In a recent study, DRD4 knockout mice were observed to be less behaviorally responsive to novelty in several approach-avoidance paradigms [17]. A polymorphism in the promoter region of the DRD4 gene is a particularly attractive candidate for further investigation on the role of the DRD4 gene in the modulation of novelty-related behavioral tendencies. The polymorphism is a C/T substitution 521 bp upstream of the translation start site [18]. The presence of the –521T allele is associated with an approximately 40% lower transcriptional efficiency [18, 19]. In a Japanese [19] and in a Hungarian sample [20], the presence of the T allele has been reported to be associated with significantly reduced scores in novelty seeking, assessed with the Temperament and Character Inventory (TCI [21]). Both samples were relatively small (n = 86, and n = 109, respectively), and in the Hungarian sample, the presence of the T allele was associated with lower novelty seeking scores only in the female subsample (n = 54). However, 3 recent studies have not provided any evidence for an association between DRD4 –521C/T and novelty seeking [22–24].

The aim of the present study was to further investigate whether DRD4 exon III and the –521C/T polymorphism are associated with individual differences in novelty seeking and extraversion. Given the relatively few replication studies on the proposed association between DRD4 –521C/T and novelty seeking, it seemed useful to provide further data on that particular issue in order to help evaluate the current evidence on a possible association. Although most meaningful results in association studies are obtained through the use of family-based designs, replication studies based on samples of unrelated individuals are still an important tool in association research, given that the samples are of sufficient size.

Methods and Materials

Participants

The sampling frame of the present study was the German Observational Study of Adult Twins (GOSAT [25]). In the GOSAT, 300 adult twin pairs of German origin who were recruited through newspaper and magazine announcements as part of a larger twin study on the etiology of personality and temperament in adulthood [26] took part in a psychological testing at the University of Bielefeld, Germany. Apart from a reimbursement of their travel and subsistence expenses, the participants did no receive any additional payment. Informed consent was collected from all participants, and blood samples were obtained from the participants for purposes of DNA extraction and subsequent determination of zygosity.

Because it was initially not intended to examine this sample with regard to possible associations between genetic polymorphisms and personality traits, sufficient amounts of DNA were available only for a subsample, and the relatively small number of dizygotic twins discordant for DRD4 exon III and –521C/T genotypes, respectively, rendered family-based analyses impractical. Therefore, a sample of unrelated individuals was randomly selected from the subsample. The final sample consisted of 115 unrelated healthy volunteers (86 women and 29 men) with a mean age of 33.0 (± 12.4) years and a range of 18–67 years. All of the participants completed the German version of the NEO-FFI, which consists of 60 items and allows the reliable and valid assessment of personality along the dimensions 'neuroticism', 'extraversion', 'openness to experience', 'agreeableness', and 'conscientiousness' [27].

DNA Analyses

DNA was extracted from whole blood, and PCR amplification was carried out blind to the participants' identity. Genotypes were determined as previously described for DRD4 exon III [6] and DRD4 –521C/T [23], respectively. DRD4 exon III allele frequencies in the sample were: 2-repeat allele, 7.3%; 3-repeat allele, 4.3%; 4-repeat allele, 66.5%; 5-repeat allele, 0.9%; 6-repeat allele, 0.4%; 7-repeat allele, 19.1%, and 8-repeat allele, 1.3%. DRD4 –521C/T allele frequencies were: T allele 60.0%, and C allele 40.0%. Calculation of linkage disequilibrium between the two polymorphisms using the 2LD program (http://www.iop.kcl.ac.uk/IoP/Departments/PsychMed/GEpiBSt/software.stm) revealed that the markers were not in linkage disequilibrium ($D' = 0.07$, $p > 0.05$).

Statistical Analyses

Statistical analyses were carried out using SPSS for Windows 9.0.1. Similar to Benjamin et al. [7], who used NEO-PI-R scale scores to predict TPQ scale scores in their analysis of an association between DRD4 exon III and novelty seeking, we estimated TCI novelty seeking scores from z-standardized NEO-FFI scale scores by

Table 1. Means and standard deviations of estimated TCI novelty seeking and of the NEO-FFI scales (raw scores) in subjects with different DRD4 exon III and –521C/T genotypes

Polymorphism	Groups	n	Est. NS	N	E	O	A	C
DRD4 exon III	7-repeat absent	75	–0.00 ± 0.54	31.7 ± 7.6	43.3 ± 6.3	41.9 ± 5.6	45.0 ± 4.9	45.9 ± 6.4
	7-repeat present	40	0.00 ± 0.65	33.5 ± 8.8	42.4 ± 7.6	41.9 ± 7.0	45.1 ± 5.4	44.9 ± 7.4
DRD4 –521C/T	TT	47	0.08 ± 0.57	33.1 ± 8.7	43.1 ± 6.2	41.5 ± 6.8	44.5 ± 5.5	44.0 ± 6.7
	CT	44	–0.09 ± 0.59	31.8 ± 7.7	42.3 ± 7.8	42.1 ± 6.1	45.4 ± 4.3	46.6 ± 6.3
	CC	24	0.02 ± 0.56	31.9 ± 7.5	44.2 ± 5.7	42.1 ± 4.7	45.3 ± 5.4	46.4 ± 7.4
	CT and TT	91	–0.01 ± 0.58	32.5 ± 8.2	42.7 ± 7.0	41.8 ± 6.5	44.9 ± 5.0	45.3 ± 6.6

Est. NS = TCI novelty seeking, estimated from the NEO-FFI scales (z-standardized scores); N = neuroticism; E = extraversion; O = openness to experience; A = agreeableness; C = conscientiousness. All mean differences between groups in personality scale scores are not significant according to the results of the analyses of variance.

weighted equations. The regression weights were obtained from a sample of 216 individuals who had completed the German versions of both the TCI and the NEO-PI-R [Ostendorf F, pers. commun., November 14, 2001]. Because the NEO-PI-R includes all of the items of the NEO-FFI, NEO-FFI scale scores were calculated for this sample, and as univariate normality was warranted (Kolmogorov-Smirnov test, $p > 0.20$), the NEO-FFI scale scores were used to predict the TCI novelty seeking total score by means of multiple regression (multiple correlation between novelty seeking and NEO-FFI scales $R = 0.60$, adjusted squared multiple correlation $R^2 = 0.37$; weighted equation: NS = –0.03 *N + 0.35*E + 0.24*O – 0.06*A – 0.38*C).

NEO-FFI scale scores and estimated novelty seeking scores were normally distributed, and homogeneity of error variances of the dependent variables was proven via Levene tests (all $p > 0.05$). Therefore, possible associations between the two DRD4 polymorphisms and personality scales were analyzed by means of analyses of variance, and a two-tailed level of significance of 0.05 was chosen for type I error for all analyses. In the first analysis, DRD4 exon III (7-repeat allele absent vs. present) was the independent variable. In the second analysis, DRD4 –521 (CC vs. CT vs. TT) was the independent variable. Because Ronai et al. [20] found no significant differences between the CT and TT genotypes for any personality dimensions analyzed in their study, they regarded the –521 T allele as dominant and combined individuals with CT and TT genotypes for their analyses. This agglutination also appears to be justified by the impaired transcriptional efficiency in the presence of the T allele [18]. Therefore, a third analysis of variance was performed with DRD4 –521 (CC vs. CT and TT) as the independent variable. To control for possible effects of demographic variables, all analyses were repeated, with age and gender as covariates.

Because Ronai et al. [20] observed that the presence of the T allele was associated with lower novelty seeking scores only in the female subsample, separate one-way analyses of variance with DRD4 –521C/T as independent variable were performed only for the female subsample (n = 86). The analysis of gender-specific effects on an association between –521C/T and novelty seeking by means of two-way analyses of variance was not possible because of limited cell frequencies (male participants, CC genotype: n = 5). Similarly, an analysis of interaction effects of the two polymorphisms would not have provided meaningful results (DRD4 exon III 7-repeat allele present, –521CC genotype: n = 5).

Results

Table 1 presents the means and standard deviations of the z-standardized estimated novelty seeking scores and the raw NEO-FFI scale scores for groups defined by the absence or presence of the DRD4 exon III 7-repeat allele, and by the –521C/T genotypes, respectively.

No differences in estimated novelty seeking scores were observed between individuals with or without the DRD4 exon III 7-repeat allele ($F_{1, 113} = 0.001$, $p = 0.98$). Furthermore, there were no significant effects on extraversion ($F_{1, 113} = 0.45$, $p = 0.50$), on conscientiousness ($F_{1, 113} = 0.55$, $p = 0.46$) or on the other NEO-FFI scales ($p > 0.05$). When age and gender were considered in the analysis, similar results were obtained (data not shown).

With regard to a potential association between DRD4 –521C/T and novelty seeking, analyses of variance showed that there were no significant differences in estimated novelty seeking between groups defined by –521 C/T genotypes, neither when comparing individuals according to CC vs. CT vs. TT genotypes ($F_{2, 112} = 0.98$, $p = 0.38$) nor when comparing individuals according to CC vs. CT and TT ($F_{2, 112} = 0.03$, $p = 0.86$). Furthermore, no significant associations between DRD4 –521C/T and the NEO personality scales emerged, neither for the CC vs.

CT vs. TT comparison nor for the CC vs. CT and TT comparison (all $p > 0.05$). Again, inclusion of age and gender as covariates did not alter the respective results (data not shown).

Following Ronai et al. [20], who observed that the presence of the T allele was associated with lower novelty seeking scores only in the female subsample, separate one-way analyses of variance with DRD4 –521C/T as independent variable were performed only for the female subsample. There were no significant associations between the polymorphism and estimated novelty seeking (all $p > 0.05$).

Although we performed multiple tests of significance in the present study, a Bonferroni correction of the level of significance was not necessary because all results obtained were not significant at the conventional level of significance.

Discussion

Based on results from previous studies, the present study provides a further investigation on the role of polymorphisms of the DRD4 gene in the modulation of individual differences in personality traits. Our results do not support earlier evidence for associations between the DRD4 polymorphisms and the personality traits novelty seeking or extraversion. There were no significant differences in estimated novelty seeking, neither between individuals with or without the DRD4 exon III 7-repeat allele nor between groups defined by –521C/T genotypes. Moreover, no effects of DRD4 exon III or –521C/T on individual differences in NEO-FFI personality factors were observed. Finally, there were no associations between the DRD4 –521C/T polymorphism and estimated novelty seeking, as might have been expected from the results of Ronai et al. [20].

Among the limitations of our study, the relatively small sample size may contribute to our failure to replicate the initial findings. However, several studies that have observed an association between DRD4 exon III and novelty seeking [6, 12] or between DRD4 –521C/T and novelty seeking [19, 20] have been based on samples of about the same size. Furthermore, based on the effect size of $f = 0.5$ for the overall association between DRD4 –521C/T and novelty seeking in the original study by Okuyama et al. [19], the power of the present study was over 0.99 given an alpha of 0.05. Second, our sample of unrelated individuals did not allow to control for possible stratification effects. Although there were no influences of demographic variables like age or gender, and although admixture is unlikely in the population studied, we cannot exclude the possibility that our results are false-negative findings. Third, the distribution of the DRD4 –521 C/T genotypes in our sample differed markedly from that in previous studies, and also among these studies, a considerable variation in genotype distributions can be observed (frequencies of TT/CT/CC genotypes in percent, present report: 41/38/21; Okuyama et al. [19]: 25/42/33; Ronai et al. [20]: 34/45/21; Strobel et al. [23]: 25/50/25; Jönsson et al. [24]: 31/54/15). This marked variation in genotype distributions between and even within ethnic groups may at least in part explain the inconsistencies in the current evidence on a possible association between DRD4 –521C/T and novelty seeking. Finally, novelty seeking scores were not directly assessed with the TPQ or with the TCI in the present study, but were estimated from NEO-FFI scale scores by means of weighted regressions. This method was successfully applied in a previous study on an association between DRD4 exon III and novelty seeking [7]; nevertheless, estimated scores may have provided an inadequate measure of novelty seeking in our sample.

Despite these limitations, our data are in line with other recent studies that have not found any associations either between the two DRD4 polymorphisms and novelty seeking or extraversion [14, 15, 22–24]. Nevertheless, further studies are needed before denoting the findings of associations between DRD4 polymorphisms and novelty seeking or extraversion as false-positive findings. Among several issues to consider in further studies, sufficiently large samples of related individuals should be employed to control for stratification effects.

References

1 Le Moal M, Simon H: Mesocorticolimbic dopaminergic network: Functional and regulatory roles. Physiol Rev 1991;71:155–234.
2 Cloninger CR: A systematic method for clinical description and classification of personality variants. A proposal. Arch Gen Psychiatry 1987;44:573–588.
3 Depue RA, Collins PF: Neurobiology of the structure of personality: Dopamine, facilitation of incentive motivation, and extraversion. Behav Brain Sci 1999;22:491–569.
4 Van Tol HHM, Bunzow JR, Guan HC, Sunahara RK, Seeman P, Niznik HB, Civelli O: Cloning of the gene for a human dopamine D_4 receptor with high affinity for the antipsychotic clozapine. Nature 1991;350:610–614.
5 Lichter JB, Barr CL, Kennedy JL, Van Tol HHM, Kidd KK, Livak KJ: A hypervariable segment in the human dopamine receptor D_4 (D4DR) gene. Hum Mol Genet 1993;2:767–773.
6 Ebstein RP, Novick O, Umansky R, Priel B, Osher Y, Blaine D, Bennett ER, Nemanov L, Katz M, Belmaker RH: Dopamin D_4 receptor (D4DR) exon III polymorphism associated with the personality trait of Novelty Seeking. Nat Genet 1996;12:78–80.
7 Benjamin J, Li L, Patterson C, Greenberg BD, Murphy DL, Hamer DH: Population and familial association between the D_4 dopamine receptor gene and measures of Novelty Seeking. Nat Genet 1996;12:81–84.
8 Paterson AD, Sunohara GA, Kennedy JL: Dopamine D_4 receptor gene: Novelty or nonsense? Neuropsychopharmacology 1999;21:3–16.
9 Tarazi FI, Baldessarini RJ: Dopamine D_4 receptors: Significance for molecular psychiatry at the millennium. Mol Psychiatry 1999;4:529–538.
10 Cloninger CR, Przybeck TR, Svrakic DM: The Tridimensional Personality Questionnaire: US normative data. Psychol Rep 1991;69:1047–1057.
11 Noble EP, Ozkaragoz TZ, Ritchie TL, Zhang X, Belin TR, Sparkes RS: D_2 and D_4 dopamine receptor polymorphisms and personality. Am J Med Genet 1998;81:257–267.
12 Strobel A, Wehr A, Michel A, Brocke B: Association between the dopamine D_4 receptor (DRD4) exon III polymorphism and measures of Novelty Seeking in a German population. Mol Psychiatry 1999;4:378–384.
13 Costa PT, McCrae RR: Revised NEO Personality Inventory (NEO-PI-R) and NEO Five-Factor Inventory (NEO-FFI), Professional Manual. Odessa, Psychological Assessment Resources, 1992.
14 Pogue-Geille M, Ferrell R, Deka R, Debski T, Manuck S: Human novelty seeking personality traits and dopamine D_4 receptor polymorphisms: A twin and genetic association study. Am J Med Genet 1998;81:44–48.
15 Kuhn KU, Meyer K, Nöthen MM, Gansicke M, Papassotiropoulos A, Maier W: Allelic variants of dopamine receptor D_4 (DRD4) and serotonin receptor 5-HT2C (HTR2C) and temperament factors: Replication tests. Am J Med Genet 1999;88:168–172
16 Persson ML, Wasserman D, Geijer T, Frisch A, Rockah R, Michaelovsky E, Apter A, Weizman A, Jönsson EG, Bergman H: Dopamine D_4 receptor gene polymorphism and personality traits in healthy volunteers. Eur Arch Psychiatry Clin Neurosci 2000;250:203–206.
17 Dulawa SC, Grandy DK, Low MJ, Paulus MP, Geyer MA: Dopamine D_4 receptor-knock-out mice exhibit reduced exploration of novel stimuli. J Neurosci 1999;19:9550–9556.
18 Okuyama Y, Ishiguro H, Toru M, Arinami T: A genetic polymorphism in the promoter region of DRD4 associated with expression and schizophrenia. Biochem Biophys Res Commun 1999;258:292–295.
19 Okuyama Y, Ishiguro H, Nankai M, Shibuya H, Watanabe A, Arinami T: Identification of a polymorphism in the promoter region of DRD4 associated with the human novelty seeking personality trait. Mol Psychiatry 2000;5:64–69.
20 Ronai Z, Szekely A, Nemoda Z, Lakatos K, Gervai J, Staub M, Sasvari-Szekely M: Association between Novelty Seeking and the −521 C/T polymorphism in the promoter region of the DRD4 gene. Mol Psychiatry 2001;6:35–38.
21 Cloninger CR, Przybeck TR, Svrakic DM, Wetzel RD: The Temperament and Character Inventory (TCI): A Guide to Its Development and Use. St Louis, Washington University Press, 1994.
22 Ekelund J, Suhonen J, Järvelin M-R, Peltonen L, Lichtermann D: No association of the −521 C/T polymorphism in the promoter of DRD4 with novelty seeking. Mol Psychiatry 2001;6:618–619.
23 Strobel A, Lesch KP, Hohenberger K, Jatzke S, Gutzeit HO, Anacker K, Brocke B: No association between dopamine D_4 receptor gene exon III and −521C/T polymorphism and novelty seeking. Mol Psychiatry 2002;7:537–538.
24 Jönsson EG, Ivo R, Gustavsson JP, Geijer T, Forslund K, Mattila-Evenden M, Rylander G, Cichon S, Propping P, Bergman H, Åsberg M, Nöthen MM: No association between dopamine D_4 receptor variants and Novelty Seeking. Mol Psychiatry 2002;7:18–20.
25 Spinath FM, Riemann R, Hempel S, Schlangen B, Weiss R, Borkenau P, Angleitner A: A day in the life: Description of the German Observational Study on Adult Twins (GOSAT) assessing twin similarity in controlled laboratory settings; in Mervielde I, Deary I, De Fruyt F, Ostendorf F (eds): Personality Psychology in Europe. Tilburg, Tilburg University Press, 1999, vol 7, pp 311–328.
26 Riemann R, Angleitner A, Strelau J: Genetic and environmental influences on personality: A study of twins reared together using the self- and peer report NEO-FFI scales. J Pers 1997;65:449–475.
27 Borkenau P, Ostendorf F: NEO-Fünf-Faktoren Inventar (NEO-FFI), Handanweisung. Göttingen, Hogrefe, 1993.