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Dopamine D4 receptor gene polymorphism and personality traits in healthy volunteers

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Abstract An association between long alleles of a variable number tandem repeat (VNTR) polymorphism in the dopamine receptor D4 gene and the extraversion related personality traits Excitement and Novelty Seeking has been reported in healthy subjects.

In an attempt to replicate the previous findings, 256 healthy Caucasian volunteers were analysed for a potential relationship between the dopamine receptor D4 exon III VNTR polymorphism and Extraversion as assessed by the Revised Neo Personality Inventory (NEO PI-R). The present study did not yield evidence for an association between Extraversion and the dopamine receptor D4 polymorphism.

Key words Dopamine receptor D4 · Genetics · Personality inventory · Polymorphism · Excitement-Seeking

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Introduction

Evidence for genetic influence has been found for most behavioural disorders and personality traits (Loehlin 1992; Cloninger et al. 1993; Plomin et al. 1994; Bouchard 1994). It has been hypothesised that certain personality traits may correlate with activity in different neuronal systems. Novelty Seeking, characterised by "excitement in response to novel stimuli" has been suggested to be mediated by dopamine neurotransmission (Cloninger 1987). Recently, an association between a variable number tandem repeat (VNTR) polymorphism in exon III of the dopamine D4 receptor gene (DRD4) and Novelty Seeking was observed in Israeli volunteers (Ebstein et al. 1996). Simultaneously, Benjamin et al. (1996) reported an association between the same DRD4 polymorphism and a similar personality item, Excitement-Seeking measured by the NEO PI-R questionnaire (Costa and McCrae 1992). The proposed relationship between DRD4 and Novelty Seeking was to some extent supported with various degree of evidence in additional Israeli as well as Japanese, Finnish, German and American studies (Ebstein et al. 1997, 1998; Ono et al. 1997; Noble et al. 1998; Ekelund et al. 1999; Strobel et al. 1999; Tomitaka et al. 1999). However, several other studies investigating healthy Swedish (Jönsson et al. 1997, 1998), Finnish alcoholic (Malhotra et al. 1996), healthy or alcohol-dependent German (Sander et al.1997; Kühn et al. 1999), American substance-dependent, personality-disorder or healthy (Vandenbergh et al. 1997; Gelernter et al. 1998; Pogue-Geile et al. 1998), New Zealand depressed or alcohol-related (Sullivan et al. 1998) and Brazilian alcohol-dependent subjects (Bau et al. 1999), could not replicate the proposed association.

It has been claimed that the DRD4 polymorphism reflects exploratory, extravagant, and extraverted, rather than impulsive and monotony-avoidant subtypes of Novelty Seeking (Strobel et al. 1999). The two Swedish reports previously published (Jönsson et al. 1997, 1998) used the Karolinska Scales of Personality questionnaire (KSP; Schalling et al. 1987) for the measurement of personality.

The aspects of Novelty Seeking measured by the KSP is covered by the two scales Monotony Avoidance and Impulsiveness, i. e. scales not associated with DRD4 according to the study by Strobel et al. (1999). In an attempt to replicate the proposed association between the DRD4 polymorphism and Excitement-Seeking we investigated a Swedish sample assessed with the personality instrument, NEO PI-R. This instrument was used in one of the original studies (Benjamin et al. 1996) and it covered aspects of the extraversion domain not accounted for in the KSP.

Subjects and methods

Subjects

The study was approved by the Ethics Committee of the Karolinska Hospital, Stockholm. Healthy volunteers (n= 330) were recruited in the Stockholm region through inquiries at different work places and professional and non-profit organisations from a broad spectrum of categories in society: hospital staff, firemen, elderly retired, industrial workers, administrators and teachers. A questionnaire [the survey module of the Swedish version of SCID-I and also, where appropriate, other parts of the SCID manual] (Spitzer et al. 1986) was used to assess the presence of psychiatric illness.

Among them 261 individuals had answered to the NEO PI-R questionnaire and 323 individuals had also been genotyped for the DRD4 receptor polymorphism. Both NEO PI-R and genotype data were available for 256 subjects. They were all Caucasian individuals of European background, 142 men (mean age 39.3 years SD=9.8) and 114 women (mean age 43.0 years SD=11.5).

DNA extraction

Venous blood from all individuals was collected in EDTA-containing tubes. DNA isolation was performed as previously described (Geijer et al. 1994).

DRD4 polymorphism marker

The 48 bp-repeat polymorphism (varying from 2–8 and 10 repeats) in exon III of the DRD4 gene was assayed using the polymerase chain reaction (PCR) primers previously described (Lichter et al. 1993).

Personality assessment

The subjects were asked to complete the NEO personality inventory (NEO PI-R, Form S) (Costa and McCrae 1992). The Swedish NEO PI-R is an authorised translation but Swedish norms have not yet been developed. In the present study we used normative values from the American manual (Costa and McCrae 1992) in order to calculate T scores.

Data analysis

In accordance with Benjamin et al. (1996), the DRD4 genotypes were divided into two groups: subjects with alleles containing 2 to 5 repeats (S-group) and subjects with one or two alleles containing ≥ 6 repeats (L-group). The rationale for this dichotomisation was based upon altered pharmacological binding properties of the expressed DRD4 (Van Tol et al. 1992).

Associations between DRD4 genotypes and Extraversion dimension T scores were compared using the unpaired t-test. Analyses were also performed separately in men and women, respectively, and in age-groups ≤ 35 years or > 35 years, respectively. Statistical analysis was performed using the computer program StatView (Abacus Concepts, Inc., Berkley, CA, 1994).

The data reported by Benjamin et al. (1996) suggested an effect size of 0.37. Analysis was not performed if the power was less than 80 % at an effect size of 0.37 and α=0.05 for the total sample. In the analysis of subgroups restricted by gender and age, analysis was not performed if the power was less than 0.80 at an effect size of 0.8 and an alpha of 0.05. Power was estimated with the GPower program (Erdfelder 1996).

Results

The observed DRD4 exon III allele frequencies were 2 repeats (6.4 %), 3 repeats (6.6 %), 4 repeats (66.2 %), 5 repeats (0.6 %), 6 repeats (0.6 %), 7 repeats (18.4 %), and 8 repeats (1.2 %). No 9 or 10 repeat alleles were observed. These allele frequencies were in the same range as previously reported in the Swedish and other Caucasian populations (Benjamin et al. 1996; Ebstein et al. 1996; Sander et al. 1997; Jönsson et al. 1998; Pogue-Geile et al. 1998; Ekelund et al. 1999; Strobel et al. 1999).

Analyses of the individual facets that comprise the Extraversion dimension are shown in Table 1. No association between DRD4 genotypes and Excitement-Seeking or any of the facets in the Extraversion dimension was observed.

Discussion

The previous finding of an association between DRD4 genotypes and the personality trait Excitement-Seeking was not replicated. This is consistent with the observations of several recent studies reviewed in the introduction. Previous studies of Swedish subjects using the KSP questionnaire did not find any association between DRD4 genotypes and Novelty-Seeking related scales (Jönsson et al. 1997, 1998). Using the same questionnaire as in one of the original studies (Benjamin et al. 1996) we were not able to replicate the proposed association in the present study. This argues that the association between DRD4 genotypes and Excitement-Seeking is not likely to be valid in the Swedish population.

The reason for the discrepancy between different studies is unclear. Several explanations are possible. The present lack of association may be explained as type II errors. In analyses including all subjects, a similar effect size as in the study of Benjamin et al. (1996) resulted in a power of more than 80 %. However, in analyses restricted to each gender and age group, respectively, the same power could only be maintained at an effect size of 0.8. Thus, small effects associated with the DRD4 polymorphism may have escaped detection. Nevertheless, large effects restricted to either gender or age group might have been part of the explanation of previous inconsistent results. Our data did not support such a hypothesis. The DRD4 polymorphism may interact differently with other genetic and/or environmental factors in different populations. The DRD4 polymorphism could be in linkage disequilibrium with a polymor-

phism, which is truly associated with the personality trait Excitement-Seeking. The latter polymorphism may be differently distributed in different populations. A special case of this is indicated, as the alleles of the DRD4 exon III polymorphism vary not only in the number of repeats but also in the sequence of the repeats and the order in which they appear (Lichter et al. 1993). Thus, in different populations, variation of allele frequencies may explain discrepancies (Lichter et al. 1993; Chang et al. 1996). As in all previous reports, reviewed in the introduction, we studied only the number of repeats, but not their sequence or order. Therefore, we can not exclude the possibility that individual variation in these two factors is relevant to Excitement-Seeking. Spurious associations may reflect stratification effects and finally, the trivial explanation that all positive findings may represent chance findings can never be entirely excluded.

The present results do not support the view that long alleles of the DRD4 polymorphism contribute to individual differences in the behavioural trait Excitement-Seeking. Although the negative result for the DRD4 polymorphism was obtained, it does not rule out the possible influence of dopaminergic mechanisms in Novelty and Excitement-Seeking.

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Table 1 Extraversion facets (T scores) in subjects with the short (S) vs. long (L) genotype

Extraversion facets		Mean T score (SD)				
		N	S group	N	L group	p
Warmth	Total	161	49.0 (10.4)	95	47.3 (10.5)	0.214
	men	98	49.0 (10.0)	44	46.6 (12.1)	0.222
	women	63	49.0 (11.1)	51	47.9 (8.9)	0.578
	≤35 y.	50	49.6 (9.3)	28	47.1 (10.3)	0.281
	>35 y.	111	48.7 (10.9)	67	47.3 (10.6)	0.428
Gregariousness	Total	161	58.2 (9.5)	95	57.5 (9.7)	0.579
	men	98	58.3 (9.1)	44	56.5 (9.8)	0.285
	women	63	58.0 (10.3)	51	58.3 (9.5)	0.839
	≤35 y.	50	60.4 (7.7)	28	59.8 (9.3)	0.770
	>35 y.	111	57.2 (10.1)	67	56.5 (9.7)	0.666
Assertiveness	Total	161	53.4 (10.1)	95	51.4 (10.4)	0.139
	men	98	53.4 (9.4)	44	51.2 (9.7)	0.186
	women	63	53.3 (11.2)	51	51.7 (11.1)	0.434
	≤35 y.	50	54.0 (11.0)	28	51.8 (9.9)	0.378
	>35 y.	111	53.1 (9.7)	67	51.3 (10.7)	0.241
Activity	Total	161	50.1 (9.0)	95	49.9 (8.2)	0.855
	men	98	49.4 (8.6)	44	49.4 (8.7)	0.989
	women	63	51.2 (9.5)	51	50.3 (7.8)	0.586
	≤35 y.	50	51.1 (9.6)	28	51.4 (7.3)	0.895
	>35 y.	111	49.7 (8.7)	67	49.3 (8.5)	0.779
Excitement-Seeking	Total	161	48.9 (9.5)	95	49.4 (9.4)	0.665
	men	98	49.8 (9.5)	44	51.9 (10.5)	0.237
	women	63	47.5 (9.3)	51	47.3 (7.8)	0.896
	≤35 y.	50	52.8 (9.3)	28	53.0 (9.1)	0.900
	>35 y.	111	47.2 (9.1)	67	47.9 (9.1)	0.590
Positive Emotions	Total	161	54.5 (12.6)	95	54.6 (12.6)	0.940
	men	98	55.8 (12.2)	44	55.2 (10.3)	0.772
	women	63	52.6 (12.9)	51	54.2 (10.4)	0.471
	≤35 y.	50	57.1 (11.3)	28	58.4 (7.6)	0.592
	>35 y.	111	53.4 (13.0)	67	53.1 (11.0)	0.878

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