Jari Lahti
Katri Räikkönen
Jesper Ekelund
Leena Peltonen
Olli T. Raitakari
Liisa Keltikangas-Järvinen

Novelty Seeking: Interaction Between Parental Alcohol Use and Dopamine D4 Receptor Gene Exon III Polymorphism Over 17 Years

Recent meta-analyses have questioned the association between the dopamine receptor D4 (DRD4) gene polymorphism and the temperament trait of novelty seeking, and proposed an interaction between the polymorphism and other factors. We wanted to test whether parental alcohol use during childhood moderated the effect of an offspring dopamine receptor gene (DRD4) polymorphism on the temperament trait of novelty seeking in adulthood. A population-based sample of children and adolescents ($n = 2149$) and their parents was examined in 1980 and 1983 on parental alcohol use and rearing practices. In 1997, study participants completed the Temperament and Character Inventory for the novelty-seeking temperament trait, and a subsample ($n = 150$) was genotyped for the DRD4 exon III polymorphism. For the participants with the father, but not the mother, reporting more frequent alcohol consumption or drunkenness in examinations 17 and/or 14 years before the novelty-seeking assessment, an association between the short (two- or five-repeat) alleles of the DRD4 gene and extremely high novelty-seeking scores was observed. When the father reported less frequent alcohol consumption or drunkenness, the genotype was not associated with novelty seeking. The association remained after controlling for sex, age, and maternal childrearing. These results provide preliminary information on gene-environment interaction on the temperament trait of novelty seeking and may partly explain the heterogeneity of findings concerning the association between DRD4 polymorphisms and novelty seeking.

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Introduction

Genetic variability in dopamine transmission may influence the temperament dimension of novelty seeking (NS) (Cloninger *et al.,* 1993). In accordance with this hypothesis, a polymorphism in the dopamine D4 receptor gene (DRD4) exon III has been identified that may be associated with NS. Some empirical evidence shows that long alleles, mostly representing the seven-repeat, are associated with higher NS scores (Benjamin *et al.,* 1996, 2000; Ebstein *et al.,* 1996, 1997; Noble *et al.,* 1998; Strobel *et al.,* 1999; Tomitaka *et al.,* 1999). Evidence also exists that the seven-repeat allele is associated with lower NS scores in substance abusers (Malhotra *et al.,* 1996; Gelernter *et al.,* 1997), and that the DRD4 polymorphism and NS are not associated (Malhotra *et al.,* 1996; Gelernter *et al.,* 1997; Ono *et al.,* 1997; Sander *et al.,* 1997; Pogue-Geile *et al.,* 1998; Sullivan *et al.,* 1998; Bau *et al.,* 1999; Kuhn *et al.,* 1999; Comings *et al.,* 2000; Gebhardt *et al.,* 2000; Herbst *et al.,* 2000; Mitsuyasu *et al.,* 2001; Soyka *et al.,* 2002). Moreover, two- or five-repeat alleles were shown to contribute to higher NS scores in two independent Finnish samples (Ekelund *et al.,* 1999; Keltikangas-Järvinen *et al.,* 2003).

Recent meta-analyses (Kluger *et al.,* 2002;

Schinka *et al.,* 2002) showed that the divergence among the studies does not appear random, but is likely to reflect true heterogeneity between the studies, indicating that there are unknown moderators in the association between the DRD4 polymorphisms and NS, such as environmental factors (Bouchard, 1994; Plomin *et al.,* 1994). We have recently demonstrated that the association between the DRD4 polymorphism and NS in adulthood was moderated by the early childhood rearing environment (Keltikangas-Järvinen *et al.,* 2004), such that when the rearing environment was more negatively tuned, the two- or five-repeat alleles were more common in a group scoring high on NS, and when the rearing environment was less negatively tuned, the genotype and NS were not significantly associated. Negatively tuned childhood environment was characterized as mother-reported emotional distance, low tolerance towards the child's normal activity, and a strict disciplinary style.

A specific potential moderator of the association between the DRD4 polymorphism and NS may be parental alcohol consumption. Parental alcoholism and/or alcohol use may predict high NS in the offspring (Sher *et al.,* 1991; Ravaja and Keltikangas-Järvinen, 2001), and may increase the risk of early onset alcohol use in the offspring (Webb and Baer, 1995); NS, in turn, has been shown to predict early onset alcohol abuse (Cloninger *et al.,* 1988). A recent study showed that adolescent sons of alcoholic fathers exhibited significantly higher extraversion scores—a personality trait closely correlated with NS temperament (Zuckman and Cloninger, 1996)—than sons of nonalcoholics, if they carried the minor alleles of the DRD2 gene, whereas the father's alcoholism did not affect the DRD4 seven-repeat and extraversion association (Ozkaragoz and Noble, 2000). Finally, some of the previous studies have identified that the seven-repeat allele of the DRD4 polymorphism is associated with low NS scores in substance-abusing subgroups (Malhotra *et al.,* 1996; Gelernter *et al.,* 1997).

Our aim in the current study was to find out whether interactions between parental alcohol use during the childhood/adolescence of their offspring and DRD4 polymorphism predicted NS temperament in adulthood over 17 years. In addition to focusing on two- or five-repeat alleles of the DRD4 gene, which have been shown to contribute to higher NS scores in the current sample (Keltikangas-Järvinen *et al.,* 2003) and another independent Finnish sample (Ekelund *et al.,* 1999), we tested whether the parental alcohol consumption moderated any potential associations of the seven-repeat allele of the DRD4 gene and NS.

MATERIALS AND METHODS

STUDY PARTICIPANTS

In the context of the 1997 survey of the population-based Cardiovascular Risk in Young Finns Study (Åkerblom *et al.,* 1991), 2149 women and men from six cohorts, aged between 20 and 35, completed the Temperament and Character Inventory for NS (Cloninger *et al.,* 1993). From this sample, those with extremely high or extremely low NS scores (participants scoring above the 90th percentile and below the 10th percentile on the sample distribution of the overall NS scale) were invited to participate in the genetic part of the study [for selective genotyping see e.g. Lebowitz *et al.* (1987) or Darvasi and Soller (1992)]. A total of 154 participants (51% women) agreed to participate and gave blood samples. Alleles were not identifiable in four of the participants, resulting in a final sample size of 150. This study was conducted in accordance with the Helsinki declaration, and the ethical committees of the participating university hospitals approved the study protocol.

Data on parental alcohol use were available from examinations conducted in 1980 and 1983, that is, 17 and 14 years before the NS testing. In 1980, the participants were from 3 to 18 years old, and in 1983 they were from 6 to 21 years old.

TEMPERAMENT

The participants filled in the Temperament and Character Inventory to measure NS (Cloninger *et al.,* 1993). The original true/false response format was modified in that each item was rated on a five-point scale, ranging from 1 (not true of me at all) to 5 (true of me). The modification of the response format from a two- to a five-point scale widens the response options, which allows more latitude and finer distinctions. This has resulted in higher item validity and reliability in other personality inventories (Comrey and Montag, 1982). The reliability of the NS scale was good (Cronbach's $\alpha = 0.86$).

PARENTAL ALCOHOL USE

Parental alcohol use was measured twice, in 1980 and 1983, using identical structured self-report questions (for more detail, see Ravaja and Keltikangas-Järvinen, 2001). Both parents reported alcohol use separately on questions regarding (1) the frequency of alcohol consumption ('How often have you drunk alcohol during the last 12 months?') and (2) the frequency of feeling drunk on alcohol ('How often have you been drunk on

alcohol during the last 12 months?'). The response options were 'every day', 'a couple of times a week', 'once a week', 'a couple of times a month', 'about once a month', 'every second month', 'three or four times a year', and 'never'.

The frequency-of-alcohol-consumption and feeling-drunk variables were dichotomized for analysis in order to allow sufficient cell size. Thus, we defined *more frequent consumption of alcohol* as daily to a couple of times a month, and *less frequent consumption of alcohol* as never to once a month. *More frequent drunkenness* was defined as daily to every second month, and *less frequent drunkenness* as never to three or four times a year.

DRD4 POLYMORPHISM GENOTYPING

A polymerase chain reaction was performed as described by Lichter *et al.* (1993), with slight modifications. One primer was fluorescently labelled with Cy5 for size separation on an automated DNA sequencer (ALF express; Pharmacia Biotech AB, Uppsala, Sweden). Allelinks software was used for the genotyping (Pharmacia Biotech AB). DRD4 alleles were classified in two ways: on the basis of the presence or absence of the exon III seven-repeat allele, and according to whether the participant had any or no two- or five-repeat alleles.

STATISTICAL ANALYSIS

Logistic regression analyses were performed, and risk ratios and 95% confidence intervals (CIs) were computed to test whether extremely high and low NS scores in the offspring were predicted by interactions between parental alcohol use and DRD4 gene polymorphism. Significant interactions were probed further by conducting separate χ^2-tests in groups separated according to more or less frequent consumption of alcohol or more or less frequent drunkenness by the parents. As two sets of data on parental alcohol use were available from the examinations conducted in 1980 and 1983, we also tested whether a stable status in terms of more versus less frequent alcohol consumption, and more versus less frequent drunkenness (e.g. more frequent alcohol consumption in 1980 and 1983), moderated associations between the DRD4 polymorphism and NS. Only eight to 14 parents showed any change in alcohol use category and thus we do not present our findings regarding the interactions between changing category over time and DRD4 on NS.

We have shown previously in the current sample that the mother's child-rearing characterized by emotional distance to the child (e.g. 'My child is not significant to me.') and her strict disciplinary style (e.g. 'Disciplinary actions are not sufficiently enough to restrict my child's behaviour.') moderated the association between DRD4 two- or five-repeat alleles and NS (Keltikangas-Järvinen *et al.,* 2004). Therefore, the main effect of maternal childrearing, and the moderation effect of DRD4 by maternal child-rearing were controlled for in all analyses. Also, sex and age were statistically controlled for.

RESULTS

The distribution of the DRD4 alleles was comparable with the results of previous studies (Ekelund *et al.,* 1999; Herbst *et al.,* 2000). Frequencies of 8.3, 7.7, 63.7, 4.3, 0, 15.7 and 0.4% were found for alleles 2, 3, 4, 5, 6, 7, and 8, respectively. The distribution of the DRD4 genotypes were as follows: 37.3% of the participants carried the 4/4 genotype, 25.3% the 7/4 genotype, 12.0% the 4/3 genotype, 10.7% the 4/2 genotype, 4.0% the 5/4 genotype, 2.0% the 3/2, 7/2, or 7/5 genotype, and 0.7% the 2/2, 5/2, 5/3, 5/5, 7/3, 7/7, or 8/4 genotype. When the participants were pooled on the basis of the DRD4 alleles, 23.3% carried any and 76.7% carried no two- or five-repeat alleles, whereas 30.7% carried any, and 69.3% carried no seven-repeat alleles.

More fathers than mothers belonged to the group of more frequent alcohol consumption and drunkenness. In 1980, 60.9% of the fathers versus 39.1% of the mothers belonged to the more-frequent-consumption group ($P < 0.001$), and in 1983, the respective figures were 59.8 and 38.5% ($P < 0.001$). Similarly, in 1980, 43.2% of the fathers versus 16.7% of the mothers belonged to the more-frequent-drunkenness group ($P < 0.001$), whereas in 1983, the respective figures were 42.3 versus 18.7% ($P < 0.001$).

Parental alcohol use was highly stable over the examinations in 1980 and 1983. Of the fathers belonging to the more-frequent-consumption group in 1980, 88.9% belonged to the more-frequent-consumption group in 1983, and 82.0% of the fathers belonging to the less-frequent-consumption group in 1980, belonged to the same group in 1983 ($\kappa = 0.71$, approx $t = 7.9$, $P < 0.001$); 83.7% of the fathers reported consistently more and 84.7% consistently less frequent drunkenness in 1980 and 1983 ($\kappa = 0.68$, approx $t = 7.5$, $P < 0.001$). Of the mothers, 80.0% reported consuming alcohol consistently more and 83.1% consistently less frequently in 1980 and 1983 ($\kappa = 0.63$, approx $t = 7.4$, $P < 0.001$), and 70.8% reported consistently more and 89.6% consistently less frequent drunkenness in 1980 and 1983 ($\kappa = 0.56$, approx $t = 6.6$, $P < 0.001$).

Table 1. The Results of Logistic Regression Analyses Testing Gene-Environment Interactions on Extremely Low and High Scores of Novelty Seeking (NS)

	Offspring extremely low versus high NS group[c]					
	Parental alcohol use (more or less frequent)		DRD4 gene (any or no two or five repeats)		Parental alcohol use × DRD4 gene	
	B (SE)[a]	*P*	*B* (SE)[a]	*P*	*B* (SE)[a]	*P*
Father's frequency of alcohol consumption						
in 1980 (n = 135[b])	1.90 (0.83)	0.023	0.29 (0.75)	0.70	−1.85 (0.93)	0.048
in 1983 (n = 124[b])	2.79 (0.96)	0.004	1.29 (0.84)	0.13	−3.41 (1.06)	0.001
in 1980 and 1983 (n = 105[b])	3.09 (1.2)	0.011	1.43 (1.1)	0.20	−3.46 (1.3)	0.008
Father's frequency of drunkenness						
in 1980 (n = 134[b])	1.99 (0.82)	0.015	−0.36 (0.59)	0.54	−1.30 (0.92)	0.16
in 1983 (n = 124[b])	1.99 (0.85)	0.019	0.23 (0.61)	0.71	−2.28 (0.96)	0.018
in 1980 and 1983 (n = 102[b])	1.99 (0.89)	0.026	0.38 (0.66)	0.56	−1.77 (1.02)	0.08
Mother's frequency of alcohol consumption						
in 1980 (n = 148[b])	1.01 (0.72)	0.16	−0.56 (0.54)	0.30	−0.51 (0.82)	0.54
in 1983 (n = 139[b])	0.92 (0.73)	0.21	−0.47 (0.54)	0.39	−0.55 (0.83)	0.51
in 1980 and 1983 (n = 113[b])	1.06 (0.78)	0.18	−0.50 (0.58)	0.39	−0.64 (0.91)	0.49
Mother's frequency of drunkenness						
in 1980 (n = 148[b])	0.36 (0.83)	0.67	−0.98 (0.45)	0.03	1.01 (0.98)	0.31
in 1983 (n = 140[b])	0.69 (0.82)	0.40	−0.69 (0.47)	0.14	0.00 (0.96)	1.00
in 1980 and 1983 (n = 120[b])	0.18 (0.92)	0.30	−0.62 (0.49)	0.20	1.18 (1.14)	0.30

[a] B is the unstandardized regression coefficient and (SE) is the standard error in a logistic regression analysis. [b] The total number of study participants is 150 and the variation is because of missing values. [c] Regression models include main effects of parental alcohol use and the dopamine D4 receptor (DRD4) gene, and their interaction.

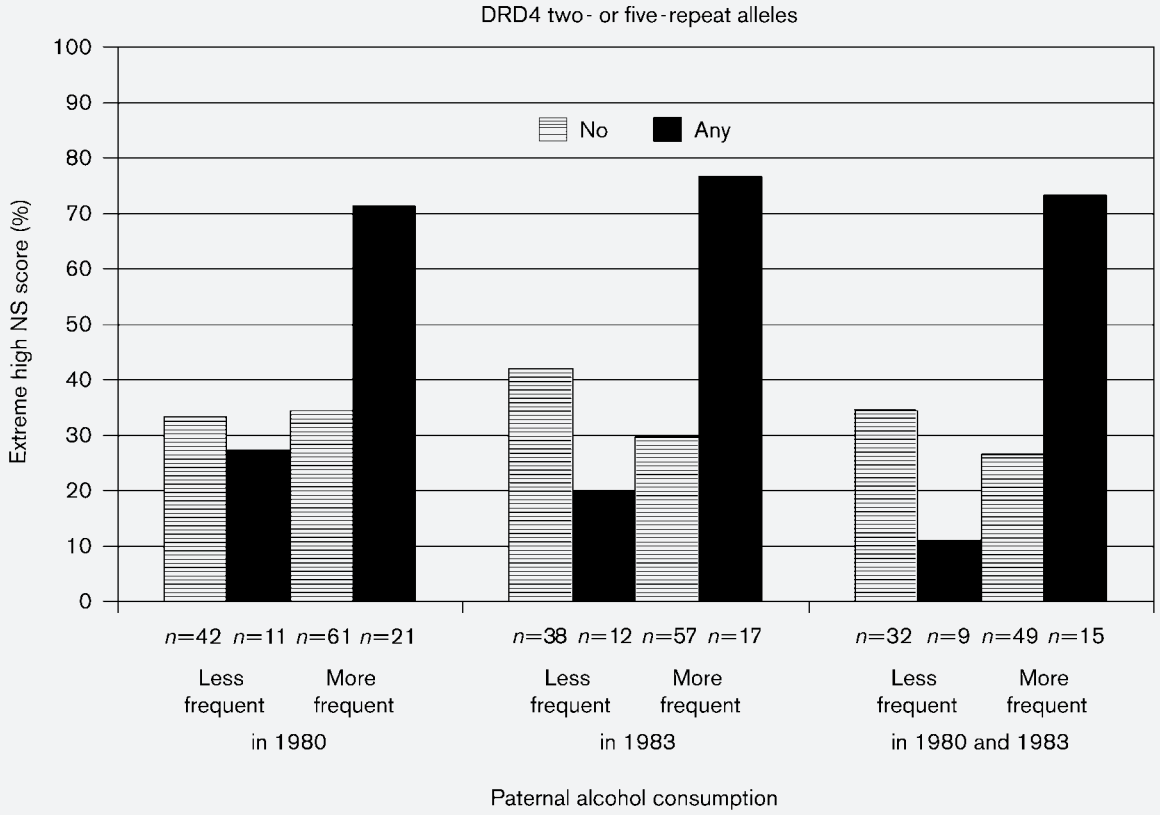
As previously reported by Keltikangas-Järvinen *et al.* (2003), the participants carrying any two- or five-repeat alleles of the DRD4 gene had a significantly greater risk of exhibiting NS scores that were above the 90th percentile on a population distribution than those carrying none (odds ratio = 2.41, 95% CI = 1.11–5.20).

Reports of parental alcohol use in 1980 showed that more frequent experiences of feeling drunk by the mothers ($\chi^2 = 6.9$; df = 1; $P < 0.01$) and the fathers ($\chi^2 = 7.4$; df = 1; $P < 0.01$) were associated with higher NS scores in the offspring 17 years later (cf. Ravaja and Keltikangas-Järvinen, 2001).

Table 1 shows the results of the logistic regression analyses testing gene-environment interaction on NS. Paternal alcohol consumption moderated the association between the DRD4 polymorphism and NS in the offspring. When the father reported more frequent consumption of alcohol in 1980 (odds ratio = 4.76, 95% CI = 1.61–14.08), in 1983 (odds ratio = 8.33, 95% CI = 2.36–29.38), and at both points in time (odds ratio = 7.62, 95% CI = 2.06–28.18), the participants carrying any versus no two- or five-repeat alleles had a significantly greater risk of belonging to the group scoring above the 90th percentile on the population distribution of NS (extremely high NS). When the father reported consuming alcohol less frequently, the allelic diversity of the DRD4 gene had no effect on NS (all *P*-values > 0.17). Figure 1 shows the proportion of participants belonging to the 90th percentile group on NS according to DRD4 two- or five-repeat allele status and frequency of paternal alcohol consumption. When we controlled for the main effect of maternal child-rearing, and the moderation effect of DRD4 by child-rearing, the associations remained significant (all *P*-values < 0.04) with one exception: the moderation effect of DRD4 by paternal alcohol consumption in 1980 became nonsignificant (*P*-values > 0.06).

Further, when the father reported feeling drunk more frequently in 1983, the participants with any versus no two- or five-repeat alleles had a significantly greater risk of belonging to the group scoring above

Figure 1.



Proportion of Study Participants with Extremely High Novelty-Seeking (NS) Scores When the Participant is Carrying Any Versus No Two- or Five-Repeat Alleles of The Dopamine D4 Receptor (Drd4) Gene, and When The Participant's Father Reported More or Less Frequent Alcohol Consumption 17–14 Years Earlier In 1980, 1983, and at Both Points In Time.

the 90 percentile (extreme high NS) on the population distribution of NS (odds ratio = 7.78, 95% CI = 1.81–33.38; 10 out of 13 participants for any two or five repeats of the DRD4 gene belonged to extremely high NS group versus 12 out of 40 participants for no repeat). When the father reported less frequent drunkenness, the offspring DRD4 alleles had no effect on NS (all *P*-values > 0.56). This moderation effect became non-significant when the main effect of maternal child-rearing, and the moderation effect of DRD4 by maternal child-rearing were controlled for (*P*-values > 0.056).

Maternal alcohol consumption did not moderate the association between the DRD4 two- or five-repeat alleles and NS (all *P*-values > 0.30). Parental alcohol consumption did not interact with the DRD4 seven-repeat allele in the analysis of NS (all *P*-values > 0.13). Statistical controls for age and sex did not alter the significant associations.

Discussion

In the current study, we tested whether parental alcohol use during the childhood/adolescence of their offspring moderated the effect of the DRD4 polymorphism on NS temperament over 17 years. The results showed that when the father, but not the mother, reported more frequent alcohol consumption (daily to a couple of times a month) or drunkenness (daily to every second month) 17 and/or 14 years before the assessment of NS, the offspring carrying two- or five-repeat alleles of the DRD4 gene had a 4.76–8.33 times greater risk of belonging to the extremely high NS group than those carrying other alleles of the same gene. The genotype had no effect on NS when the father reported less frequent alcohol consumption or drunkenness. Maternal alcohol consumption did not moderate any of the associations. Nor did we find any associations between parental alcohol consumption, the seven-repeat variant of the DRD4 gene and NS temperament.

Ozkaragoz and Noble (2000) recently demonstrated that adolescent sons of alcoholic fathers carrying the minor alleles (A1+, B1+, 1+) of the DRD2 gene, showed significantly higher extraversion scores than the sons of non-alcoholic fathers. Given these findings, they proposed that individu-

als with minor alleles of the DRD2 gene might cope with a stressor (i.e. the consequences of paternal alcoholism) by increasing their level of activity while children with major alleles of the DRD2 gene would decrease their activity. Berman *et al.* (2002) hypothesized that the developmental mechanism of NS in combination with the DRD2 minor allele (A1+) is based on negative reinforcement or self-medication, whereas the DRD2 major allele (A1−) is associated with NS based on positive reinforcement or the fulfillment of appetitive drives. Even though DRD2 and DRD4 belong to the same family of dopamine receptors, direct comparisons between the results involving the DRD2 and DRD4 genes cannot be made. However, it could be asked to what extent the current findings reflect differences in reaction to chronic environmental stress according to the DRD4 variant. Parental alcoholism has been associated with increased stress in the offspring (Reich *et al.,* 1988; Roosa *et al.,* 1988). Individuals with DRD4 two- or five-repeat alleles may cope with that stress by increasing their level of activity, which becomes manifested as NS temperament. This is consistent with findings on DRD4 receptor knockout mice, suggesting that one function of the dopamine receptor D4 is to regulate anxiety and stress reactions (Falzone *et al.,* 2002).

Another potential explanation for the current findings is that there may exist an unknown common underlying factor that exerts effects on both the father and the offspring. This factor may be either another gene polymorphism, resulting in epistasis with the DRD4 gene, or other environmental or demographic factors.

We have recently demonstrated that a negatively tuned maternal rearing environment moderated the association between the DRD4 two- and five-repeat alleles and NS (Keltikangas-Järvinen *et al.,* 2004). The current finding adds to our previous result by showing that there may be multiple, partly overlapping and partly independent, environmental moderators that may have complex associations with each other. Controlling for the rearing environment diminished the moderating effects of paternal drunkenness, but did not have a significant effect on the moderating effects of the frequency of paternal alcohol consumption. This suggests that a negatively tuned rearing environment partly overlaps with parental alcohol use, but that paternal alcohol consumption also has a significant independent role as a moderator.

To our knowledge, no studies have found environmental moderators of the association between the DRD4 seven-repeat allele and NS. This is indeed important, because there may be two developmentally different NS phenotypes, as suggested by Berman *et al.* (2002), with different genetic backgrounds and environmental moderators.

In future studies, questions regarding the possible passive gene-environment correlation between the DRD4 gene, parental alcohol use, and NS need to be addressed. Because parental genotype determines offspring genotype fully and the environment in which the child develops partially, parental genes (e.g. the DRD4 gene) could be responsible for both parental alcohol use and offspring NS. Consequently, Enoch *et al.* (2003) have suggested that NS might have a role as an intermediate phenotype in the search for the genetics of alcoholism. However, studies connecting DRD4 and alcoholism have failed to find an association (cf. review by Dick and Foroud, 2003).

One limitation of the present study is the small sample size. However, the participants who scored above the 90th percentile and below the 10th percentile on NS were selected for the current study from a population sample of 2149 participants. The population sample decreases the possibility of distortions in associations between the variables (Cohen and Cohen, 1984), and selective genotyping was shown to increase the statistical power per genotype fivefold compared with random genotyping, provided that the number of individuals phenotyped is increased fourfold (Darvasi and Soller, 1992). Because of the small sample size, testing the effects separately by birth cohort and sex remains a future study question. Another limitation is the non-standardized assessment of parental alcohol consumption. However, questions regarding frequency of consumption and heavy drinking are typical in epidemiological studies because they provide the necessary variance in population-based samples. The under-reporting of alcohol use by parents also remains a possibility because of the social undesirability of this behaviour. However, parental alcohol consumption was measured at two points in time. The measures showed high individual stability, and the findings on the moderating role of parental alcohol consumption were highly comparable in the two examinations conducted 3 years apart.

We have taken into consideration the points made by Lusher *et al.* (2001), who recently suggested that studies on DRD4 and NS associations should comprise participants under 45 years of age, should utilize personality scales with high reliability and validity such as the Temperament and Character Inventory, should study the effects in a homogenous sample according to ethnicity, and should consider the effects of sex on the results.

To our knowledge, this study is one of the very few to have tested gene-environment interaction in the context of a specific personality trait, and to have utilized a prospective design extending over different developmental stages. The findings underline the importance of taking both nature and nurture into consideration when trying to form a clear picture of genetic bases of complex human behavioural patterns.

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