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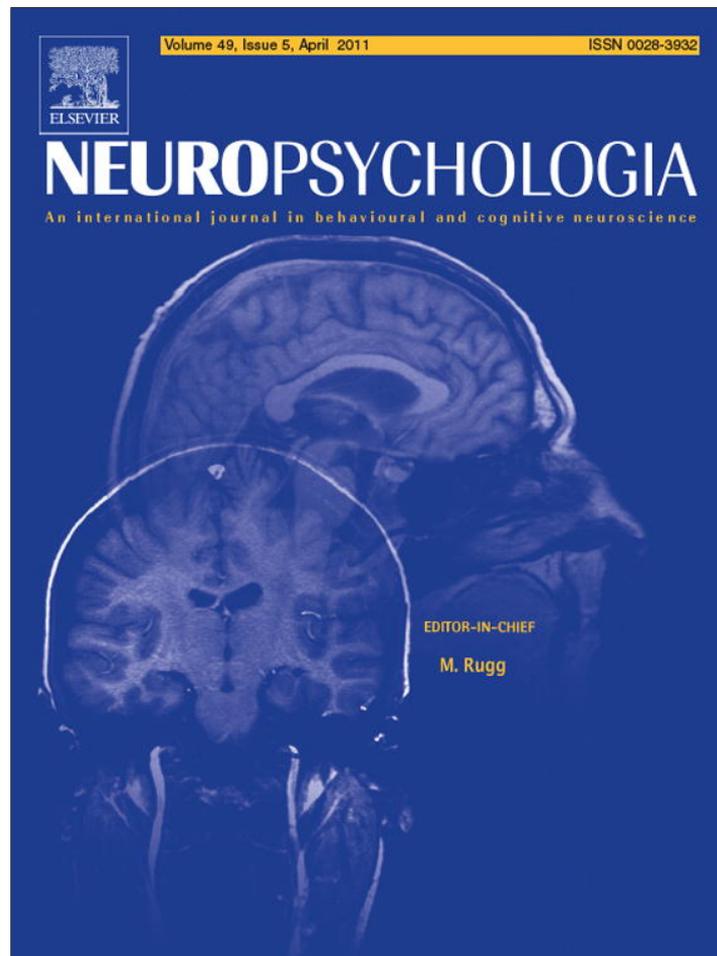
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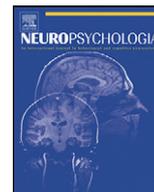
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Brief communication

L-DRD4 genotype not associated with sensation seeking, gambling performance and startle reactivity in adolescents: The TRAILS study

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ABSTRACT

The purpose of the present study was to investigate whether a length polymorphism in the dopamine receptor D4 gene (DRD4) was associated with approach related traits in adolescents. Data were used from TRAILS (TRacking Adolescents' Individual Lives Survey), a population based cohort of Dutch adolescents. Sensation seeking, assessed with personality questionnaires from the participants themselves and their biological father and mother ($n = 1282$) was not associated with DRD4 genotype. Gambling performance ($n = 591$) and startle reactivity ($n = 432$) were not associated with DRD4 genotype either. Explanations for the dissociation might be sought in differences in development of the limbic system and the prefrontal cortex, both with high dopamine receptor D4 densities and both involved in approach related behaviours.

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1. Introduction

Individuals carrying the 7 repeat (7R) of the dopamine D4 receptor gene (L-DRD4) have a reduced sensitivity to dopamine when compared to individuals carrying only shorter variants (S-DRD4), resulting in hypodopaminergic functioning (Oak, Oldenhof, & Van Tol, 2000). Carrying the L-DRD4 has been associated with approach-related traits such as (male) substance use (Laucht, Becker, El-Faddagh, Hohm, & Schmidt, 2005), reduced startle reactivity (Pauli et al., 2010; Roussos, Giakoumaki, & Bitsios, 2009), and reduced gambling performance (Roussos et al., 2009). DRD4 genotype has inconsistently been linked to approach-related personality traits (Munafò, Yalcin, Willis-Owen, & Flint, 2008).

In the present study, we will investigate if L-DRD4 is associated with sensation seeking, gambling performance and startle reactivity in adolescents. This developmental stage is marked by neurodevelopmental changes resulting in an increase in impulsive, risk-taking behaviours (Casey, Getz, & Galvan, 2008). Indeed, scores

on approach related personality traits have been shown to increase from age 11 to 16 (Caspi, Roberts, & Shiner, 2005) and decrease afterwards (Steinberg et al., 2008) and gambling performance has also been shown to develop into adulthood (Crone & van der Molen, 2004). It is unknown, however, if the associations of DRD4 with approach related traits are different in adolescents compared to adults.

2. Methods

2.1. Subjects

Data from the third wave of TRAILS (TRacking Adolescents' Individual Lives Survey) were used. TRAILS is a representative, prospective cohort study of Dutch adolescents for which three data collection waves have been completed (for a detailed description of the cohort see de Winter et al., 2005; Huisman et al., 2008). Mean age was 11.09 ($SD = 0.59$) years at the first wave, response rate was 76% ($n = 2230$, 51% girls). Mean age was 16.13 ($SD = 0.59$) years at the third wave, response rate was 81.4% ($n = 1816$, 52% girls). At this wave, blood or buccal samples were collected for DNA analysis.

At the third measurement wave, a focus sample of 744 adolescents was invited to perform a series of laboratory tasks (hereafter referred to as the experimental session) on top of the usual assessments. Of these adolescents, 715 (96.1%) agreed to do so. Adolescents with one or more risk factors for mental health problems had a greater chance of being selected for the experimental session. The risk factors were defined based on temperament (high frustration and fearfulness, low effortful control), lifetime parental psychopathology, and living in a single-parent family. In total, 66.0% of the focus sample had at least one of the above-described risk factors;

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the remaining 34.0% were selected randomly from the low-risk TRAILS participants. Please note that the focus sample still represented the whole range of problems seen in a normal population of adolescents. Genetic information was available for 591 subjects who participated in the experimental session.

2.2. DNA extraction and genotyping

DNA was extracted from blood samples ($n = 1238$) or buccal swabs (Cytobrush®) ($n = 361$) using a manual salting out procedure as described by Miller, Dykes, and Polesky (1988). The 48 bp direct repeat polymorphism in exon 3 of *DRD4* was genotyped on the Illumina BeadStation 500 platform (Illumina Inc., San Diego, CA, USA). The genotyping assay was carried out in a CCKL quality-certified laboratory and has been validated earlier. Three percent blanks as well as duplicates between plates were taken along as quality controls during genotyping. Determination of the length of the alleles was performed by direct analysis on an automated capillary sequencer (ABI3730, Applied Biosystems, Nieuwerkerk a/d IJssel, The Netherlands) using standard conditions. Information on length polymorphisms was available for 1465 subjects. Call rate for *DRD4* was 99.4%. After excluding one of each sibling pair ($n = 12$) and subjects who were not from Dutch ancestry ($n = 157$), genetic data for 1282 participants was included. The presence of one or two L-*DRD4* alleles was considered a genetic risk marker compared to the absence of the L-*DRD4* allele (i.e., presence of two S-*DRD4* alleles).

2.3. Personality questionnaires

At the third measurement wave participants were rated on characteristics of sensation seeking by themselves, their biological mother and their biological father with the subscale Excitement Seeking from the Dutch version of the Revised NEO-Personality Inventory (NEO-PI-R Costa & McCrae, 1992; Hoekstra, Ormel, & De Fruyt, 2007). This scale measures the adolescents' need for environmental stimulation. It consists of 8 items with a Cronbach's alpha of .58, .62 and .61 for the different informants respectively. In addition, one of the parents (89.9% mothers) filled out the Revised Early Adolescent Temperament Questionnaire (Oldehinkel, Hartman, De Winter, Veenstra, & Ormel, 2004) including a High Intensity Pleasure scale (i.e. the pleasure derived from activities involving high-intensity or novelty). This scale consisted of 6 items and had a Cronbach's alpha of .71.

2.4. Experimental session

The experimental session consisted of a number of different challenges, in chronological order: a spatial orienting task, a gambling task, a startle reflex task, and a social stress test. The session was preceded and followed by a 40-min period of rest. The participants filled out a number of questionnaires at the start and end of the session. The experimental sessions took place in sound-proof rooms with blinded windows at selected locations in the participants' towns of residence. The total session lasted about three and a half hours. Following the social stress test, the participants were debriefed about the experiment and could relax for about 15 min (for more information see Bouma, Riese, Ormel, Verhulst, & Oldehinkel, 2009).

2.4.1. Gambling task

The gambling task performed was very similar to the Bangor Gambling Task reported by Bowman and Turnbull (2004). Briefly, participants were presented with a deck of 100 playing cards, with 38 'high' cards (Jack, Queen, King, Ace), producing financial gain, and 62 'low' cards (between 2 and 10), producing financial loss. The deck of 100 cards consisted of five blocks of 20 cards, with increasing probabilities of loss, requiring adjustment of strategy from gambling to not-gambling over the course of the task (Bowman & Turnbull, 2004). Participants could choose to gamble or not to gamble as often as they liked. If they chose not to gamble, regardless of the card, they did not incur any consequences or benefits. If they chose to gamble and received a 'high' card, they won the amount on the face of that card, whereas if they received a 'low' card they lost the amount on the face of that card. At the start of the game the participants were given €5.00, and were told that they could keep any money they won. Unlike the Bowman study, participants were not given new gambling money once they had depleted their funds. 73.6% of the participants completed the task. Other participants ran out of money before turning 100 cards, mostly during the fifth block. All participants turned at least 71 cards. Scores were (a) the number of non-gambling choices minus the number of gambling choices over the first 71 cards, (b) total money won, and (c) strategy adjustment defined as the difference between block 4 and block 1 in the number of non-gambling choices minus the number of gambling choices.

2.4.2. Startle reflex test

The startle reflex task performed was very similar to the task administered by van Goozen, Snoek, Matthys, van Rossum, and van Engeland (2004). Two minor differences were the reference electrode, which was placed on the shoulder, and the fact that pictures were presented on a computer monitor. In sum, auditory startle stimuli were administered 4.5, 5.5 or 6.5 s after onset of presentation of 18 out of 27 pictures with either positive, neutral or negative valence (van Goozen et al., 2004).

EMG recordings of startle reflexes were registered by the physiological data acquisition software package BIOPAC (version 3.8.1) and processed according to the

recommendations by Blumenthal et al. (2005). In short, a 50 Hz bandstop filter was applied to the raw signal which was sampled at 1000 Hz. After this, high and low pass filters were applied (28–500 Hz) before the signal was rectified and smoothed by a lowpass filter at 15.9 Hz. Startle amplitude was expressed in microvolts (μV). Affective startle modulation was defined as the startle reflex on trials with positive or negative pictures relative to neutral pictures. Startle data of a subject were included if a startle reflex could be scored in at least 9 trials and at least one of each valence by probe onset combination, resulting in 432 subjects.

Following the startle experiment all pictures were shown again and participants were asked to rate the pleasantness of each picture on a visual-analogue scale. Participants' feelings of arousal, unpleasantness and control were assessed with self-assessment manikins (Bradley & Lang, 1994) immediately after the startle reflex task with reference to the task. Pre-test feelings were assessed after 40 min rest. Both picture ratings and scores on self-assessment manikins were translated into a nine-point scale.

2.5. Statistical analyses

Student *t*-tests were used to compare genders and to compare genotypes in outcome variables that were not associated with gender and presence of a risk factor for mental health problems. Analyses of variance with gender and/or presence of a risk factor as covariates were used to test associations between genotype and outcome variables associated with gender and/or presence of a risk factor. Repeated measures analyses of variance (with or without adjustment) were used to test associations between genotype and learning over the first four blocks of the gambling task and between genotype and affective startle modulation. Significance level was set at $p < .05$, effect sizes are reported as partial eta-squared. Power analyses showed that 100 subjects give a power of 80% to detect a medium sized difference with a minor allele frequency of .21.

3. Results

Eight hundred and three subjects were classified as S-*DRD4* and 479 subjects as L-*DRD4*. This distribution was within Hardy-Weinberg equilibrium. Genotype was related to gender ($\chi^2(1) = 5.06, p < .05$). More females were classified as S-*DRD4*, more males were classified as L-*DRD4*. Population stratification analyses with 768 SNPs showed that participants with or without one or more risk factors for mental health problems were not genetically different.

3.1. Personality and gambling

Table 1 shows demographic data as well as personality and gambling performance stratified for gender and genotype. Significant gender differences were found on self rating of Excitement Seeking ($t(1656) = 7.38$) and parent rating of High Intensity Pleasure ($t(1506) = 2.44$). Adolescents who had one or more risk factors for mental health problems, and therefore had a higher chance of being selected for participation in the experimental session had lower High Intensity Pleasure compared to adolescents without specified risk factors ($t(666) = 2.05$). Therefore, gender was included as a covariate in analysis of self-rating of Excitement Seeking and both gender and presence of risk factors were included as covariates in analysis of High Intensity Pleasure.

t-Tests showed no differences between genotypes on age ($t(1248) = -0.03$) nor at ratings of Excitement Seeking by the biological mother ($t(945) = -1.36$) or father ($t(727) = -0.05$). ANCOVAs showed no differences between genotypes on self rating of Excitement Seeking ($F(1245, 1) = 3.6, \eta^2 = .00$), and High Intensity Pleasure ($F(551, 1) = 0.85, \eta^2 = .00$).

On the gambling task, adolescents with one or more risk factors for mental health problems and males did not adjust their game strategy as much as adolescents without those risk factors ($t(571) = 2.15$). Therefore, both gender and presence of risk factors were included as covariates in the analysis. ANCOVAs showed that L-*DRD4* individuals did not gamble more ($F(577, 3) = 0.10, \eta^2 = .00$), did not lose more money ($F(572, 3) = 0.36, \eta^2 = .00$), and had equal levels of strategy adjustment ($F(569, 3) = 0.33, \eta^2 = .00$) when compared to the S-*DRD4* individuals. A 4×2 (block by genotype) repeated measures ANCOVA revealed a significant main effect

Table 1
Demographic and personality characteristics for each DRD4 VNTR group stratified by gender.

		Males				Females			
		S-DRD4 (n = 362)		L-DRD4 (n = 247)		S-DRD4 (n = 441)		L-DRD4 (n = 232)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age		16.17	0.66	16.18	0.69	16.23	0.69	16.23	0.73
Personality									
Excitement Seeking	Participant ^a	28.39	4.18	28.73	4.21	26.93	3.95	27.50	4.13
	Mother	24.92	3.57	25.07	4.12	24.94	3.81	25.51	4.11
	Father	25.38	3.76	24.84	3.79	25.33	3.81	25.89	3.85
High Intensity Pleasure ^a		3.54	0.78	3.59	0.88	3.43	0.84	3.45	0.84
Bangor Gambling task ^b									
Non-gambling	Block 1	0.29	6.75	-0.53	6.20	-2.23	5.82	-1.30	5.75
Minus gambling	Block 2	-0.96	7.32	-1.82	6.77	-1.44	5.35	-1.44	6.28
Choices	Block 3	0.38	7.48	-0.97	7.87	0.60	6.28	0.59	6.89
	Block 4	5.43	7.71	4.30	8.61	4.49	7.11	4.71	7.07
	Total (71 cards)	-1.94	19.98	2.62	21.46	-0.03	18.45	-2.16	15.25
Total money won		1.77	1.86	2.13	1.96	1.86	1.82	1.73	1.78
Total learning		4.84	9.90	5.17	8.43	5.99	7.93	6.74	8.33
Startle reflex task ^b									
Affective picture ratings									
	Positive	7.20	0.87	7.32	0.94	7.38	0.82	7.33	0.91
	Neutral ^a	5.15	0.88	5.3	0.97	5.16	0.80	5.22	1.14
	Negative	2.83	1.15	2.93	1.36	2.46	0.98	2.36	0.97
Self assessment manikins test-pre test difference									
	Arousal	-0.23	1.63	-0.47	1.61	-0.16	1.74	0.02	1.52
	Unpleasantness	0.86	1.79	1.23	1.9	0.73	1.6	0.98	1.98
	Control	0.04	1.2	-0.24	1.6	-0.17	1.32	0.07	1.19
Startle amplitudes									
4.5 s	Positive	0.032	0.036	0.028	0.034	0.039	0.042	0.034	0.034
	Neutral	0.026	0.036	0.024	0.038	0.036	0.044	0.031	0.038
	Negative	0.027	0.038	0.024	0.038	0.041	0.046	0.037	0.047
5.5 s	Positive	0.019	0.030	0.019	0.033	0.032	0.039	0.026	0.036
	Neutral	0.029	0.037	0.027	0.034	0.044	0.044	0.042	0.046
	Negative	0.028	0.039	0.027	0.032	0.044	0.047	0.040	0.046
6.5 s	Positive	0.026	0.036	0.022	0.033	0.034	0.039	0.032	0.040
	Neutral	0.033	0.040	0.027	0.035	0.044	0.043	0.042	0.044
	Negative	0.027	0.038	0.024	0.037	0.038	0.046	0.029	0.036

^a Significantly different between males and females. None of the variables were different for S-DRD4 and L-DRD4 individuals.

^b The Bangor Gambling task and the Startle reflex task were performed in part of the TRAILS sample (see Section 2.1). Excitement Seeking was a scale of the NEO Personality Inventory, High Intensity Pleasure was a scale of the Early Adolescent Temperament Questionnaire.

for block ($F(1707, 3) = 83.25$, $\eta^2 = .13$), and significant interactions between gender and block ($F(1707, 3) = 5.95$, $\eta^2 = .01$), and presence of risk factors and block ($F(1707, 3) = 4.02$, $\eta^2 = .01$). L-DRD4 and S-DRD4 individuals did not significantly differ in overall learning across block 1–4 ($F(1707, 3) = 0.76$, $\eta^2 = .00$).

3.2. Startle testing – subjective ratings

A repeated measures ANOVA did not show differences between S-DRD4 and L-DRD4 individuals on pre and post-test ratings of arousal, unpleasantness and control ($F_{\text{arousal}}(589, 1) = 1.38$, $\eta^2 = .002$; $F_{\text{unpleasantness}}(589, 1) = 1.32$, $\eta^2 = .002$; $F_{\text{control}}(589, 1) = 1.37$, $\eta^2 = .002$). The main effects of test were all significant ($F_{\text{arousal}}(589, 1) = 8.51$, $\eta^2 = .014$; $F_{\text{unpleasantness}}(589, 1) = 7.50$, $\eta^2 = .013$; $F_{\text{control}}(589, 1) = 8.37$, $\eta^2 = .014$), showing lower arousal, higher unpleasantness and lower control during the startle test compared to before the experiments (Table 1). *t*-Tests showed that picture ratings did not differ between S-DRD4 and L-DRD4 either ($t_{\text{positive}}(588) = -0.41$; $t_{\text{negative}}(588) = -0.02$; $t_{\text{neutral}}(588) = -1.35$).

3.3. Affective startle modulation

A *t*-test showed significantly higher startle amplitudes for females compared to males ($t(430) = 3.13$), therefore, gender was included as a covariate. A $3 \times 3 \times 2$ (valence by probe onset by genotype) repeated measures ANCOVA did reveal a significant main effect for valence ($F(858, 2) = 23.38$, $\eta^2 = .05$) and a sig-

nificant two-way interaction between valence and probe onset ($F(1716, 4) = 19.49$, $\eta^2 = .04$). Highest startle amplitudes were found in the neutral valence condition, lowest amplitudes were found in the positive valence condition. In the neutral valence condition lowest amplitudes were found with a probe onset of 4.5 s, in the positive valence condition with a probe onset of 5.5 s, while in the negative valence condition lowest startle amplitudes were found with a probe onset of 6.5 s. Significant interactions with gender and valence ($F(858, 2) = 3.64$, $\eta^2 = .01$) and with gender and probe onset ($F(858, 2) = 4.86$, $\eta^2 = .01$) showed larger startle attenuation with positive compared to neutral pictures in females compared to males and a decrease instead of an increase of startle amplitudes with a probe onset of 4500 ms in males compared to females. The main effect of genotype was not significant ($F(429, 1) = 1.04$, $\eta^2 = .00$), nor were any of the interactions with genotype (all F 's < 1, $\eta^2 = .00$).

3.4. Analyses stratified for gender and presence of risk factors

Stratified analyses, corrected for multiple testing, yielded the same results: no significant effect of genotype.

4. Discussion

In this study no association was found between DRD4 genotype and sensation seeking, gambling performance and startle reactivity in a large population cohort of Dutch adolescents. In adults, inconsistent findings with regard to the association with approach-

related personality traits have been observed (Munafò et al., 2008). The only study in adolescents reported an association between DRD4 and novelty seeking exclusively in males (Laucht et al., 2005). In our study, stratifying analysis for gender gave the same results for males and females: no association. Thus, it must be concluded that DRD4 is inconsistently associated with approach related personality traits in adolescents as well.

The association between DRD4 and startle reactivity has consistently been found in two earlier studies with adults (Pauli et al., 2010; Roussos et al., 2009), but was not found in our adolescent sample. An association with gambling performance has been reported in adults (Roussos et al., 2009), but was not found in our adolescent sample either. Possibly, developmental differences between adolescents and adults might account for the differences between studies. In adolescence, the pre-frontal cortex is still developing while the limbic system has fully matured (Casey et al., 2008). This immature prefrontal cortex does not only contribute to an increase in impulsive and risk-taking behaviours during adolescence (Casey et al., 2008), but possibly to differences in startle reactivity and gambling performance as well. Indeed, our adolescent sample showed patterns of affective startle modulation that resemble results in children with startle attenuation instead of potentiation in the negative affect condition (Waters, Lipp, & Spence, 2005). Although we know that adolescents perform worse than adults on an equivalent of the Iowa gambling task (Crone & van der Molen, 2004), adolescents in our sample seemed to perform equally well on the Bangor gambling task compared to the adults in Bowman and Turnbull's study (2004). Thus, more research is needed to investigate whether these tasks measure emotional decision making in the same way.

Both the prefrontal cortex and the limbic system have a high expression of dopamine D4 receptors (Missale, Nash, Robinson, Jaber, & Caron, 1998), which has been used to explain the association between DRD4 genotype and affective startle modulation (Pauli et al., 2010). Possibly, the finding that DRD4 genotype was not associated with approach related traits in our adolescent sample might be explained by differences in development of the limbic system and the prefrontal cortex.

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